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INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

WHO

IPCS Harmonization Project

WHO Human Health Risk Assessment Toolkit: Chemical Hazards

IOMC

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

World Health Organization

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Harmonization Project Document No. 8

WHO HUMAN HEALTH RISK ASSESSMENT TOOLKIT: CHEMICAL HAZARDS

This project was conducted within the IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

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

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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TABLE OF CONTENTS

PREFACE viii

PROCESS FOR DEVELOPMENT OF THE TOOLKIT x

ACKNOWLEDGEMENTS xiii

LIST OF ACRONYMS AND ABBREVIATIONS xiv

1. INTRODUCTION 1
   1.1 Purpose and intended audience 1
   1.2 Scope of the Toolkit 2

2. DESCRIPTION OF HUMAN HEALTH RISK ASSESSMENT OF CHEMICALS 4
   2.1 Definition of risk assessment 4
   2.2 Uses of human health risk assessments of chemicals 5

3. DESCRIPTION OF THE TOOLKIT 7
   3.1 The Toolkit as a road map 7
   3.2 Tiered assessments in the Toolkit 10
   3.3 Generic road maps 12
      3.3.1 Hazard identification 12
         3.3.1.1 Chemical identity 12
         3.3.1.2 Hazardous properties 14
      3.3.2 Hazard characterization/guidance or guideline value identification 15
         3.3.2.1 Health-based guidance values derived by international organizations 18
         3.3.2.2 Media-specific guideline values (“quality guideline values”) derived by international organizations 21
         3.3.2.3 Evaluating the appropriateness of available guidance or guideline values for a specific problem 22
      3.3.3 Exposure assessment 22
         3.3.3.1 Routes and pathways of exposure 23
         3.3.3.2 Estimating exposures: modelling or measurement approaches 23
         3.3.3.3 Duration of exposure 26
         3.3.3.4 Concentration and rate of exposure 27
         3.3.3.5 Biomarkers of exposure 28
      3.3.4 Risk characterization 28
         3.3.4.1 Comparison with a guidance or guideline value 28
         3.3.4.2 Estimation of cancer risk 30

4. INTERNATIONAL RISK ASSESSMENT RESOURCES 31
   4.1 Introduction 31
   4.2 Organization 31
   4.3 Directories of resources 32
   4.4 General resources on risk assessment 32
      4.4.1 Resources on risk assessment methodology 33
      4.4.2 Resources on susceptible populations 33

4.5 Chemical-specific resources 34
4.5.1 JMPR monographs 34
4.5.2 JECFA monographs 34
4.5.3 EHC monographs 35
4.5.4 CICADs 35
4.5.5 Drinking-water quality background documents 35
4.6 Hazard identification resources 35
4.6.1 International Chemical Safety Cards 36
4.6.2 Screening Information Datasets for High Production Volume Chemicals 36
4.6.3 WHO Recommended Classification of Pesticides by Hazard 36
4.6.4 UN Recommendations for the Transport of Dangerous Goods 37
4.6.5 IARC monographs 37
4.6.6 Hazardous Substances Data Bank 37
4.6.7 European Chemical Substances Information System 37
4.6.8 EU Classification and Labelling System 38
4.6.9 International Chemical Control Toolkit 38
4.7 Hazard characterization/guidance or guideline value resources 38
4.7.1 Guidance values for exposure rates 39
4.7.1.1 Pesticides 39
4.7.1.2 Food additives and contaminants, naturally occurring toxicants and residues of veterinary drugs in food 39
4.7.2 Guideline values for exposure concentrations 39
4.7.2.1 WHO drinking-water guidelines 39
4.7.2.2 WHO air quality guidelines 39
4.7.3 Guidance and guideline values from chemical-specific monographs 40
4.7.4 International Toxicity Estimates for Risk (ITER) database 40
4.7.5 Occupational exposure limits (OELs) 40
4.8 Exposure assessment resources 40
4.8.1 General guidance on exposure assessment 41
4.8.2 Emission sources and scenarios 41
4.8.3 Emission rates 42
4.8.4 Transport and fate 43
4.8.5 Exposure concentrations 44
4.8.6 Exposure factors 45
4.9 Risk characterization resources 45

5. DRINKING-WATER CASE-STUDY 46
5.1 Objective 46
5.2 Statement of the problem 46
5.3 Hazard identification 47
5.4 Hazard characterization/guidance or guideline value identification 49
5.5 Exposure assessment 50
5.6 Risk characterization 55
5.7 Summary 57

6. RESPIRABLE PARTICULATE MATTER (PM_{10}) CASE-STUDY 58
6.1 Objective 58
6.2 Statement of the problem 58
6.3 Hazard identification 59
6.4 Hazard characterization/guidance or guideline value identification 59

6.5 Exposure assessment....62
6.6 Risk characterization....65
6.7 Summary....66

7. PESTICIDE CASE-STUDY....67
7.1 Objective....67
7.2 Statement of the problem....67
7.3 Hazard identification....67
7.4 Hazard characterization/guidance or guideline value identification....69
7.5 Exposure assessment....71
7.6 Risk characterization....75
7.7 Summary....77

8. REFERENCES AND WEB LINKS....79

LIST OF FIGURES

Figure 1 An environmental health paradigm and its relationship to the human health risk assessment framework 6
Figure 2 Generic road map for chemical risk assessment in the context of the Toolkit following the conventional risk assessment paradigm....8
Figure 3 Generic road map for hazard identification in the context of the Toolkit 13
Figure 4 Generic road map for hazard characterization/guidance or guideline value identification in the context of the Toolkit 17
Figure 5 Generic road map for exposure assessment in the context of the Toolkit 24
Figure 6 Possible exposure media and corresponding means of contact 25
Figure 7 Generic road map for risk characterization in the context of the Toolkit....29
Figure 8 Case-specific road map for hazard identification: drinking-water case-study ...48
Figure 9 Case-specific road map for hazard characterization/guidance or guideline value identification: drinking-water case-study....51
Figure 10 Case-specific road map for exposure assessment: drinking-water case-study ...54
Figure 11 Case-specific road map for risk characterization: drinking-water case-study 56
Figure 12 Case-specific road map for hazard identification: particulate matter case-study....60
Figure 13 Case-specific road map for hazard characterization/guidance or guideline value identification: particulate matter case-study 63
Figure 14 Case-specific road map for exposure assessment: particulate matter case-study....65
Figure 15 Case-specific road map for hazard identification: pesticide case-study 70
Figure 16 Case-specific road map for hazard characterization/guidance or guideline value identification: pesticide case-study 72
Figure 17 Case-specific road map for exposure assessment: pesticide case-study....76
Figure 18 Case-specific road map for risk characterization: pesticide case-study 78

LIST OF TABLES

Table 1 Paradigm for risk assessment, including problem formulation 4
Table 2 Output from the framework for chemical risk assessment in the context of the Toolkit....9
Table 3 Tiers of risk assessment included in the Toolkit....11
Table 4 Human health effects included in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS)....15
Table 5 Guidance and other values commonly used in chemical evaluations....18
Table 6 Sources of guidance values for chemicals developed by international organizations....20
Table 7 Sources of guideline values for chemicals developed by international organizations....21
Table 8 Two compilations of hazard identification, hazard characterization, exposure assessment and risk characterization information for chemicals....32
Table 9 WHO documents on principles of human health risk assessment for chemicals....33
Table 10 International sources of information on harmonization of risk assessment methodology 33
Table 11 International sources of information on susceptible populations 34

Table 12 WHO resources on identification of chemical hazards....35
Table 13 General content of international hazard identification resources 36
Table 14 International resources on hazard characterization....39
Table 15 Examples of freely available national resources for occupational exposure limits (OELs) 41
Table 16 International sources of information on media and routes of exposure....41
Table 17 International sources of guidance on exposure assessment 42
Table 18 Widely accepted resources on emissions....43
Table 19 Summary of selected exposure factors published by WHO 45
Table 20 International guidance and guideline values for cadmium 49
Table 21 Cadmium concentrations in five samples of water obtained from each of three locations in the vicinity of Rivertown....53
Table 22 WHO air quality guideline values for PM_{10} 61
Table 23 WHO interim targets for PM_{10}: annual mean concentrations....61
Table 24 Relevance of study findings to an African country: template 74

PREFACE

The production and use of chemicals are increasing worldwide. For example, the global output of chemicals increased approximately 10-fold between 1970 and 2010. In this respect, an important trend is being observed: chemical production continues to grow faster in countries that are not members of the Organisation for Economic Co-operation and Development (OECD) than in OECD countries, and this trend is expected to continue and even accelerate. OECD estimates that non-OECD countries, which were responsible for about 17% of the global production of chemicals in 1970, will be producing 31% of an even larger world production in 2020.

The World Health Organization (WHO) estimates that more than 25% of the global burden of disease is linked to environmental factors, including exposures to toxic chemicals. Lead exposure, for example, accounts for 3% of the cerebrovascular disease burden and 2% of the ischaemic heart disease burden worldwide. Some 9% of the global burden of lung cancer is attributed to occupational exposure to toxic substances, and 5% to outdoor air pollution. Lung cancer and mesothelioma are caused by exposure to asbestos, which remains in use in some countries. Unintentional poisonings kill an estimated 355 000 people each year, two thirds of them in developing countries, where such poisonings are strongly associated with excessive exposure to, and inappropriate use of, toxic chemicals, including pesticides.

Despite what has been known for many years about the potential public health risks that can be posed by chemicals, these problems have not been fully addressed. They persist especially in developing countries, which typically have fewer resources for chemical risk management. This, together with the projected growth in the production and use of chemicals in the developing world, is likely to result in an increase in adverse effects on health if sound chemical management is not put in place.

In contrast, many countries have recognized the need for action and have signed a number of international instruments, including multilateral environmental agreements, such as the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, the Stockholm Convention on Persistent Organic Pollutants and the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal; the Strategic Approach to International Chemicals Management; International Labour Organization conventions; and the International Health Regulations of 2005. All these instruments place requirements on countries to develop capacities for chemical management, including capacities allowing them to assess health and environmental risks associated with the use of chemicals in order to make informed decisions on whether to take action to manage these risks. However, many countries are still lacking competencies to assess risks to human health from exposure to chemicals, especially developing countries and countries with economies in transition.

The purpose of the *WHO Human Health Risk Assessment Toolkit: Chemical Hazards* is to provide its users with guidance to identify, acquire and use the information needed to assess chemical hazards, exposures and the corresponding health risks in their given health risk assessment contexts at local and/or national levels. The Toolkit provides road maps for conducting a human health risk assessment, identifies information that must be gathered to complete an assessment and provides electronic links to international resources from which

the user can obtain information and methods essential for conducting the human health risk assessment.

By doing so, the Toolkit also aims at raising awareness and promoting the use of globally accepted risk assessment information that has been developed by international organizations such as WHO, the Food and Agriculture Organization of the United Nations, the United Nations Environment Programme, the Codex Alimentarius Commission and OECD for use in countries.

The Toolkit has been developed for public health and environmental professionals, regulators, industrial managers and other decision-makers with at least some training in the principles of risk assessment who are responsible for conducting human health risk assessments and making decisions on whether to take action to manage human health risks associated with exposure to chemicals.

WHO and all those involved in the development of the publication hope that the Toolkit will have wide application, especially in developing countries and countries with economies in transition. In the future, it is hoped that, in these countries, the identification of human health risks related to chemicals as well as related management decisions and mitigation measures, including those related to international agreements, are based on best evidence through the application of best risk assessment methodology and use of available authoritative risk assessment information developed by international organizations in combination with locally relevant information.

PROCESS FOR DEVELOPMENT OF THE TOOLKIT

The *WHO Human Health Risk Assessment Toolkit: Chemical Hazards* was developed under the auspices of the International Programme on Chemical Safety (IPCS) Harmonization Project (http://www.who.int/ipcs/methods/harmonization/en/index.html). The goal of the IPCS project is to globally harmonize approaches to risk assessment by increasing understanding and developing basic principles and guidance on specific chemical risk assessment issues.

Dr K. Gutschmidt and Ms C. Vickers, Team Leader Chemical Safety, WHO Secretariat, served as the Responsible Officers for the development of this Toolkit, including its scientific content.

An initial expert meeting was convened to provide guidance for the development of the Toolkit on 5–7 March 2008 in Montreux, Switzerland. The meeting was chaired by Professor B. Chen (School of Public Health, Fudan University, China) and co-chaired by Dr P. Preuss (National Center for Environmental Assessment, Environmental Protection Agency, United States of America [USA]). The meeting was also attended by Dr C. Alonzo (Chemical Safety Unit, Department of Environmental Health, Ministry of Public Health, Uruguay), Dr A. Dawson (South Asian Clinical Toxicology Research Collaboration, Faculty of Medicine, University of Peradeniya, Sri Lanka), Dr J.F.M. de Kom (Senior Policy Advisor, Toxicology Focal Point, Secretariat Director, Ministry of Health, Suriname), Dr I. Dobrev (Fraunhofer Institute for Toxicology and Experimental Medicine, Germany), Dr S.H. Inayat-Hussain (Associate Professor of Toxicology, Environmental Health Program, Faculty of Allied Health Sciences, Universiti Kebangsaan Malaysia, Malaysia), Dr M.E. Meek (Associate Director, Chemical Risk Assessment, McLaughlin Centre for Population Health Risk Assessment, Canada), Dr K. Olokun (Deputy Director, Chemical Safety Management Programme, Food and Drug Services Department, Federal Ministry of Health, Nigeria) and Dr M. Ruchirawat (Office of Academic Affairs, Chulabhorn Research Institute, Thailand). Representatives of the International Life Sciences Institute (Dr S.S. Olin, ILSI Research Foundation, USA), OECD (Mr R. Diderich, Environment, Health & Safety Division, Environment Directorate, OECD, France) and the United Nations Environment Programme (Ms A. Sundén Byléhn, Senior Scientific Affairs Officer, Chemicals Branch, Division of Technology, Industry and Economics, UNEP, Switzerland) were also in attendance. WHO provided the Secretariat (Ms C. Vickers and Ms S. Kunz, IPCS, WHO, Switzerland).

Initial draft material was developed by Professor B. Chen (China) and Dr P. Preuss (USA). A teleconference was held on 23 September 2008, attended by Dr B. Chen (Chair), Dr P. Preuss (Co-chair), Dr I. Dobrev (Germany), Dr S.H. Inayat-Hussain (Malaysia), Dr M.E. Meek (Canada), Dr K. Olokun (Nigeria) and Dr M. Ruchirawat (Thailand). Representatives from ILSI (Dr S.S. Olin) and UNEP (Mr C. Siewe and Ms A. Sundén Byléhn) also participated. The Secretariat consisted of Ms C. Vickers and Dr K. Walker (consultant, USA). Further initial draft material was developed by Dr K. Walker (USA) until February 2009. The first comprehensive Toolkit was drafted by Dr D.L. MacIntosh (Harvard School of Public Health, USA), taking into account previously developed material.

The draft Toolkit was pilot tested from August to October 2009 in three Asian countries: Thailand, Malaysia and China. A meeting was held to lead into the pilot phase on 30–31 July 2009 at the Chulabhorn Research Institute in Bangkok, Thailand. The meeting was organized in close collaboration with the Rotterdam Convention Secretariat, who identified participants

from Designated National Authorities for the Rotterdam Convention in pilot countries. The meeting was attended by Ms P. Chareonsong (Director of Hazardous Substance Section, Waste and Hazardous Substance Management Bureau, Pollution Control Department, Thailand), Mr C. Goh Choo Ta (Research Fellow, Institute for Environment and Development, Universiti Kebangsaan Malaysia, Malaysia), Ms P. Klaimala (Pesticide Risk Assessment Programme, Pesticide Research Group, Office of Agricultural Production Science Research & Development, Department of Agriculture, Thailand), Ms H.H Mohd (Assistant Director, Pesticides Control Division, Department of Agriculture, Ministry of Agriculture and Agro-based Industry, Malaysia), Mr S. Ruengrotvriya (Designated National Agency, Rotterdam Convention, Thailand), Dr M. Ruchirawat (Chulabhorn Research Institute, Thailand), Ms W. Thangnipon (Senior Research Scientist, Pesticide Risk Assessment Programme, Pesticide Research Group, Office of Agricultural Production Science Research & Development, Department of Agriculture, Thailand), Dr Z. Shan (Professor, Nanjing Institute of Environmental Sciences, Ministry of Environmental Protection, China), Ms S. Sirichuaychoo (Senior Agricultural Scientist, Pesticide Regulatory Sub-division, Office of Agricultural Regulation, Department of Agriculture, Thailand), Ms P. Tarin (Environmental Scientist, Waste and Hazardous Substance Management Bureau, Pollution Control Department, Thailand) and Dr J. Zhang (Professor, Department of Environmental Pollution and Health, Chinese Research Academy of Environmental Sciences, Ministry of Environmental Protection, China). The Rotterdam Convention Secretariat was represented by Ms N. Grasser (Scientific Affairs Officer, Rotterdam Convention Secretariat, UNEP, Switzerland). WHO was represented by Dr K. Gutschmidt (Department for Public Health and Environment, Health Security and Environment, WHO, Switzerland) and Dr D.L. MacIntosh (Harvard School of Public Health, USA).

In parallel to the pilot testing in the three countries, the draft Toolkit underwent international peer review from August to October 2009. A final review meeting was held to provide recommendations to finalize the WHO Toolkit by taking into account the lessons learnt from the pilot phase and comments from the peer review. The final review meeting was held on 29–30 October 2009 at the WHO Office in Lyon, France. The meeting was co-chaired by Professor B. Chen (China) and Dr P. Preuss (USA). The meeting was further attended by Mr S. Adu-Kumi (Chemicals Control and Management Centre, Environmental Protection Agency, Ghana), Dr I. Dobrev (Germany), Mr J. Fawell (consultant, United Kingdom), Mr C. Goh Choo Ta (Malaysia), Dr S.H. Inayat-Hussain (Malaysia), Dr M. Ruchirawat (Thailand), Dr D. Russell (Head of Unit, Chemical Hazards and Poisons Division, Deputy Director, WHO Collaborating Centre, The Health Protection Agency, United Kingdom) and Dr J. Satayavivad (Chulabhorn Research Institute, Thailand). Representatives of OECD (Mr M. Oi, Environment, Health and Safety Division, Environment Directorate, OECD, France), the Rotterdam Convention Secretariat (Ms N. Grasser, UNEP) and UNEP (Ms A. Sundén Byléhn, UNEP) were also in attendance. WHO provided the Secretariat (Dr K. Gutschmidt, WHO; Dr J. Thomas-Crusells, Department for Public Health and Environment, Health Security and Environment, WHO, Switzerland, WHO; and Dr D.L. MacIntosh, Harvard School of Public Health, USA).

The final Toolkit was prepared by Dr D.L. MacIntosh (USA) and Dr K. Gutschmidt (WHO).

The *WHO Human Health Risk Assessment Toolkit: Chemical Hazards* is a parallel and complementary effort to the development of the OECD Environmental Risk Assessment Toolkit. At the 44th Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology held in June 2009, OECD member countries

endorsed the OECD project on environmental risk assessment. In addition, the 44th Joint Meeting agreed that the OECD Secretariat would identify OECD documents for and contribute to the development and review of the WHO Toolkit.

ACKNOWLEDGEMENTS

The contributions of all who participated in the preparation and finalization of the *WHO Human Health Risk Assessment Toolkit: Chemical Hazards*, including those who provided their comments during the peer review process, are gratefully acknowledged. Special thanks go to those who pilot tested the Toolkit in Thailand, Malaysia and China and provided invaluable comments from their experience to further the development of the Toolkit.

LIST OF ACRONYMS AND ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ARfD	acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
BMR	benchmark response
CAS	Chemical Abstracts Service
CICAD	Concise International Chemical Assessment Document
C&L	Classification and Labelling
CLP	classification, labelling and packaging
DDE	*p*,*p*-dichlorodiphenyldichloroethene
DDT	*p*,*p*-dichlorodiphenyltrichloroethane
DEH	Department of Environmental Health
ECHA	European Chemicals Agency
EHC	Environmental Health Criteria
ESIS	European Chemical Substances Information System
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
ICSC	International Chemical Safety Card
ILO	International Labour Organization
IPCC	Intergovernmental Panel on Climate Change
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
ML	maximum limit
MOE	margin of exposure
MRL	maximum residue limit
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
PEL	permissible exposure limit
$PM_{2.5}$	particulate matter less than (or equal to) 2.5 μm in aerodynamic diameter
PM_{10}	particulate matter less than (or equal to) 10 μm in aerodynamic diameter
PPE	personal protective equipment
PTMI	provisional tolerable monthly intake
PTWI	provisional tolerable weekly intake
RDEH	Rivertown Department of Environmental Health
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
REL	recommended exposure limit
RIVM	National Institute for Public Health and the Environment (Netherlands)
SF	slope factor

SIDS	Screening Information Dataset for High Production Volume Chemicals
TDI	tolerable daily intake
TLV	threshold limit value
UN	United Nations
UNEP	United Nations Environment Programme
URL	unique record locator
USA	United States of America
USEPA	United States Environmental Protection Agency
WEL	workplace exposure limit
WHO	World Health Organization

1. INTRODUCTION

Risk analysis is a process that incorporates three components: risk assessment, risk management and risk communication. The first component, risk assessment, consists of scientific analyses, the results of which are quantitative or qualitative expressions of the likelihood of harm associated with exposure to a chemical.

The assessment of human health risk requires identification, compilation and integration of information on the health hazards of a chemical, human exposure to the chemical and relationships among exposure, dose and adverse effects. Acquisition of information appropriate to a scenario of interest is a fundamental challenge in risk assessment. Numerous sources of such information can be readily found through literature searches facilitated by electronic tools. Compilations of relevant data prepared by international and other organizations also provide rapid access to information on chemical hazards, exposures and risks.

1.1 Purpose and intended audience

This World Health Organization (WHO) Human Health Risk Assessment Toolkit was developed to help people make decisions about chemicals by assessing the magnitude of potential risks to human health associated with exposure to the chemicals. In so doing, the Toolkit helps its users to 1) identify and acquire the information needed to assess chemical hazards, exposures and risks and 2) use that information to estimate potential exposure to hazardous chemicals and the corresponding health risks.

It is envisioned that the Toolkit will be used to address a wide range of circumstances that are relevant to the management of public health. For example, principles, approaches and resources described in the Toolkit can aid risk assessments of chemical incidents; retrospective evaluations conducted in support of information on the incidence of illness or related concerns; and prospective analyses of potential impacts of a proposed policy, land use, permitting or management decision. Specific examples of risk assessment are described in the case-studies presented in sections 5, 6 and 7.

Although the Toolkit alone cannot answer all of the questions regarding risks from chemical exposures, it will provide important information to public health and environmental specialists, regulators, industrial managers and other decision-makers involved with chemical safety and protection. The Toolkit has been developed particularly for people with at least some training in the principles of risk assessment who are responsible for conducting health risk assessments (e.g. public health and environmental, scientific or engineering professionals) and making decisions on whether to take action to manage environmental risks (e.g. officials in health or environmental regulatory bodies or in private businesses).

The Toolkit was developed in recognition that complementary initiatives are under way within WHO and other international organizations. For example, a comprehensive and concise discussion of risk management strategies may be found in supporting documentation for the WHO *Guidelines for drinking-water quality*, such as *Chemical safety of drinking-water: assessing priorities for risk management* (WHO, 2007). In addition, the Organisation for Economic Co-operation and Development (OECD) is developing Internet-based resources for environmental risk assessment in parallel with the Toolkit (OECD, 2010d). Similarly, the

World Bank has established Internet-based training modules and interactive tools that are intended to enable use of risk-based approaches to prioritize and manage land sites contaminated with persistent organic pollutants and other hazardous substances (World Bank, 2010). Finally, the Toolkit is complementary to the Chemical Information Exchange Network initiative of the United Nations Environment Programme (UNEP) to facilitate interactions and transfer of knowledge between networks of people involved in the management of chemicals (UNEP, 2010).

1.2 Scope of the Toolkit

The Toolkit is a manual on how to identify and characterize chemical hazards, assess exposures to these chemicals and determine whether these exposures are dangerous to public health. The Toolkit also provides references, including electronic links to risk assessment information and data published by international organizations. Where there are gaps in the information available from international organizations, generally accepted scientific guidance or methods from national resources were selected, based upon expert judgement, for presentation in the Toolkit. Finally, the Toolkit focuses on assessment of health risk for human populations and therefore does not encompass environmental risk assessment. As mentioned above, the Toolkit is complementary to the Environmental Risk Assessment Toolkit developed by OECD (OECD, 2010d). Characterization of health risks is the end-point of the methodology described in the WHO Toolkit. Therefore, both risk management and risk communication, the two components of risk analysis that follow risk assessment, are outside the scope of the Toolkit.

To assist with performance of a risk assessment, the Toolkit:

- provides road maps for conducting chemical risk assessments;
- identifies information that must be gathered to complete an assessment; and
- provides references, including unique record locators (URLs), for international resources from which an assessor can obtain information and methods essential to a risk assessment.

The description of chemical risk assessment in the context of the Toolkit depicts the starting and ending points of an assessment and the pathways that connect various types of information. In this way, the Toolkit is analogous to a road map that describes how to conduct a chemical risk assessment and interpret its results using publicly available resources from international organizations. The road map concept is illustrated in case-studies of risk assessments for a chemical in drinking-water, respirable particulate matter in air and a pesticide. The general description of the Toolkit in section 3 and the case-studies in sections 5–7 walk the user through the components of a chemical risk assessment, linking each component to relevant international sources of information. While international sources of information are referenced in the Toolkit, an understanding of the local exposure situation is also needed. In this regard, it is important to note that valuable knowledge may also be gained from national and local authorities, academia and research institutions, employees, plant managers or members of the community. These institutions and individuals may have useful and important information about the history of a site, process or problem, chemical usage, human activities and past, current and future land uses that can be used to identify chemical hazards or to assess chemical exposures.

This document also presents a tiered approach to chemical risk assessment in which the methods used to assess risk reflect the problem and resources at hand. For example, a relatively low-level tier of risk assessment may consist of comparing existing information on exposure with an applicable guidance or guideline value for an environmental medium (e.g. air) or food published by an international organization. This Toolkit focuses on lower tiers of chemical risk assessment that are similar to this example: situations that can be described as practical applications of existing information to assess potential health risks of chemical exposure. Therefore, the Toolkit is focused on chemicals and exposure scenarios that are reasonably well described in the scientific literature and publications of international organizations such as WHO.

The Toolkit also provides links to more resource-intensive methodologies, such as hazard characterization of new chemicals or new health outcomes associated with an existing chemical. In those cases, a quantitative evaluation of toxicity based on laboratory animal models or epidemiological studies may be required. That type of assessment often requires new laboratory or observational studies to characterize the physical and toxicological properties of a chemical, all of which may take months or years to complete. The information required for a chemical risk assessment of this type is described in documents published by various international organizations, including the OECD Guidelines for the Testing of Chemicals (OECD, 2010a).

The Toolkit is organized into sections that provide:

- an introduction to the purpose and scope of the document (section 1);
- a description of human health risk assessment of chemicals (section 2);
- a detailed description of the Toolkit (section 3);
- references to international sources (and regional and national sources, where there are gaps in international sources) of information useful for conducting chemical risk assessments (section 4);
- case-studies that illustrate how the Toolkit can be used to address a human health risk assessment question (sections 5–7); and
- a reference list, which contains URLs for nearly all of the information resources.

2. DESCRIPTION OF HUMAN HEALTH RISK ASSESSMENT OF CHEMICALS

2.1 Definition of risk assessment

Human health risk assessment is a process intended to estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system (IPCS, 2004). It is the first component in a risk analysis process that also includes risk management and risk communication. Human health risk assessment of chemicals refers to methods and techniques that apply to the evaluation of hazards, exposure and harm posed by chemicals, which in some cases may differ from approaches used to assess risks associated with biological and physical agents.

The risk assessment process begins with problem formulation and includes four additional steps: 1) hazard identification, 2) hazard characterization, 3) exposure assessment and 4) risk characterization (IPCS, 2004). The risk assessment paradigm, incorporating problem formulation, is summarized in Table 1. A full description of the concepts presented in the table may be found in chapter 3 of WHO Environmental Health Criteria (EHC) 239 (IPCS, 2009). A detailed description of risk assessment, including technical issues, is provided by van Leeuwen & Vermeire (2007).

Table 1: Paradigm for risk assessment, including problem formulation.

Step	*Description*	*Content*
Problem formulation	Establishes the scope and objective of the assessment	Defining the question Prior knowledge Desired outcomes
Hazard identification	Identifies the type and nature of adverse health effects	Human studies Animal-based toxicology studies In vitro toxicology studies Structure–activity studies
Hazard characterization	Qualitative or quantitative description of inherent properties of an agent having the potential to cause adverse health effects	Selection of critical data set Modes/mechanisms of action Kinetic variability Dynamic variability Dose–response for critical effect
Exposure assessment	Evaluation of concentration or amount of a particular agent that reaches a target population	Magnitude Frequency Duration Route Extent
Risk characterization	Advice for decision-making	Probability of occurrence Severity Given population Attendant uncertainties

Source: Adapted from IPCS (2009).

Risk assessors should be aware that their work products will often be incorporated into risk management and policy decisions. This use of risk assessments is appropriate, in that environmental health policy decisions should be based on established links among emission sources, human exposures and adverse health effects. The environmental health chain published originally in EHC 214 (IPCS, 2000) is reproduced in Figure 1. The chain of events depicted in Figure 1 is an "environmental health paradigm": a simplified representation of the key steps between emission of toxic agents into the environment and the final outcome as potential disease or dysfunction in humans. This sequential series of events serves as a useful framework for understanding and evaluating human health risks. It is directly related to the risk assessment process. Human health risk assessment for chemical hazards is a means of integrating the components of the environmental health chain in a manner that is useful for analysis and management of chemical-mediated risks.

2.2 Uses of human health risk assessments of chemicals

Human health risk assessments of chemicals can be performed to evaluate past, current and even future exposures to any chemical found in air, soil, water, food, consumer products or other materials. They can be quantitative or qualitative in nature. Risk assessments are often limited by a lack of complete information. To be protective of public health, risk assessments are typically performed in a manner that is unlikely to underestimate the actual risk. Regardless, chemical risk assessments rely on scientific understanding of pollutant behaviour, exposure, dose and toxicity. In general terms, risk depends on the following factors:

- the amount of a chemical present in an environmental medium (e.g. soil, water, air), food and/or a product;
- the amount of contact (exposure) a person has with the pollutant in the medium; and
- the toxicity of the chemical.

Obtaining knowledge to describe these three factors is the cornerstone or foundation of most chemical risk assessments. As these data are not always available, many risk assessments require that estimates or judgements be made regarding some data inputs or characterizations. Consequently, risk assessment results have associated uncertainties, which should be characterized as much as possible.

Despite these uncertainties, human health risk assessment of chemicals can help to answer basic questions about potential dangers from exposure to chemicals, such as:

- What chemical exposures pose the greatest risks? Can the risks be ranked to allow a country to spend its resources in the most efficient way?
- What are the risks of drinking this water? Should drinking-water be provided from a different, safer source?
- Is this chemical spill dangerous? What is the appropriate emergency response?
- Is it "safe" to build homes on this old hazardous waste site? Should we clean up this contaminated soil?
- What, if any, limits on chemical exposure should be established in occupational settings, in consumer products, in environmental media and in food?
- Should limits be set for chemical emissions from industrial, agricultural or other human activities?

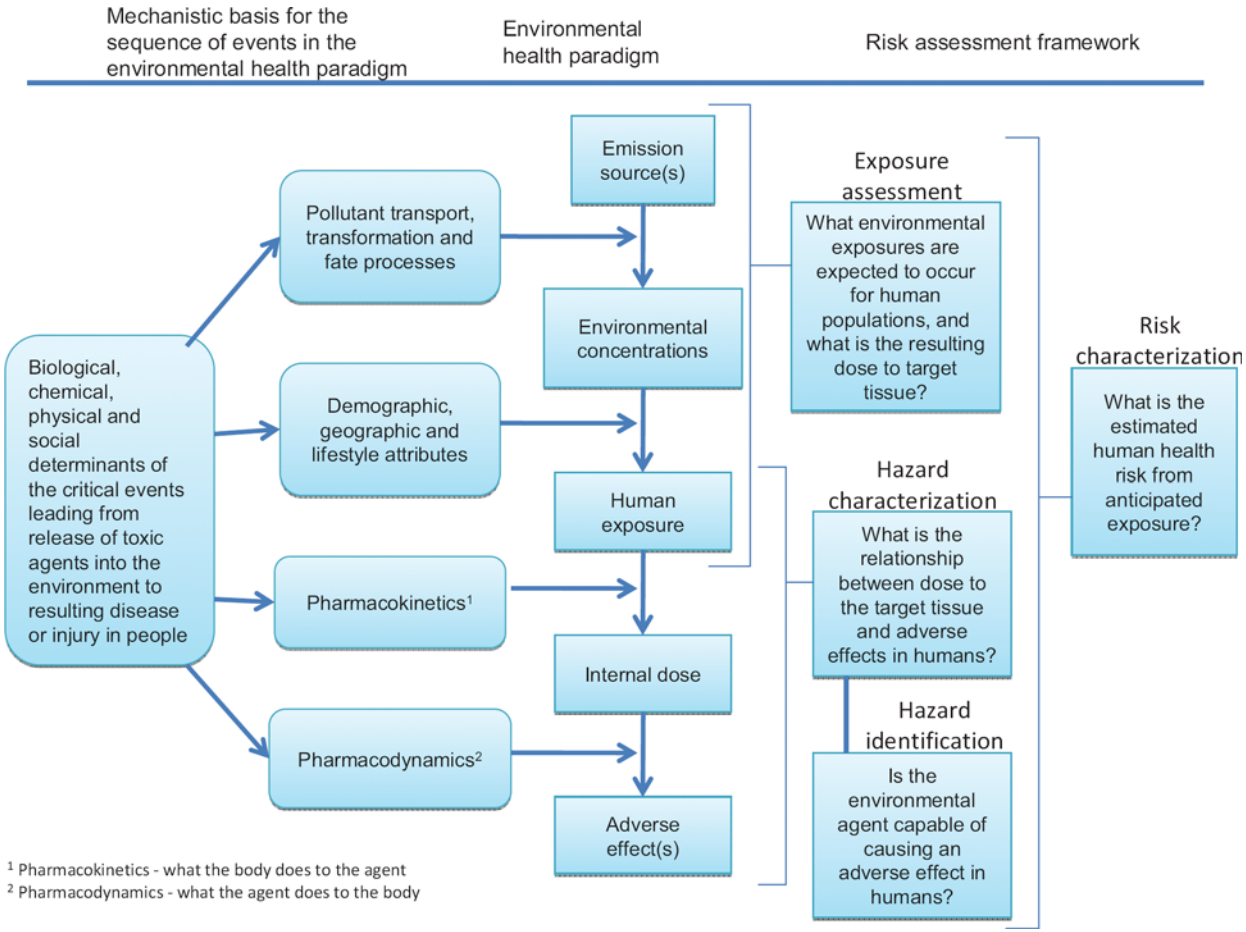


Figure 1: An environmental health paradigm and its relationship to the human health risk assessment framework (adapted from Sexton et al., 1995; IPCS, 2000).

3. DESCRIPTION OF THE TOOLKIT

The WHO Human Health Risk Assessment Toolkit follows the traditional risk assessment paradigm but guides the reader through the various components of the paradigm in an applied manner. Therefore, the Toolkit does not contain detailed discussion of the inputs to a human health risk assessment, but instead focuses on the interpretation and assembly of those inputs for characterizing risk. Two practical aspects of the Toolkit that are intended to facilitate its use—1) the presentation of the risk paradigm as a road map and 2) the introduction of a tiered approach based on the attributes of the assessment question and the available data—are described below. These brief descriptions are followed by generic road maps for the four components of risk assessment: hazard identification, hazard characterization, including guidance value and guideline value identification, exposure assessment and risk characterization.

The terminology used in the Toolkit is generally in line with the definitions and practice established by WHO/International Programme on Chemical Safety (IPCS) in numerous other publications. Throughout the document, frequent reference is made to guidance values and guideline values. The reader should note that WHO is not entirely consistent in the usage of these terms and that, for the purpose of the Toolkit, guidance values are those values developed entirely from toxicological and epidemiological information, such as the acceptable daily intake (ADI) and tolerable daily intake (TDI), whereas guideline values, such as concentration in air or water, are derived after allocation of the reference dose among the different possible media (routes) of exposure. The reader is referred to section 3.3.2 for further information on guidance and guideline values.

3.1 The Toolkit as a road map

As described more fully below, the risk posed by chemicals can be determined based on the toxicity of the chemicals and on who is exposed to these chemicals, in what amount and through what route. Ultimately, each of these considerations will be critical to a determination of health risk or a risk management decision. Risk managers and other Toolkit users will draw on this information to help decide how to protect people from these chemicals.

For the purposes of the Toolkit, the risk assessment paradigm is presented as a road map that extends from hazard identification to risk characterization (Figure 2). Each step in the paradigm is represented by a set of questions that an assessor can follow to information and resources that are appropriate for estimating risk. A generic road map that an assessor can follow to answer these questions is presented for each step in section 3.3. As noted above, the data gathering and analysis associated with these steps for the purposes of the Toolkit may differ somewhat from a de novo assessment of risk conducted for a new chemical, proposed use or health end-point.

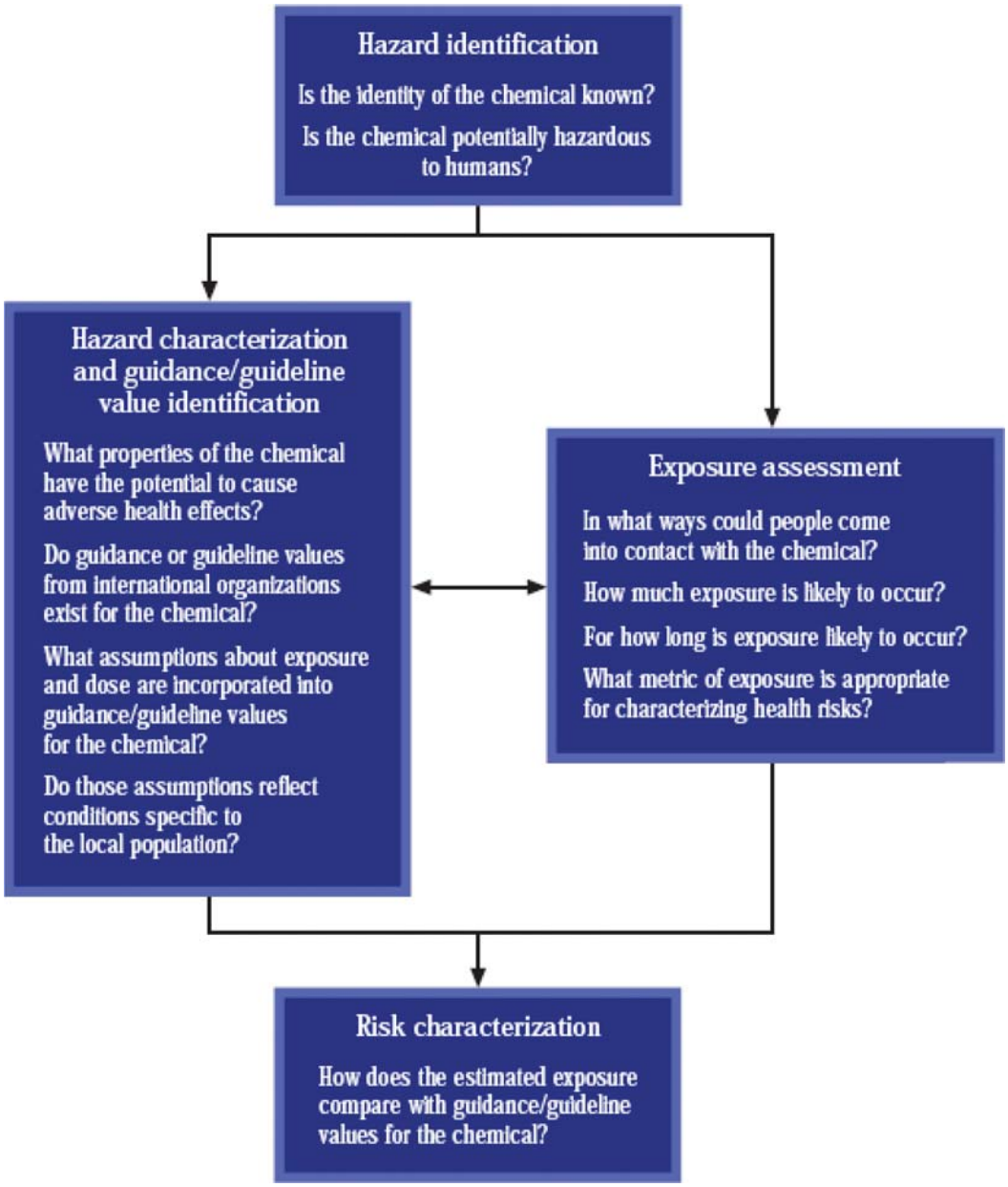


Figure 2: Generic road map for chemical risk assessment in the context of the Toolkit following the conventional risk assessment paradigm.

Examination of Figure 2 reveals that the purpose of the hazard identification (section 3.3.1) step is to determine the identity and the hazardous properties of the chemical. In the context of the Toolkit, hazard identification is followed by the hazard characterization/guidance or guideline value identification and exposure assessment steps, which are complementary and connected efforts. Hazard characterization/guidance or guideline value identification (section 3.3.2) is used to obtain a guidance or guideline value for the chemical that matches the anticipated route and duration of exposure (e.g. inhalation and long-term exposure). Guidance and guideline values are normally the result or output of hazard characterizations and involve dose–response assessment. Exposure assessment (section 3.3.3) is used to determine the most

likely routes, pathways, duration and intensity of exposure to the identified chemical. As these two steps are connected, information obtained in these two steps must be compared in the risk assessment process to ensure that the exposure and hazard characterization metrics are aligned appropriately. In the final step, risk characterization, the hazard identification, hazard characterization and exposure information is combined to yield a statement of risk. As described in section 3.3.4, the quantitative form of the risk characterization will vary depending upon the type of information available on hazard characterization and exposure. In some cases, the available information is sufficient to support only a qualitative characterization of risk, the results of which can nonetheless be an important contribution to risk management decisions (see the case-study in section 7 for an example).

The questions posed in Figure 2 provide a structure for chemical risk assessment in the context of the Toolkit. By answering the questions, an assessor obtains the information needed to identify the hazard, characterize the hazard, assess the exposure and characterize the risk. Output anticipated from answering the questions is shown in Table 2.

Table 2: Output from the framework for chemical risk assessment in the context of the Toolkit.

Question	*Output*
Hazard identification	
Is the identity of the chemical known?	Clear identification of chemical in question through CAS registry number
Is the chemical potentially hazardous to humans?	Description of health hazards obtained from internationally available information
Hazard characterization/guidance or guideline value identification	
What properties of the chemical have the potential to cause adverse health effects?	Qualitative or quantitative description of the inherent properties of the agent having the potential to cause adverse health effects
Do guidance or guideline values from international organizations exist for the chemical?	List of guidance or guideline values (rates or concentrations) for the chemical obtained from internationally available resources
What assumptions about exposure and dose are incorporated into guidance/guideline values for the chemical?	List of assumptions about contact rates, absorption and other factors incorporated into the guidance or guideline values
Do those assumptions reflect conditions specific to the local population?	A reference value that reflects exposure and dose parameters specific to the local culture and demographics
Exposure assessment	
In what ways could people come into contact with the chemical?	Qualitative description of the relevant media and exposure routes
What metric of exposure is appropriate for characterizing health risks?	Determination from the guidance or guideline value of whether an exposure concentration or exposure rate is needed to perform the risk characterization
Risk characterization	
How does the estimated exposure compare with guidance/guideline values for the chemical?	A quantitative or qualitative statement of non-cancer or cancer risk

CAS, Chemical Abstracts Service

3.2 Tiered assessments in the Toolkit

In practical terms, the user of the risk assessment Toolkit must consider the apparent magnitude of the issue at hand, the resources that can be allocated to an environmental health concern and societal norms for risk. Depending upon the nature of the problem as well as time, cost and human and technical resource considerations, the amount of information applied to each step may differ, with some steps requiring more detailed and some requiring less detailed information gathering.

Varying degrees of information gathering represent tiers of analysis. These tiers are characterized by the amount of quantitative or qualitative data obtained to answer a question posed in any given step of the risk paradigm. As shown in Table 3, the Toolkit includes four tiers of risk assessment.

Tier 1 (screening level) refers to screening-level risk assessments that rely solely upon existing guidance and guideline values and other information and make no adjustments to the hazard characterization for local conditions or other considerations. Consider an example where there is strong anecdotal information that use of a certain chemical is associated with a significant or specific health outcome among workers of a certain industry. Further, hazard identification information on toxicological properties of the chemical and experiences in other countries are consistent with the anecdotal reports. Faced with this situation, a public health official may conclude that occupational health risks of using the chemical under current conditions are intolerable. In a move intended to protect health, the official may seek to ban the chemical from that particular use or from the country at large based on generalizing risk information from international sources to the local uses and conditions. The pesticide case-study described in section 7 of this document is an example of a Tier 1 risk assessment.

Tier 2 (adaptive level) refers to risk assessments that reflect local exposure conditions, which can be incorporated through the exposure assessment or hazard characterization stages (as applied in this Toolkit). In a Tier 2 assessment, local exposure conditions are derived from existing information. Such information may be the result of routine monitoring conducted for regulatory or other purposes, the application of a model to a known or suspected source of pollutant emissions or some other metric that was generated for a purpose other than the current assessment. The particulate matter case-study presented in section 6 is an example of a Tier 2 risk assessment that yields a qualitative result. In that case-study, the risk assessor evaluates the relationship between concentrations of respirable particles in ambient air (particulate matter less than 10 µm in aerodynamic diameter, or PM_{10}[1]) and personal exposure to PM_{10} in the assessor's own country and compares it with the same relationship in the studies from which the WHO air quality guideline for PM_{10} was derived (WHO, 2006). The evaluation is qualitative in this example, but nonetheless involves a more rigorous analysis than a Tier 1 risk assessment.

[1] Whereas WHO defines PM_{10} as particulate matter less than 10 µm in aerodynamic diameter, most jurisdictions define PM_{10} as particulate matter less than or equal to 10 µm in aerodynamic diameter.

Table 3: Tiers of risk assessment included in the Toolkit.[a]

Tier	*Description*	*Hazard identification*	*Hazard characterization/ guidance or guideline value identification*	*Exposure assessment*	*Risk characterization*
1: Screening	Existing hazard and exposure data from international sources	Identify the chemical; obtain hazard information from international resources	Apply appropriate existing guidance or guideline values from international organizations	Existing qualitative or quantitative estimates; local exposure conditions	Qualitative or quantitative
2: Adaptive	Existing hazard data from international sources reflecting local conditions; existing local exposure data	Identify the chemical; obtain hazard information from international resources	Adjust guidance or guideline values from international organizations for local conditions	Existing quantitative estimates; local exposure conditions	Qualitative or quantitative
3: Modelling or field-based	Existing hazard data from international sources; new local exposure data	Identify the chemical; obtain hazard information from international resources	Adjust guidance or guideline values from international organizations for local conditions	Conduct measurement or modelling campaign	Qualitative or quantitative
4: De novo	Locally conducted hazard and exposure assessments	Independent review of original hazard data or controlled experimental trials, gather local observations	Establish new guidance or guideline value	Estimate from measure-ments or models	Qualitative or quantitative

[a] Some organizations have defined the tiers differently using different terminology. For example, OECD considers three tiers, calling them preliminary, refined and comprehensive assessments.

Tier 3 (modelling or field-based level) risk assessments involve quantitative characterization of exposure conditions through a measurement or modelling campaign, but otherwise are similar to a Tier 2 assessment. Tier 3 assessments require the design and execution of a quantitative exposure assessment. In many situations, the exposure assessment will consist of a survey; in others, the assessment may be hypothesis driven. A field campaign would require a plan for collection and analysis of samples as well as management and interpretation of the data. Similarly, a modelling campaign would require selection of an appropriate modelling tool, identification of values needed to parameterize the model, resources to execute the model and data management and analysis skills to manage and interpret the model results. Tier 3 risk assessments are distinct from Tier 2 assessments, in that the former requires generation or gathering of new exposure information, whereas the latter does not. The drinking-water case-study presented in section 5 is an example of a Tier 3 risk assessment.

Tier 4 (de novo) risk assessments are unique in that they can involve the review of original data or the generation of new information concerning the hazardous properties of a chemical. In addition, Tier 4 risk assessments involve measurement or modelling approaches for the quantitative assessment of exposure that is specific to local conditions. Tier 4 assessments apply to chemicals or chemical forms whose toxicological properties have not been evaluated previously, as well as to new routes of exposure to existing chemicals. In general, these assessments are beyond the scope of the Toolkit. Nonetheless, guidance from international organizations on approaches and considerations for filling the data gaps presented by these situations is identified in section 4. Readers are referred to these documents for assessments that require techniques that are more advanced than the methods addressed in the Toolkit.

3.3 Generic road maps

3.3.1 Hazard identification

Hazard identification is generally the first step in a risk assessment and is the process used to identify the specific chemical hazard and to determine whether exposure to this chemical has the potential to harm human health. For the purposes of the Toolkit, hazard identification involves establishing the identity of the chemical of interest and determining whether the chemical has been considered hazardous by international organizations and, if so, to what degree. A process for gathering information in support of hazard identification is illustrated in Figure 3.

3.3.1.1 Chemical identity

Given sufficient time and resources, the surest way for potentially hazardous chemicals to be identified is sample collection and chemical analysis. Collection and analysis of samples, however, generally require preliminary identification of the chemical of interest, as the appropriate collection and laboratory analysis method will depend on the specific chemical. Thus, even when chemical analyses are planned, some preliminary identification of the chemical is needed. In cases where chemical analyses are not possible, this preliminary identification may comprise the entire hazard identification step.

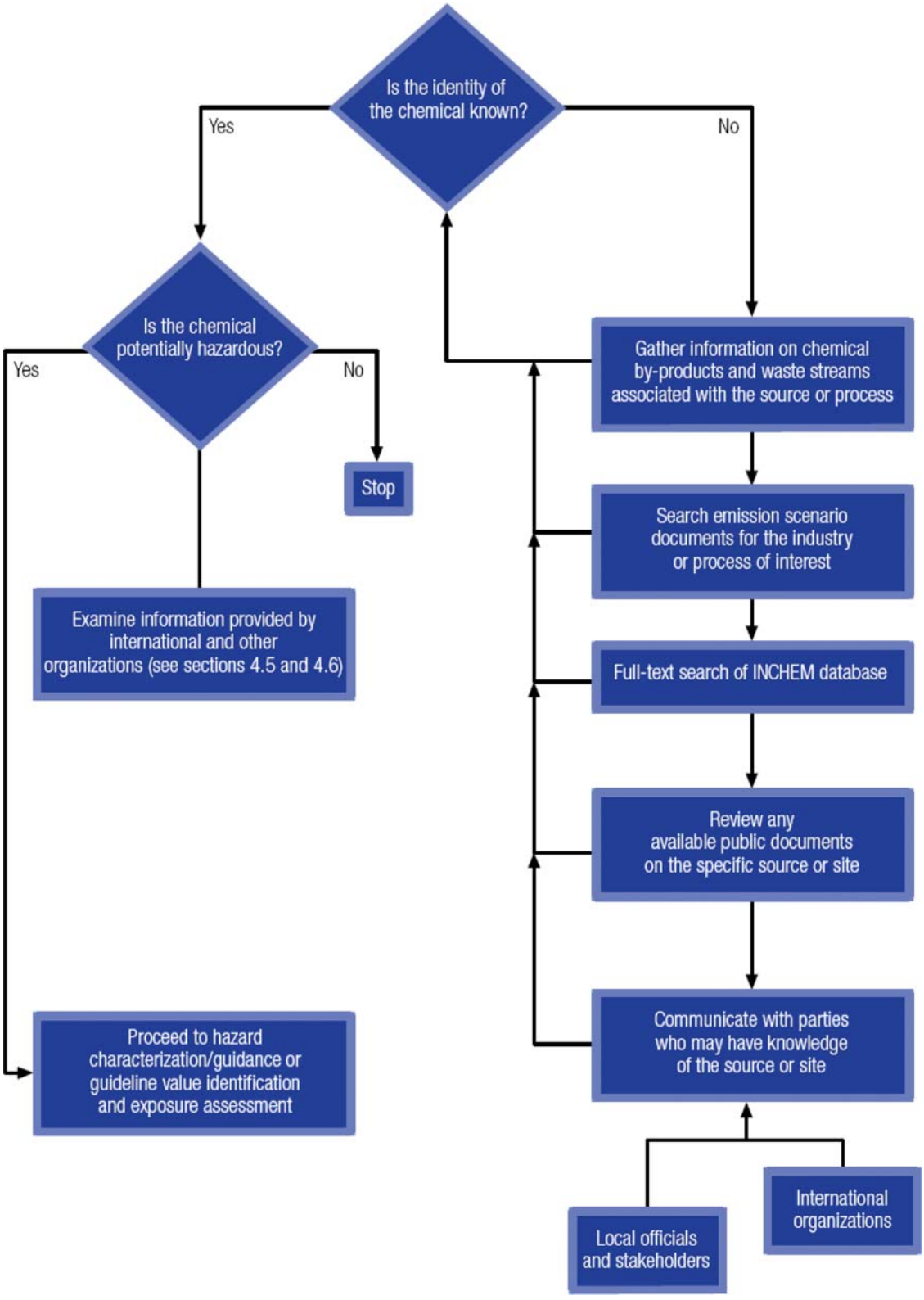


Figure 3: Generic road map for hazard identification in the context of the Toolkit.

Chemicals and their hazards can be identified from a number of internal and external sources. Internal sources include company documents and people who work with the chemical—for example, a plant manager or operator. Generally, in cases where the source of the chemical is easily identified, the chemical is listed as an ingredient on the chemical packaging, on the associated chemical safety card or material safety data sheet or on a list of chemicals used in the industrial process. The same identification materials can be relied upon for cases in which the chemicals of concern come from multiple sources; however, this identification may also involve additional determinations of whether any identified chemicals will behave differently or will form different chemicals when mixed together.

If the identity of the chemical is not known, the assessor should gather information from various resources and infer the types of chemicals of concern. In situations where an industrial process or operation is of interest, the assessor should search the emission scenario documents referred to in section 4.8.2 for information relevant to the current situation. Emission scenario documents published by OECD contain descriptions of sources, production processes, pathways and use patterns of numerous commercial industrial operations with the aim of quantifying the releases of chemicals into water, air, soil or solid waste. Emission scenario documents can be used to generate hypotheses about contaminants of concern that may be associated with a particular source, such as a manufacturing operation, laboratory, disposal area or waste site. In addition to OECD's work in this area, the European Union (EU) publishes emission scenario documents in support of risk assessments for new and existing substances. The emission scenario documents describe environmental releases for different industrial categories and biocidal products.

A full-text search feature of the INCHEM database (see section 4.3 for further information on INCHEM) can also help to identify a chemical. In addition to these international resources, permits or building plans that may have been filed with local or provincial authorities may contain useful information on operations and emissions from a particular type of operation. Finally, initiating dialogues with representatives of the facility and other members of the community may also be helpful for identifying contaminants of concern.

3.3.1.2 Hazardous properties

Once identified, the potential hazard of the chemical can be determined from the available scientific data on the chemical, generally data from toxicological or epidemiological studies. A chemical may be associated with one or more hazards to human health. Several schemes for classification of hazard information have been developed. In general, chemicals are classified according to human health hazards that they pose, such as neurological, developmental, reproductive, respiratory, cardiovascular and carcinogenic effects. There are many international sources of this information, as noted in sections 4.5, 4.6 and 4.7

In the case of Tier 4 risk assessments (see section 3.2), where the hazardous properties of a chemical have not yet been identified, the reader is referred to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE, 2010a). The GHS was initiated by international organizations in recognition of the varying criteria for determination of hazardous substances among countries and the extensive global trade of chemicals. The GHS includes 1) harmonized criteria for classifying substances and mixtures according to their health, environmental and physical hazards and 2) harmonized hazard communication elements, including requirements for labelling and safety data sheets. The human health hazard classification scheme is detailed and includes a broad range of potential health effects

(see Table 4). For some of these effects, the hazards of individual chemicals or mixtures of chemicals are further categorized by their toxicological potency, the extent of evidence for effects in humans and related considerations.

Table 4: Human health effects included in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Health effect	*Number of hazard categories*	*Criteria for categories*
Acute toxicity	5	LD_{50} and LC_{50}
Skin corrosion/irritation	3	Corrosive, irritant, mild
Serious eye damage/irritation	1	Irreversible effects
Respiratory sensitizer	3	Evidence for effects in humans
Skin sensitizer	3	Evidence for effects in humans
Germ cell mutagenicity	2	Evidence for effects in humans
Carcinogenicity	2	Evidence for effects in humans
Toxic to reproduction	2	Evidence for effects in humans
Effects on or via lactation	1	Concern for effects
Specific organ toxicity (acute exposure)	3	Strength of the evidence
Specific organ toxicity (repeated exposure)	2	Strength of the evidence
Aspiration hazard	2	Evidence for effects in humans

LC_{50}, median lethal concentration; LD_{50}, median lethal dose

The weight of evidence for carcinogenic effects of a chemical in humans is another important feature of hazard identification. The International Agency for Research on Cancer (IARC) categorizes chemicals and other agents into one of five categories based on the strength of evidence that an agent could alter the age-specific incidence of cancer in humans:

- Group 1: the agent is *carcinogenic to humans*
- Group 2A: the agent is *probably carcinogenic to humans*
- Group 2B: the agent is *possibly carcinogenic to humans*
- Group 3: the agent is *not classifiable as to its carcinogenicity to humans*
- Group 4: the agent is *probably not carcinogenic to humans*

A cancer hazard in the context of the IARC classification system is an agent that is capable of causing cancer under some circumstances. A thorough description of the IARC cancer hazard classifications and other fundamental aspects of the assessment objectives and methods of IARC can be found in the preamble that is included in each monograph published by the agency (IARC, 2006).

3.3.2 Hazard characterization/guidance or guideline value identification

The objective of hazard characterization/guidance or guideline value identification is to obtain a qualitative or quantitative description of the inherent properties of the agent having the potential to cause adverse health effects as a result of exposure. There are, however, chemicals that are essential to the human body. Adverse health effects can be observed if exposure to these is below a required level as well as above an upper tolerable level.

Hazard characterization typically consists of a qualitative or quantitative description of the inherent properties of an agent having the potential to cause adverse health effects. Quantitative descriptions often consist of a dose–response assessment, including identification of, for example, a no-observed-adverse-effect level (NOAEL), no-observed-effect level (NOEL) or cancer potency factor, and the application of uncertainty factors to account for interspecies and intraspecies variability, data quality and other uncertainties (see section 3.3.2.1). This information is used to develop guidance values, such as the TDI and ADI (see section 3.3.2.1 and Tables 5 and 6). In turn, human exposure factors, such as intake rates (see section 4.8.6 and Table 19), are then considered to develop guideline values for chemicals in media such as air, water and food (see section 3.3.2.2 and Table 7).

In the context of the Toolkit, the user identifies available guidance and guideline values (the output of traditional hazard characterization) and discusses the applicability of the assumptions embedded within them to the situation of interest (e.g. exposure duration and allocation of total exposure among routes of exposure). Therefore, users of the Toolkit should identify a guidance or guideline value for the chemical under investigation that matches the anticipated route and duration of exposure (e.g. inhalation and long-term exposure). Figure 4 illustrates considerations that are key to determining whether an international guidance or guideline value is appropriate for a specific situation.

Hazard characterization in the context of the Toolkit requires an understanding of how the guidance or guideline values were derived by international organizations, including:

- guidance values developed entirely from toxicological and epidemiological information ("health-based guidance values"), such as the ADI and TDI, which provide an estimate of the amount of chemical that can be taken in orally (mainly by food and drinking-water) by a person without appreciable health risk (see also Tables 5 and 6 in section 3.3.2.1 below); and
- media-specific guideline values ("quality guideline values") for chemical concentrations in drinking-water, air and food (the exposure medium). Based on ADIs and TDIs, these values usually take into account multimedia exposure scenarios (e.g. the WHO *Guidelines for drinking-water quality*) or are based on agricultural practices and climate scenarios, such as in the case of maximum residue limits (MRLs) of pesticide residues in food.

The development of these guidance or guideline values by international organizations is described in the next sections. That information is followed by a discussion of factors that a risk assessor should consider to evaluate the extent to which a guidance or guideline value applies to a specific situation or assessment question. Additional information is presented in section 4.7 as well as in the case-studies (sections 5–7).

In addition to guidance or guideline values developed by international organizations, many countries have developed national quality standards for chemicals in media (e.g. food, water, air, soil). Usually, the development of national standards follows two stages. The first stage is a scientific process that either determines the exposure levels for a substance that are unlikely to produce adverse effects or establishes cancer slope factors. This stage is similar to the derivation of health-based guidance values or quality guideline values by international organizations. The second stage is an administrative process to determine acceptable risk in consideration of scientific uncertainty, risk management options, economic benefits and costs, relevant laws and social norms. The identification and use of national standards are

beyond the scope of the Toolkit. In the event, however, that a risk assessor decided to use a national standard from another country (e.g. a national air quality standard), consideration must be given to the relevant socioeconomic factors. A national air quality standard, for example, might be higher than the relevant WHO air quality guideline value because it takes into account the feasibility of air pollution control measures in a particular country.

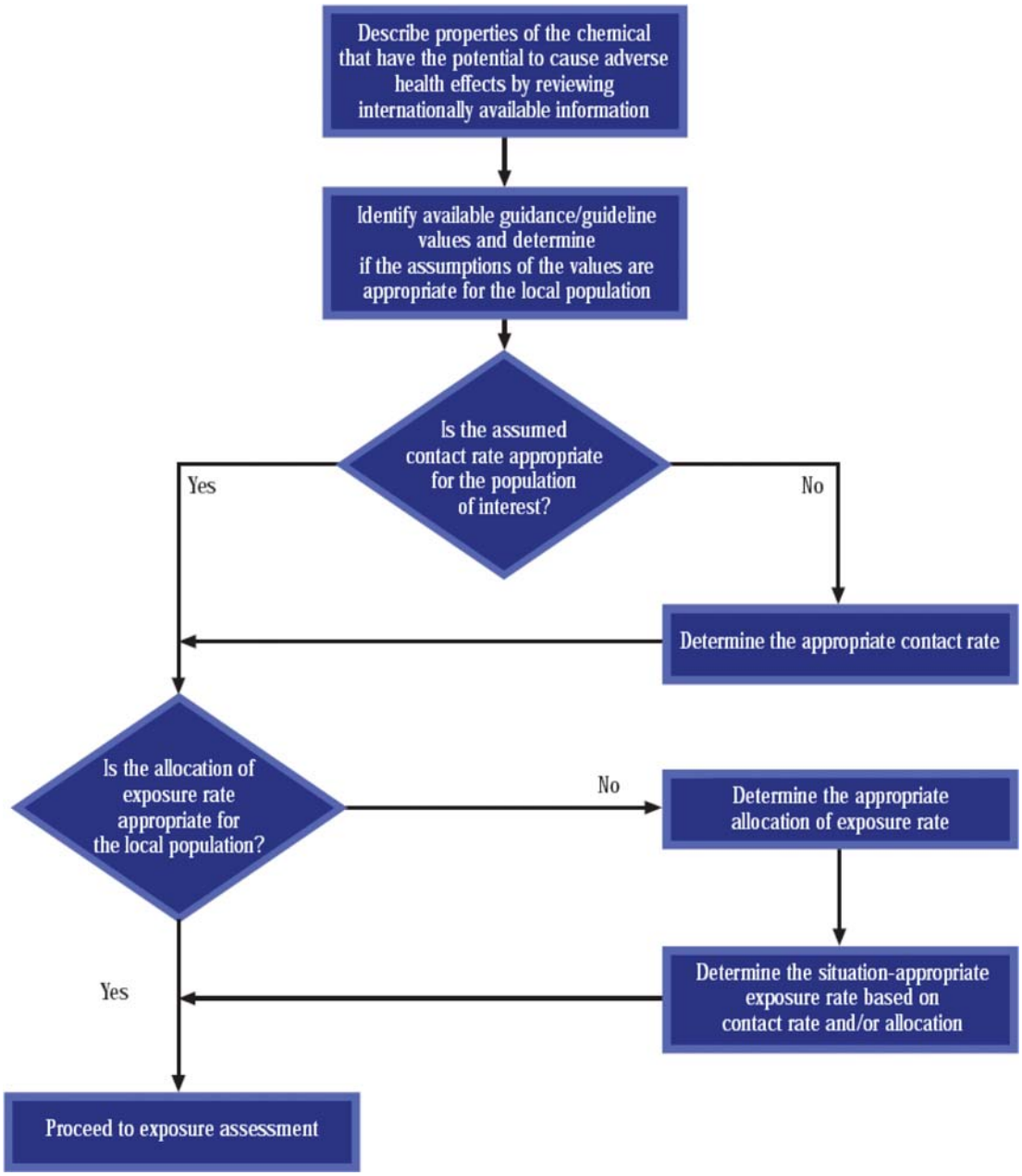


Figure 4: Generic road map for hazard characterization/guidance or guideline value identification in the context of the Toolkit.

Table 5: Guidance and other values commonly used in chemical evaluations.

Type of outcome	*Term (units)*[a]	*Abbreviation*	*Definition*
Non-cancer, including laboratory animal carcinogens not relevant to humans	Tolerable daily intake (mg/kg body weight per day)	TDI	An estimate of the amount of a substance in air, food, soil or drinking-water that can be taken in daily, weekly or monthly per unit body weight over a lifetime without appreciable health risk
	Provisional tolerable weekly intake (mg/kg body weight per week)	PTWI	
	Provisional tolerable monthly intake (mg/kg body weight per month)	PTMI	
	Acceptable daily intake (mg/kg body weight per day)	ADI	
	Acute reference dose (mg/kg body weight per day)	ARfD	Amount of a substance, normally in food or drinking-water, that can be ingested in a period of 24 h or less per unit body weight without appreciable health risk to the consumer
Cancer potentially relevant to humans	Oral slope factor ([mg/kg body weight per day]$^{-1}$)	SF	An estimate of the cancer risk associated with a unit dose of a chemical through ingestion or inhalation per unit body weight over a lifetime
	Slope factor in relation to a concentration of a chemical in air ([µg/m^3]$^{-1}$)		An estimate of cancer risk associated with a unit concentration of a chemical in air or water
	Slope factor in relation to a concentration of a chemical in water ([µg/l]$^{-1}$)		
Cancer highly relevant to humans	Benchmark dose (mg/kg body weight per day)	BMD	Amount of contaminant derived from studies in which experimental animals are given daily doses that produce a predefined cancer incidence (e.g. 5% or 10%).

[a] The terms ADI and TDI as used by international organizations are equivalent to the term reference dose (but not acute reference dose) that is used by some national agencies.

[b] See section 3.3.4.2 for the margin of exposure (MOE) approach recommended by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

3.3.2.1 Health-based guidance values derived by international organizations

Development of health-based guidance values (Table 5) requires the assessment of the toxicological effect of a chemical in relation to exposure. The relationship between exposure and effect is frequently derived from standardized tests of laboratory animals conducted under controlled conditions. The WHO document on chemical-specific adjustment factors provides a detailed description of the extrapolation of the results from laboratory-based

toxicology studies from experimental animals to humans (IPCS, 2005a). In other cases, observations of effects in human populations characterized with epidemiological methods are the basis of guidance value development. Arsenic and benzene are two examples of chemicals for which health-based guidance values are based on epidemiological studies (IARC, 1999, 2004).

Health-based guidance values are derived and used according to a number of widely accepted principles and conventions. Four important conventions are listed here and discussed below:

1) Dose of a known or suspected human carcinogenic chemical is assumed to have a linear relationship with risk of cancer, and effects are assumed to occur at any level of exposure (non-threshold effects).
2) The risks of adverse effects other than cancer are negligible or de minimis when exposure is less than a threshold level below which adverse effects are unlikely to occur.
3) The risk of adverse effects from exposure to a given chemical may vary depending upon the route of exposure as a result of differential absorption, metabolism or elimination following intake by inhalation, ingestion or dermal absorption.
4) Populations sensitive to the health effects of chemical exposure that are not reflected in experimental animal toxicological or human epidemiological studies are accounted for through the use of factors or procedures intended to reduce the likelihood that actual risks to humans will be underestimated.

For chemicals positive in experimental animal carcinogenicity studies, available information on mode of action is assessed in order to consider human relevance (IPCS, 2007). For chemicals that are treated as potential human carcinogens, the risk of cancer is characterized as a linear relationship with dose. The carcinogenic potency of a chemical is characterized as the slope of a line fit to the relationship between exposure to the chemical and prevalence of cancer in populations. As described in EHC 239, a polynomial equation that contains a linear term is frequently fit to dose–response data from cancer bioassay studies conducted with laboratory animals (IPCS, 2009). Analogous approaches are applied to the analysis of epidemiological data that inform chemical-mediated risks of cancer in human populations. In both cases, the coefficient estimated for the linear term of an equation fit to the dose–response data is taken as an estimate of the carcinogenic potency of the chemical. In practice, an upper-bound estimate of the coefficient, such as the 95th percentile, is selected to account for uncertainty in model fit and to provide a conservative estimate of the true but unknown actual carcinogenic potency.

Carcinogenic potencies determined from laboratory or epidemiological studies are often termed cancer slope factors, which have units of inverse dose or exposure. The units of a slope factor therefore depend upon the route of exposure and the extent of information about dose that is available to the toxicologist or epidemiologist. In laboratory studies, animals may receive a known dose of a chemical for a given period of time, expressed as milligrams per kilogram of body weight per day. The slope factor derived from such a study would therefore have units of $(\text{mg/kg body weight per day})^{-1}$. In an epidemiological study, the risk of cancer may be quantified in relation to the concentration of a chemical in air or water. In those cases, slope factors may be expressed as $(\mu\text{g/m}^3)^{-1}$ or $(\mu\text{g/l})^{-1}$, respectively. The slope factors recommended by IARC for benzene in air and arsenic in water were derived from epidemiological studies (IARC, 1999, 2004).

For contaminants that are both genotoxic and carcinogenic, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) also recommends the use of the benchmark dose (BMD) approach for hazard characterization, mostly using data derived from studies in rodents given daily doses many orders of magnitude greater than the estimated exposure in humans. Dose–response data from epidemiological studies may also be used for hazard characterization and would avoid interspecies comparisons and extrapolation over many orders of magnitude. The BMD is the dose for a predetermined level of response, called the benchmark response (BMR), such as a 5% or 10% cancer incidence. BMDs or their lower confidence limits (BMDLs) are used to determine the margin of exposure (MOE) at the risk characterization stage in the risk assessment process (see also section 3.3.4.2). JECFA establishes BMDs or BMDLs only for food contaminants; it does not use this approach for substances intentionally added (directly or indirectly) to food, such as food additives, veterinary drugs or pesticides, because it is considered to be inappropriate to intentionally add compounds with genotoxic and carcinogenic properties to food (FAO/WHO, 2006).

For effects other than cancer, where a cancer effect in laboratory animals is considered not relevant to humans or where a non-genotoxic mechanism is suggested, health-based guidance values are characterized as thresholds of exposure below which adverse effects are considered unlikely to occur. Benchmarks of risk for non-cancer effects are most frequently expressed as rates of exposure with the units of milligrams per kilogram of body weight per day. As summarized in Table 5, common terms for these values are ADI (e.g. ADIs have been developed for pesticides by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and for food additives by JECFA), TDI, PTWI, PTMI (developed for food contaminants by JECFA) and acute reference dose (ARfD) (e.g. developed for pesticides by JMPR) (see also sections 4.5.1 and 4.5.2). These benchmark values are estimates of the amount of a substance in air, food, soil or drinking-water that can be taken in daily, weekly or monthly over a lifetime or other specified period without appreciable health risk (Table 6).

Table 6: Sources of guidance values for chemicals developed by international organizations.

Guidance value	*Organization*	*Reference*
Acceptable daily intake (ADI)	FAO/WHO	IPCS (2010a)
Acute reference dose (ARfD)	FAO/WHO	IPCS (2010a)
Tolerable daily intake (TDI)	FAO/WHO, WHO	FAO/WHO (2010a); IPCS (2010b)
Provisional tolerable weekly intake (PTWI)	FAO/WHO, WHO	FAO/WHO (2010a); IPCS (2010b)
Provisional tolerable monthly intake (PTMI)	FAO/WHO, WHO	FAO/WHO (2010a); IPCS (2010b)

To account for the fact that humans may be exposed to hazardous chemicals through multiple routes of contact with differing health consequences, health-based guidance values are frequently determined separately for exposure by inhalation and ingestion, and sometimes dermal absorption, depending upon the route of exposure that is relevant to the population and chemical of interest.

For both cancer and non-cancer effects, results from laboratory animals or humans are extrapolated to the general human population using one or more uncertainty factors (sometimes referred to as safety factors, assessment factors or adjustment factors) or

procedures that are intended to reduce the likelihood that actual risks to humans will be underestimated. Separate uncertainty factors may be applied to account for:

- extrapolation of laboratory animal bioassay tests conducted over short periods of time (e.g. weeks or months) to exposures of interest over longer periods of time (e.g. years); these concepts are separate from the time course of adverse effects that can immediately follow exposure or result from cumulative or continuous exposure;
- differences between experimental animal species and humans ("interspecies differences") and the application of laboratory animal test results to humans;
- susceptible members of human populations ("intraspecies variability"); and
- other aspects, such as insufficiency of the database.

3.3.2.2 Media-specific guideline values ("quality guideline values") derived by international organizations

The ADI and TDI are estimates of exposure rate (sometimes called administered dose) and, as described above, are derived from toxicological and epidemiological information. For this reason, they consider the total (or aggregate) intake of a chemical from all routes and pathways (see section 3.3.3). In contrast, the media-specific guideline values for environmental media take into account conditions specific to the medium of interest and also vary in the extent to which aggregate exposure is considered. For instance, the MRLs are not direct public health limits, but instead reflect agricultural practices and climate scenarios, and they are normally set at levels well below amounts that might lead to an adverse health effect. In contrast, the WHO drinking-water guidelines are primarily health-based and do attempt to account for exposure through other media.

Guideline values developed by international organizations and links to further information are listed in Table 7. The use of these guideline values is described in section 3.3.4 and illustrated in the case-studies presented in sections 5–7.

Table 7: Sources of guideline values for chemicals developed by international organizations.

Guidelines	*Organization*	*Reference*
Drinking-water quality guideline values	WHO	WHO (2008a,b)
Air quality guidelines	WHO	WHO (2000, 2006)
Maximum residue limits (MRLs) of pesticides in food	FAO/WHO	FAO/WHO (2010b)
Maximum limits (MLs) of contaminants in food	FAO/WHO	FAO/WHO (2010a)

Media-specific guideline values (e.g. drinking-water quality guideline values, air quality guidelines, maximum limits in food) are available for many chemicals. Whether these guideline values are applicable to a specific case depends on the information used to establish these levels, the comparability of human populations with regards to their activity and dietary patterns and demographics, and the exposure averaging times, among other considerations.

More specifically, guideline values typically incorporate a number of assumptions about exposure, including contact rate, body weight, absorption fraction and allocation of total intake (see also section 4.8.6 and Table 19).

3.3.2.3 Evaluating the appropriateness of available guidance or guideline values for a specific problem

The flow chart shown in Figure 4 above illustrates considerations that are key to whether an international guidance or guideline value is appropriate for a specific situation. These factors are discussed briefly here; additional information is presented in both section 3.3.4 and the case-studies that appear later in the document. Contact rates related to different means of contact, as shown in Figure 6 in section 3.3.3.1, refer to assumptions about rates of water consumption, inhalation, food consumption and other forms of contact with environmental media and consumer products. Default values are typically used for those contact rates (see Table 19 in section 4.8.6). For example, health-based guideline values for contaminants in water may assume that an average adult consumes 2 litres of water per day. Yet it is recognized that population average water consumption rates can vary significantly, perhaps by a factor of 2–4, in different parts of the world, particularly where consumers are engaged in manual labour in hot climates. This example illustrates that an assessor should consider whether the default values incorporated into a health-based guideline value are appropriate for the specific population and time period of interest.

Guidance or guideline values for a given medium (e.g. drinking-water, air, food) may also assume that total exposure to a chemical occurs via multiple routes or media. For example, guideline values for a chemical in water may assume that a certain amount of exposure to that chemical also occurs through ingestion of food. Variation in natural resources, culture and lifestyle among populations may invalidate some assumptions about allocation of total intake. For example, in areas where the intake of a particular contaminant in drinking-water is known to be much greater than that from other sources (e.g. food and air), it may be appropriate to allocate a greater proportion of the ADI or TDI, for example, to drinking-water to derive a guideline value more suited to the local conditions. Where relevant exposure data are available, authorities are encouraged to develop context-specific guideline values that are tailored to local circumstances and conditions.

Cases in which a guideline value for a chemical has yet to be established by an international or other organization (Tier 4 risk assessment) are generally outside the scope of the Toolkit. Readers are referred to:

- *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits* (EHC 170) (IPCS, 1994); and
- *Principles for modelling dose–response for the risk assessment of chemicals* (EHC 239) (IPCS, 2009).

3.3.3 Exposure assessment

Exposure assessment is used to determine whether people are in contact with a potentially hazardous chemical and, if so, to how much, by what route, through what media and for how long. Because hazard characterization and risk characterization are dependent upon the route (oral, inhalation, dermal) and duration (short-term, medium-term, long-term) of exposure, knowledge of how and when people may be exposed is relevant to the determination of an appropriate guidance or guideline value. When combined with information on hazard characterization or a guidance or guideline value, exposure information is used to characterize health risks.

The exposure concentration is the concentration of a chemical in a medium with which a person is in contact. These media include air, water and soil in outdoor and indoor locations frequented by a population. Other media include food and consumer products with which people come in contact. Ideally, exposure concentrations will be obtained for media, locations and durations that are representative of potential human contact with a chemical of concern.

As indicated in Figure 5, the assessor must determine the following parameters to initiate the exposure assessment portion of the risk evaluation:

- the relevant routes and pathways of exposure;
- the environmental media expected to contain the chemical; and
- the appropriate duration of exposure.

3.3.3.1 Routes and pathways of exposure

The medium of exposure refers to air, water, soil, food or products (consumer, commercial or industrial) that are thought to contain the chemical of interest (Figure 6). These exposures may occur in occupational or community (i.e. non-occupational) settings or while using products. Ingestion exposure is associated with chemicals in food, water and soil, both indoors and outdoors. Inhalation exposure requires that chemicals be present in air, although it is important to recognize that chemicals with moderate to high vapour pressures and low solubilities can volatilize from water or soil and then be inhaled. Trichloroethene, an organic solvent, is one example of a chemical that readily volatilizes from potable water. Inhalation can also be an important route of exposure to less volatile chemicals, such as polychlorinated biphenyls, when present at elevated concentrations in soil and other solid substrates. Finally, dermal absorption requires contact between a chemical and skin, which can occur in water, during contact with soil, in the presence of high concentrations in air and during occupational or consumer use.

The scope of an exposure assessment can be narrowed with information about the chemical and its properties, from which the important exposure media and routes can be inferred. For example, health-relevant exposures to some chemicals, such as ozone, occur through only one medium, in this case air. For chemicals that can be found in several media, such as lead, pesticides and chloroform, information about the chemical properties and behaviour can point to environmental media or locations where the highest levels of the chemicals are likely. In addition, this information can suggest relevant pathways and routes of exposure. *Pathway of exposure* refers to the physical course taken by a chemical as it moves from a source to a point of contact with a person (e.g. through the environment to humans via food). *Route of exposure* refers to intake through ingestion, inhalation or dermal absorption. The exposure routes may have important implications in the hazard characterization step, as the danger posed by a chemical may differ by route.

3.3.3.2 Estimating exposures: modelling or measurement approaches

While exposure concentrations in personal air and ingested media such as drinking-water should be among the most accurate estimates of actual exposure to a chemical, in practice, they can be difficult, expensive or impractical to determine. In recognition of this limitation, risk assessments, especially screening-level risk assessments, are based upon chemical concentrations in environmental media that are relatively easy to access, such as outdoor air,

indoor air, lake water, river water and outdoor soil. These concentrations can be determined from a measurement campaign or a modelling effort.

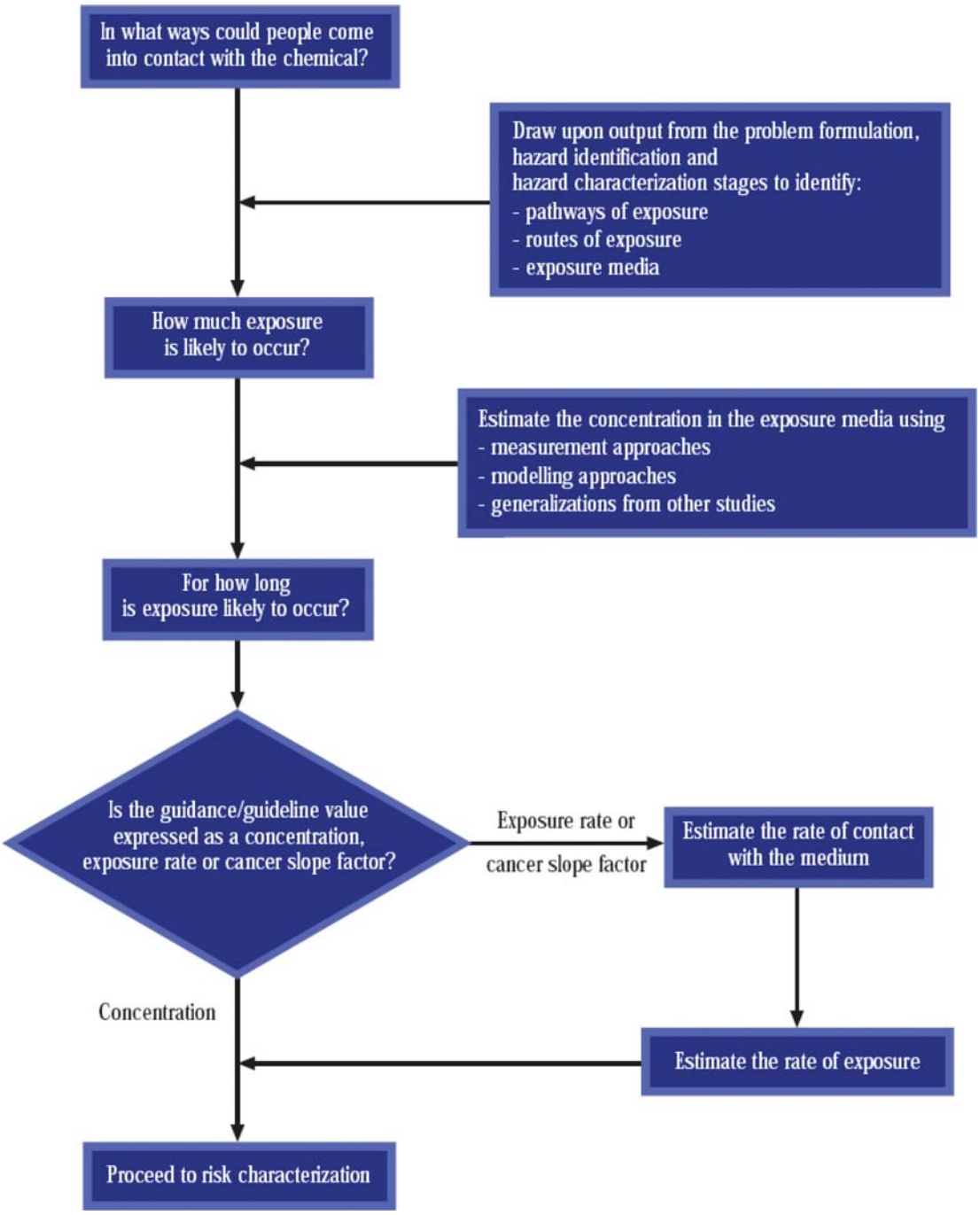


Figure 5: Generic road map for exposure assessment in the context of the Toolkit.

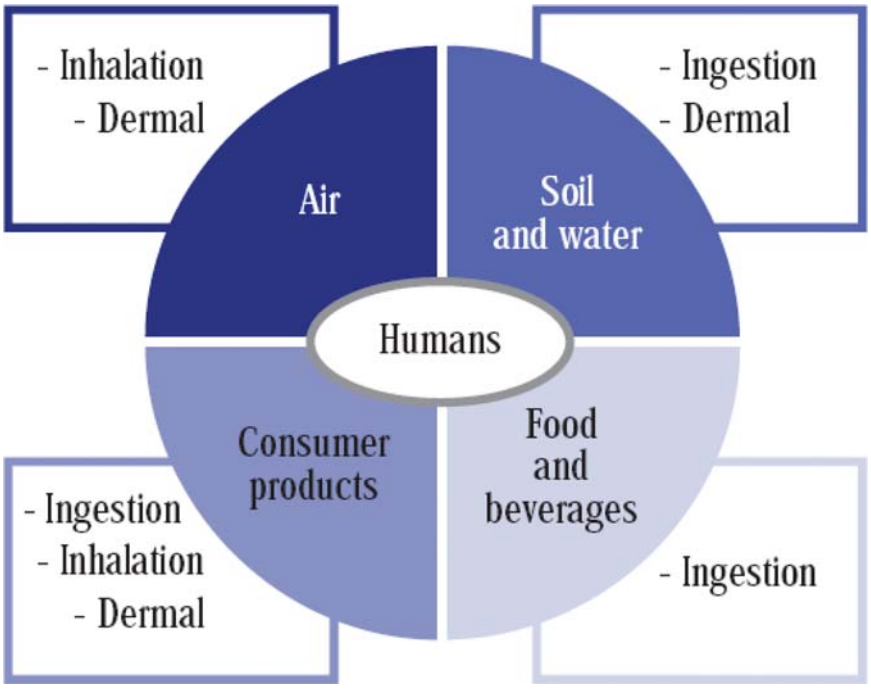


Figure 6: Possible exposure media and corresponding means of contact.

Exposures can be measured directly, estimated using models or generalized from existing data. Each requires that exposures be determined for time periods relevant to possible adverse health outcomes. For example, if the relevant health hazard is chronic in nature, exposure should be long term as well. Of the three methods, estimating exposures from existing data can often be the simplest approach; however, such data are not often available or entirely relevant to the risk assessment at hand. Measurements, on the other hand, generally provide the most accurate and relevant data, but are the most time and resource intensive, obviating their use for many risk assessments. A summary of exposure measurement and generalization methods is given in EHC 214 (IPCS, 2000).

(a) Exposure models

Exposure models generally require information about the concentration of a chemical in a medium and the period of time over which individuals are in contact with the chemical. Chemical concentrations can be measured or can be estimated from chemical usage or previous data. As described in section 4.8, concentrations in specific media can be estimated using several publicly available models that have been recommended by international organizations or have been vetted in the scientific literature and are widely adopted in the field of environmental health. These models may be used to estimate, for example, chemical releases to the atmosphere, fate and transport of chemicals in aquifers or groundwater, or distribution of chemicals among multiple environmental media. Given the complexity of many of these models, it is probable that specialized training on running the models will be necessary. In order to select the appropriate model, information about the geographic and temporal extent of the chemical exposures of interest and the exposed populations of interest should be obtained or otherwise determined.

Concentration estimates provided by models can be used—together with information about chemical contact, including who is exposed and the frequency and duration of their exposure—to estimate exposures. Information about chemical contact can be obtained using a variety of techniques, including questionnaires or inquiries with affected individuals, demographic data, survey statistics, behaviour observation, activity diaries, activity models or, in the absence of more substantive information, assumptions about behaviour. Using this information, exposures for air, water, food or soil can be estimated using mathematical equations. A summary of principles for characterizing and applying human exposure models is given in a WHO report (IPCS, 2005b). Guidance on how to address uncertainty and data quality in exposure assessments is also available from WHO (IPCS, 2008a).

(b) Exposure measurements

Exposure concentrations can also be obtained from measurements, whether they be historical, current or planned for the future. For these concentrations to be truly representative of exposures, they must measure the concentration of the chemical of interest in environmental media, such as air, water and soil, that are contacted or food that is ingested by a person. Exposure measurements are intended to match the actual media, location and duration that represent the human exposure to the chemical of concern, although this is often not possible to achieve.

To evaluate the representativeness of prior exposure measurements or to plan future measurements, many factors that are specific to the chemical of interest need to be considered. These factors include the availability, performance and sensitivity of appropriate exposure measurement devices, the size and activity patterns of the potentially exposed population, the contact rate and duration of exposures and the media through which exposures generally occur. Information about exposure measurement devices can be obtained through review of the scientific literature, with specific attention paid to their performance, as measured by their sensitivity, accuracy and precision. A complete description of these concepts is contained in EHC 214 on human exposure assessment (IPCS, 2000). Often, the cost of the measurement method is inversely related to its performance, which may result in trade-offs between cost and sample size in any measurement plan. Information about activity patterns, contact rates and exposure durations as well as other information about the potentially exposed population can be obtained through surveys and questionnaires. Together, this information can be used to determine whether the past exposure measurements pertain to the current situation or can help in the design of a measurement campaign that is efficient while providing data relevant to the risk assessment.

Further, some consideration should be given to the heterogeneity of exposures within the relevant population. For example, if the exposures are similar for all individuals, then measurements made for a relatively small subset of individuals can be generalized to a larger population. Correspondingly, if exposures vary within a population by age, sex or residential location, it is possible that exposure measurements should be made for subsets within each of these groups and generalized to the larger group. An example of a measurement-based approach to determine exposure concentrations is included in the case-study in section 5.

3.3.3.3 Duration of exposure

The duration of exposure is a critical element in assessment and estimation of health risks, as the relevant period of exposure is defined by knowledge or theory of the mechanisms of

injury or disease. Consequently, the duration of exposure is an explicit component of the design of exposure assessments as well as toxicological studies conducted for purposes of hazard identification and hazard characterization.

Single and short-term exposures over minutes, hours or a day are relevant for chemicals that have an immediate or rapid adverse effect on the body at certain concentrations. Examples of chemicals for which assessment of single and short-term exposure is important include water-soluble gases such as sulfur dioxide and asphyxiants such as carbon monoxide.

Medium-term or intermediate exposure is important for chemicals that are thought to exert adverse effects over a period of contact that ranges from weeks to months in duration. Respiratory irritants such as hydrogen sulfide are a class of chemicals for which some public health agencies have developed guidelines for intermediate exposure.

For chemicals that pose a hazard as a result of cumulative or long-term low-dose exposure, long-term average exposures are most relevant for characterization of adverse effects. Chemicals such as polychlorinated biphenyls, which have been associated with learning deficits and diabetes, are in this category. Assessments of cancer risk are a special case of long-term exposure for which lifetime average exposure is generally of interest.

3.3.3.4 Concentration and rate of exposure

In practice, exposures are generally expressed as either a concentration of the chemical in the exposure medium or a rate of contact with a chemical over a specific duration. Therefore, this step of the Toolkit must produce an estimate of exposure that is in the same form as the guidance or guideline value—that is, either a rate or a concentration, respectively (see section 3.3.2).

For example, concentrations in contact media are usually expressed in units of micrograms per cubic metre (μg/m^3) for air, micrograms per litre (μg/l) for water and milligrams per kilogram (mg/kg) for solids such as soil, dust and food. Rate of exposure for a chemical is typically referred to as average daily dose, with units of milligrams of chemical per kilogram of body weight per day (mg/kg body weight per day). In general, exposure rate is calculated as the concentration of a chemical in an exposure medium multiplied by the rate at which a person inhales or ingests that medium, divided by a representative body weight.

As shown in Equation 1, the period of exposure and averaging time of exposure are considered explicitly as well:

$$\text{Exposure rate} = \frac{\text{concentration} \times \text{contact rate} \times \text{exposure duration}}{\text{body weight} \times \text{averaging time}} \quad [1]$$

where:

- concentration is the amount of chemical per mass or volume of the medium
- contact rate is the mass or volume of the medium in contact with the body
- exposure duration is the period of time over which the person is in contact with the chemical
- body weight is the body weight over the averaging time
- averaging time is the period of time over which the exposure is relevant for health risk characterization

The averaging time used in calculation of average daily dose is typically different for estimation of non-cancer and cancer risks. For chemicals that pose a non-cancer hazard, the

average exposure during the period of contact with a chemical is generally the relevant duration of exposure for risk assessment. For cancer risk assessment, however, the averaging time is fixed at a lifetime, which is commonly assumed to be 70 years in risk assessments.

3.3.3.5 Biomarkers of exposure

Besides the above-described traditional exposure assessment, the use of biological markers is another method with which to evaluate human exposure to a chemical. Biological markers of exposure are considered measures of internal dose, whereas exposure describes the contact with a chemical at the boundary between an individual (e.g. skin, mouth or nostrils) and the environment, food or consumer product.

Numerous biological media are available for use in exposure assessment. Selection of sampling media depends on the contaminant of interest, the pattern of exposure, the timing of exposure, the population studied, ease of collection and storage and participant burden. Biological monitoring is frequently considered invasive; however, several media that can be collected in a non-invasive manner are available for exposure assessment. Blood and urine, as well as exhaled breath and saliva, can be used to document recent exposures; past exposure can be evaluated using blood and urine, as well as keratinized tissues (hair and nails), ossified tissue (teeth and bone), adipose tissue and breast milk. Adipose tissue and bone can also represent future sources of internal exposure. Other media available for biomarker studies include faeces, nasal lavage, tears, sputum, semen, cord blood and buccal cells, which can be feasible means for population exposure monitoring. Further information on biomarkers of exposure is available in IPCS (1993a, 2000, 2001b) (see also Table 17 in section 4.8).

3.3.4 Risk characterization

The last step of a chemical risk assessment—the risk characterization—is typically a quantitative statement about the estimated exposure relative to the most appropriate health-based guidance value, media-specific quality guideline value or another hazard characterization value, such as the cancer slope factor. In general, the risk statement is derived by either comparing the estimated exposure with a guidance or guideline value or calculating the excess lifetime cancer risk associated with the estimated exposure (see Figure 7).

3.3.4.1 Comparison with a guidance or guideline value

Health-based guidance values or guideline values have been established for a number of chemicals by international organizations. In some cases, the guidance or guideline value is based on an exposure concentration or rate below which adverse effects are considered to be unlikely (threshold chemical). As described in section 3.3.2.1 and 3.3.2.2, this approach applies to toxicological effects that occur when a threshold of exposure or dose is exceeded.

Guidance or guideline values are also sometimes established for chemical exposures that are thought to have a continuous hazard characterization relationship, and there is a theoretical risk of an effect at any level of exposure (non-threshold chemical). Carcinogens and some air pollutants, such as fine particulate matter, are examples of stressors that are considered to pose risk of an adverse health outcome at all levels of exposure. For these substances, guidance or guideline values are exposure concentrations or rates that correspond to levels of risk that have been determined to be tolerable. For instance, long-term average exposure to inorganic arsenic in drinking-water at a certain guideline value (i.e. concentration) may be

equivalent to a lifetime cancer risk of 1 in 100 000 (WHO, 2008a). It should be noted, however, that some groups, such as JECFA, do not establish guidance values for genotoxic carcinogens and withdrew its health-based guidance value for inorganic arsenic (see section 3.3.4.2 for more on estimation of cancer risk).

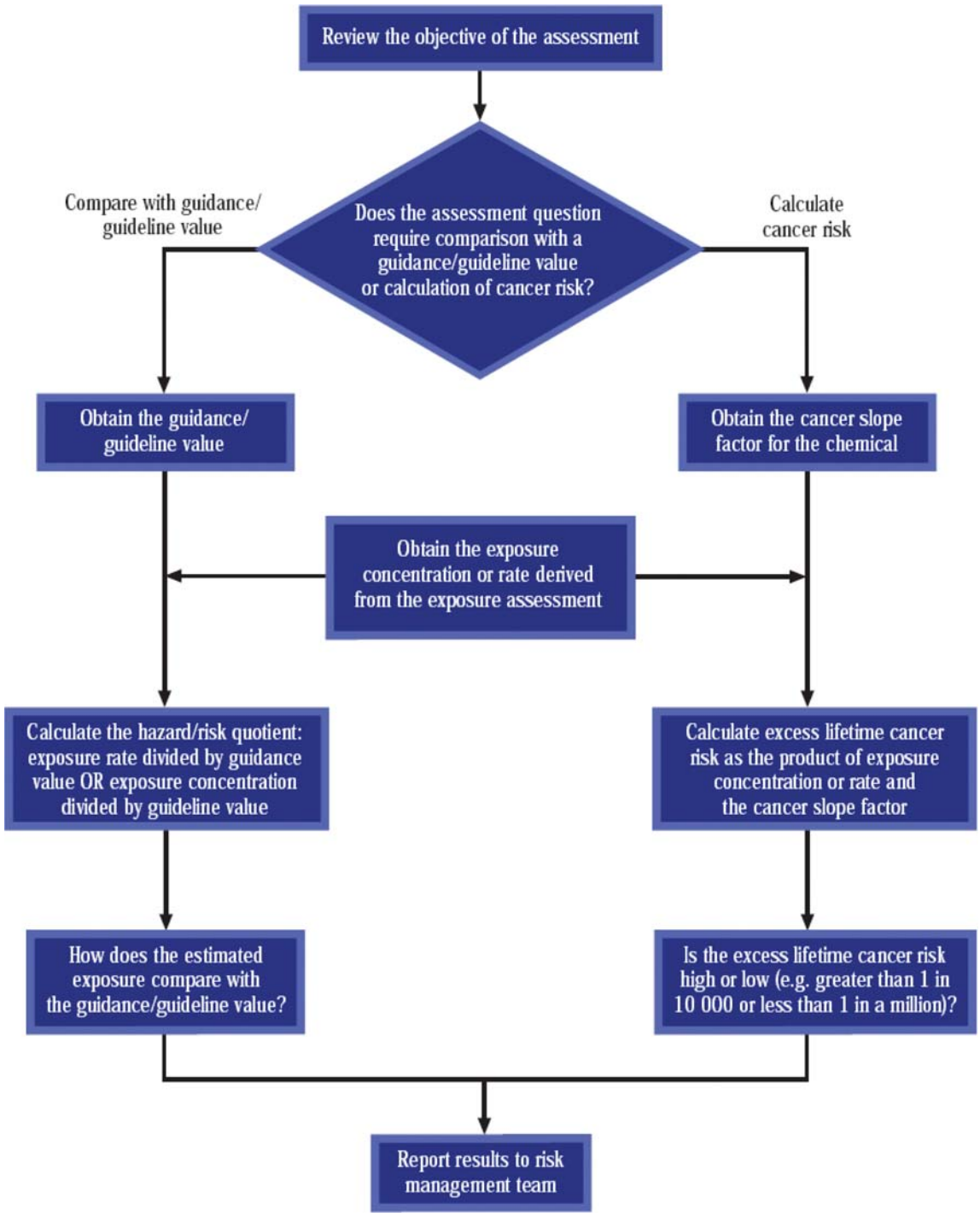


Figure 7: Generic road map for risk characterization in the context of the Toolkit.

For chemicals that have the potential to result in non-cancer effects, risk is frequently characterized as the ratio of the appropriate exposure rate (e.g. the average daily, weekly, monthly intake) to the health-based guidance value: ADI, TDI, PTWI, PTMI or ARfD (often used for pesticide residues and contaminants in food). For exposure to non-cancer chemical hazards in media such as air and drinking-water, the ratio of the chemical concentration in that medium to a reference concentration (e.g. the WHO air quality guideline or the WHO drinking-water quality guideline value) may also be used to assess risk. This ratio is sometimes referred to as the hazard or risk quotient. A hazard or risk quotient less than 1 indicates that the chemical exposure is less than the benchmark and that the exposure is unlikely to result in an adverse effect. For example, an evaluation of chemical concentrations in exposure media and rates of contact with those media may conclude that the exposure to a chemical is 15 times less than the ADI established by an authoritative organization as a benchmark for risk of an adverse effect. Conversely, a hazard or risk quotient greater than 1 indicates that the exposure is greater than the benchmark and that the sources, pathways and routes of chemical exposure should be evaluated further.

In some cases, public health organizations account for exposure to a chemical in multiple media when setting quality guidelines or standards for a particular medium. For example, drinking-water quality guideline values established by WHO allocate only a portion of the ADI or TDI to intake through water for some chemicals. In order to account for the variations in exposure from different sources in different parts of the world, a certain proportion, generally between 1% and 80%, of the ADI or TDI is allocated to drinking-water in setting guideline values for many chemicals. Where relevant exposure data are available, authorities are encouraged to develop context-specific guideline values that are tailored to local circumstances and conditions. For example, in areas where the intake of a particular contaminant in drinking-water is known to be much greater than that from other sources (e.g. air and food), it may be appropriate to allocate a greater proportion of the ADI or TDI to drinking-water to derive a guideline value more suited to the local conditions.

3.3.4.2 Estimation of cancer risk

For chemicals that may exert a carcinogenic effect, the risk characterization is typically expressed as the excess lifetime cancer risk. Characterization of cancer risk over a lifetime has become a convention primarily because cancer is thought to be a function of long-term rather than short-term exposure. Excess lifetime cancer risk is an estimate of the likelihood of cancer associated with a given level of exposure averaged over a lifetime.

For contaminants that are both genotoxic and carcinogenic, JECFA recommends the MOE approach for risk characterization, which involves the comparison of the estimated exposure with a BMD or BMDL (see section 3.3.2.1 for BMD and BDML). The MOE approach can be used to prioritize different contaminants, providing that a consistent approach has been adopted (FAO/WHO, 2006).

4. INTERNATIONAL RISK ASSESSMENT RESOURCES

4.1 Introduction

This section provides a guide to information, data and tools that are useful for conducting human health risk assessments. While the previous sections of the Toolkit and the case-studies that follow this section are intended to raise the reader's level of knowledge about human health risk assessments, this section directs the reader to sources of information that can inform a risk assessment.

The resources included in this section reflect an emphasis on information developed by international organizations, such as WHO (including IARC), the Food and Agriculture Organization of the United Nations (FAO) and OECD. Gaps in key risk assessment information available from international organizations were filled with widely accepted approaches described in the peer-reviewed scientific literature or codified in regional- and country-specific resources.

In addition to the resources noted here, readers are encouraged to seek sources of information developed within their own countries or regions that may contain data that are more specific to the populations and geographic areas of interest. Organizations within countries that may be sources of this information include universities, water resource management authorities, land use management authorities, customs and security authorities, poison control centres and health-care institutions. Chemical Information Exchange Networks established by UNEP are another source of information for people responsible for managing chemicals at the local or national level (UNEP, 2010).

4.2 Organization

The resources described in the remainder of this section are organized according to their content in the following manner:

- directories of resources;
- general resources on risk assessment;
- chemical-specific resources;
- hazard identification resources;
- hazard characterization/guidance or guideline value resources;
- exposure assessment resources; and
- risk characterization resources.

The directories of resources presented in section 4.3 are portals to technical summaries and scientific data that are relevant to risk assessment. The directories included here are maintained by international organizations. They can be accessed through the Internet and are available at no cost to the user. The portals provide access to information on all aspects of the risk assessment process that are described in section 3.

Section 4.4 is a listing of documents on risk assessment in general prepared by WHO. These resources are included in the Toolkit to provide information to readers who are interested in gaining a deeper understanding of the principles and methods that contribute to the theoretical and scientific foundation of human health risk assessment for chemical agents.

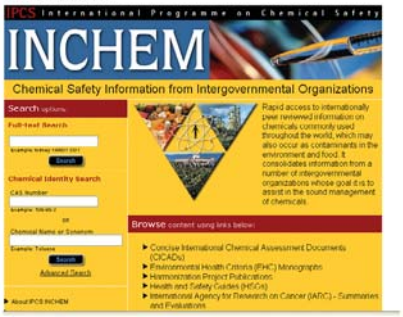
The chemical-specific resources identified in section 4.5 contain detailed summaries on numerous aspects of hundreds of chemicals that are widespread in commerce and have hazardous properties. In addition to information on hazard characterization, exposure assessment and risk characterization, these resources also provide information on the contributions of both anthropogenic and natural background sources to levels in the environment as well as body burdens in human populations.

Sources of information specific to the fundamental steps of a risk assessment, including hazard identification, hazard characterization, exposure assessment and risk characterization, are identified in sections 4.6, 4.7, 4.8 and 4.9.

4.3 Directories of resources

Comprehensive and detailed summaries of information essential to risk assessment for a wide variety of chemicals have been compiled by numerous organizations. Notable among them are the online resources INCHEM and eChemPortal, which are gateways to some sources of internationally peer-reviewed chemical risk assessment information (Table 8). Databases within INCHEM and eChemPortal that contain information specific to the principal components of a human health risk assessment (see section 2) are described in the remainder of section 4.

Table 8: Two compilations of hazard identification, hazard characterization, exposure assessment and risk characterization information for chemicals.

	INCHEM	*eChemPortal*
URL	http://www.inchem.org/	http://oecd.org/echemportal/
Sponsor	WHO/IPCS	OECD
Description	A compilation of information from a number of intergovernmental organizations whose goal is to assist in the sound management of chemicals	OECD, UNEP, WHO and national databases on physicochemical properties, environmental fate and behaviour and toxicity
Portal page		

4.4 General resources on risk assessment

The resources listed below provide information about the principles of risk assessment. In addition, they address populations that are susceptible to the effects of and exposure to chemicals.

4.4.1 Resources on risk assessment methodology

Principles and fundamentals of approaches to chemical risk assessment are described in several WHO reports, as shown in Table 9. These documents elaborate on the basic components of a risk assessment that are summarized in section 3 above. They also contain information specific to trace elements and risk-related considerations of elemental speciation.

Table 9: WHO documents on principles of human health risk assessment for chemicals.

Document title	*Reference*
Principles for the assessment of risks to human health from exposure to chemicals (EHC 210)	IPCS (1999a)
Human exposure assessment (EHC 214)	IPCS (2000)
Principles and methods for the assessment of risk from essential trace elements (EHC 228)	IPCS (2002)
Elemental speciation in human health risk assessment (EHC 234)	IPCS (2006a)

This Toolkit is a contribution to the WHO project to harmonize approaches to the assessment of risk from exposure to chemicals. The goal of this project is to globally harmonize approaches to risk assessment by increasing understanding of and developing basic principles and guidance on specific chemical risk assessment issues. Harmonization enables efficient use of resources and consistency among assessments. Relevant technical documents developed by this project are provided in Table 10.

Table 10: International sources of information on harmonization of risk assessment methodology.

Document title	*Reference*
IPCS risk assessment terminology. Part 1: IPCS/OECD key generic terms used in chemical hazard/risk assessment; Part 2: IPCS glossary of key exposure assessment terminology (Harmonization Project Document No. 1)	IPCS (2004)
Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment (Harmonization Project Document No. 2)	IPCS (2005a)
Principles of characterizing and applying human exposure models (Harmonization Project Document No. 3)	IPCS (2005b)
Skin sensitization in chemical risk assessment (Harmonization Project Document No. 5)	IPCS (2008b)
Uncertainty and data quality in exposure assessment. Part 1: Guidance document on characterizing and communicating uncertainty in exposure assessment. Part 2: Hallmarks of data quality in chemical exposure assessment (Harmonization Project Document No. 6)	IPCS (2008a)

4.4.2 Resources on susceptible populations

Young children and the elderly are generally more susceptible than non-elderly adults to chemical exposure for reasons that relate to both exposure and effect. Children, for example, take in more water, food and air per unit body weight than do adults. In addition, some organ systems (e.g. the nervous system) continue to develop in the first several years of life, which

adds another dimension to the vulnerabilities experienced by children. Likewise, aged populations may be less mobile than younger adults and children and therefore can have greater time-weighted average exposure to pollutants in and around their residences. Importantly, elderly persons may have pre-existing illness, such as respiratory or cardiovascular conditions, that can make them more likely to experience adverse effects of pollutant exposure. Further information is available from the sources listed in Table 11.

Table 11: International sources of information on susceptible populations.

Document title	*Reference*
Principles for evaluating health risks to progeny associated with exposure to chemicals during pregnancy (EHC 30)	IPCS (1984)
Principles for evaluating health risks from chemicals during infancy and early childhood: the need for a special approach (EHC 59)	IPCS (1986b)
Principles for evaluating chemical effects on the aged population (EHC 144)	IPCS (1993b)
Principles for evaluating health risks in children associated with exposure to chemicals (EHC 237)	IPCS (2006d)

4.5 Chemical-specific resources

This section identifies cross-cutting sources of comprehensive risk assessment information for specific chemicals that have been prepared by WHO and FAO. These resources include summary and in-depth reports of sources, uses, hazards, exposures and toxicities of chemicals that are either common in commerce or known to be hazardous to human health.

4.5.1 JMPR monographs

JMPR is an international expert scientific group that is administered jointly by FAO and WHO (FAO/WHO, 2010c). JMPR, which consists of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, has been meeting regularly since 1963. During the meetings, the WHO Core Assessment Group is responsible for reviewing toxicological and related data and for estimating, where possible, the ADIs as well as the ARfDs of the pesticides under consideration (see also section 3.3.2.1).

4.5.2 JECFA monographs

JECFA is an international expert scientific committee that is administered jointly by FAO and WHO (FAO/WHO, 2010a). It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food. JECFA has evaluated more than 1500 food additives, approximately 40 contaminants and naturally occurring toxicants and the residues of approximately 90 veterinary drugs. A searchable database is maintained that contains summaries of all evaluations. Each summary provides links to the most recent reports and monographs and to the specification database and provides a history of previous JECFA evaluations (see also sections 3.3.2.1 and 4.7.1.2).

4.5.3 EHC monographs

WHO has published EHC monographs on over 220 chemicals, each of which contains a detailed summary of the sources, pathways and routes of exposure to each chemical (IPCS, 2010c). Ranges of exposure reported in the scientific literature for multiple environmental media are presented in the monographs as well. As such, the EHC monographs are valuable for helping investigators prioritize exposure media and routes as part of a risk assessment.

4.5.4 CICADs

The Concise International Chemical Assessment Documents (CICADs) published by WHO join the EHC monographs as authoritative sources of information on risk assessment of chemicals (IPCS, 2010b). In addition to hazard characterization of a chemical, CICADs contain information on sources of human exposure; environmental transport, distribution and transformation; environmental levels and human exposure; and information on guidance or guideline values. The section on human exposure includes numerous environmental media, such as ambient air, indoor air, drinking-water, surface water, sediment and soil, and food, where relevant to the chemical of concern.

4.5.5 Drinking-water quality background documents

The WHO *Guidelines for drinking-water quality* include fact sheets and comprehensive review documents for many individual chemicals. For many of these, guideline values are derived. All of these can be accessed through the following source: WHO (2010a).

4.6 Hazard identification resources

The OECD Guidelines for the Testing of Chemicals are a collection of the most relevant internationally agreed testing methods used by government, industry and independent laboratories to identify chemical hazards (OECD, 2010a).

Detailed information on the principles of the identification of a variety of human health effects is contained in a number of reports published by WHO as a part of the EHC series (Table 12).

Table 12: WHO resources on identification of chemical hazards.

Document title	*Reference*
Principles and methods for the assessment of neurotoxicity associated with exposure to chemicals (EHC 60)	IPCS (1986a)
Principles and methods for the assessment of nephrotoxicity associated with exposure to chemicals (EHC 119)	IPCS (1991)
Principles and methods for assessing direct immunotoxicity associated with exposure to chemicals (EHC 180)	IPCS (1996)
Principles and methods for assessing allergic hypersensitization associated with exposure to chemicals (EHC 212)	IPCS (1999b)
Principles for evaluating health risks to reproduction associated with exposure to chemicals (EHC 225)	IPCS (2001a)
Principles and methods for assessing autoimmunity associated with exposure to chemicals (EHC 236)	IPCS (2006b)

The resources listed below contain detailed information on the identities, hazardous properties and toxicities of thousands of chemicals in commerce, provided by international organizations and others. A brief description of each database is provided in the subsections below, together with references that include the Internet addresses. As shown in Table 13, most of these resources contain detailed information specific to either chemical hazards identified through scientific investigations or the classification of chemicals according to regulatory schemes developed by international organizations.

Table 13: General content of international hazard identification resources.

Resource	*Summary or detailed content*	*Classification scheme*
International Chemical Safety Cards	Summary	Yes
Screening Information Datasets for High Production Volume Chemicals	Detailed	No
WHO Recommended Classification of Pesticides by Hazard	Summary	Yes
UN Recommendations for the Transport of Dangerous Goods	Summary	Yes
IARC monographs	Detailed	Yes
Hazardous Substances Data Bank	Detailed	No
European Chemical Substances Information System	Detailed	Yes
EU Classification and Labelling System	Detailed	Yes
International Chemical Control Toolkit	Detailed	Yes

4.6.1 International Chemical Safety Cards

International Chemical Safety Cards (ICSCs) contain a brief summary of essential information on chemical substances that was developed cooperatively by IPCS and the Commission of the European Communities (IPCS/CEC, 2010). In addition to potential health hazards, each ICSC also contains a description of fire and explosion hazards as well as appropriate responses to a spill, packaging and labelling information, and storage conditions. Basic physical, chemical and hazardous properties of chemicals are also summarized in a standard format on each ICSC.

4.6.2 Screening Information Datasets for High Production Volume Chemicals

The Screening Information Dataset for High Production Volume Chemicals (SIDS) is an extensive compilation of data on physicochemical properties and toxicity values for the most common chemicals in commerce (OECD, 2010b). In contrast to the ICSCs described above, which are brief summaries of these chemical characteristics, the SIDS includes results for a variety of environmental conditions and species. As a result, this resource can be useful for considering potential risks in unique climates and exposure scenarios.

4.6.3 WHO Recommended Classification of Pesticides by Hazard

The WHO Recommended Classification of Pesticides by Hazard distinguishes between the more and less hazardous forms of selected pesticides based on acute risk to human health (i.e. the risk of single or multiple exposures over a relatively short period of time) (WHO, 2005). The classification system takes into consideration the toxicity of the technical compound and its common formulations. It lists common technical-grade pesticides and recommended

classifications, together with active ingredients believed to be obsolete or discontinued for use as pesticides, pesticides subject to the prior informed consent procedure under the Rotterdam Convention, limitations to trade because of the Stockholm Convention on Persistent Organic Pollutants, and gaseous or volatile fumigants not classified under these recommendations.

4.6.4 UN Recommendations for the Transport of Dangerous Goods

The UN Recommendations for the Transport of Dangerous Goods have been developed by the United Nations Economic Commission for Europe's Committee of Experts on the Transport of Dangerous Goods in the light of technical progress, the advent of new substances and materials, the exigencies of modern transport systems and, above all, the requirement to ensure the safety of people, property and the environment (UNECE, 2010b). Goods, including chemicals, are classified according to hazard class. The recommendations will be harmonized with the GHS (UNECE, 2010a).

4.6.5 IARC monographs

IARC has published summaries and evaluations of the carcinogenic risk of chemicals to humans since its inception in 1969 (IARC, 2010). The monographs include single chemicals as well as chemical mixtures. The objective of the programme is to prepare, with the help of international working groups of experts, and to publish, in the form of monographs, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of chemicals to which humans may be exposed. The IARC monographs represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The monographs may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

4.6.6 Hazardous Substances Data Bank

The Hazardous Substances Data Bank (HSDB), which is maintained by the United States National Library of Medicine and can be accessed through the OECD eChemPortal, is a detailed listing of peer-reviewed toxicological data for over 5000 chemicals, including information on human health effects, emergency medical treatment, physicochemical properties, metabolism, toxicology and laboratory methods (HSDB, 2010). Unlike the European Chemical Substances Information System (ESIS) (see section 4.6.7) and ICSCs (see section 4.6.1), the toxicity information is presented in narrative form rather than tables. The HSDB also contains excerpts from case reports of humans exposed to the chemical of interest, in addition to summaries of laboratory animal studies.

4.6.7 European Chemical Substances Information System

ESIS is an electronic database that can be accessed through the eChemPortal maintained by OECD (EC, 2010a). ESIS provides information on the names, synonyms and structures of thousands of chemicals. The database also contains information on physicochemical properties that influence transport, fate and toxicity.

4.6.8 EU Classification and Labelling System

The new Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP) of the EU entered into force on 20 January 2009. The CLP Regulation implements the GHS (UNECE, 2010a). It will replace Directive 67/548/EEC (substances) and Directive 1999/45/EC (preparations) in a stepwise manner (EC, 2010b).

An online version of the Classification & Labelling (C&L) Inventory of the European Chemicals Agency (ECHA) is being prepared (status as of 23 August 2010). The inventory is a database that will contain basic classification information on chemicals according to their toxicological properties (EC, 2010c).

4.6.9 International Chemical Control Toolkit

Another source of hazard information is provided by the International Labour Organization's (ILO) International Chemical Control Toolkit (ILO, 2010a), which outlines a scheme for protection against harmful and dangerous chemicals in the workplace. It is designed for small and medium-sized enterprises in developing countries.

4.7 Hazard characterization/guidance or guideline value resources

As mentioned in section 3.3.2, hazard characterization typically consists of a qualitative or quantitative description of the inherent properties of an agent having the potential to cause adverse health effects. This information is then often used to develop guidance values or, if human exposure factors are considered, guideline values. In other words, guidance or guideline values provide a measure of the hazardous characteristics of the chemical. The challenging part of applying guidance or guideline values is to review the hazard characterization step and to assess the applicability of the assumptions embedded within it to the situation of interest (e.g. exposure duration and allocation of total exposure among routes of exposure).

The resources noted in sections 4.7.1–4.7.5 are compilations of guidance values, such as TDIs and ADIs, and guideline values, such as air and water quality guidelines, established by WHO. The guidance values are thresholds of exposure for non-cancer effects and slope factors for cancer risks, and the guideline values are concentrations of chemicals in environmental media. In addition, this section provides a link to the International Toxicity Estimates for Risk (ITER) database maintained by the United States National Library of Medicine. Finally, this section provides examples of national resources of occupational exposure limits (OELs). As described in section 3.3.4, these values can be combined with estimates of exposure to calculate the hazard or risk quotient or the excess lifetime cancer risk, indicators of non-cancer and cancer risks, respectively.

In addition, WHO has published several EHC documents on principles and methods for the hazard characterization component of human health risk assessments for chemicals (Table 14).

Table 14: International resources on hazard characterization.

Document title	Reference
Principles of studies on diseases of suspected chemical etiology and their prevention (EHC 72)	IPCS (1987)
Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits (EHC 170)	IPCS (1994)
Principles for modelling dose–response for the risk assessment of chemicals (EHC 239)	IPCS (2009)

4.7.1 Guidance values for exposure rates

4.7.1.1 Pesticides

A summary of ADIs and ARfDs that have been established by JMPR is available in IPCS (2010a). Additional information is available in Tables 5 and 6 and section 3.3.2.1.

4.7.1.2 Food additives and contaminants, naturally occurring toxicants and residues of veterinary drugs in food

TDIs, ADIs and other guidance values for food additives and contaminants, naturally occurring toxicants and residues of veterinary drugs in food have been established by JECFA (see also Tables 5 and 6 and section 3.3.2.1). A searchable database that contains all values is available in electronic form (FAO/WHO, 2010a).

4.7.2 Guideline values for exposure concentrations

4.7.2.1 WHO drinking-water guidelines

WHO has developed guidelines for concentrations of chemicals and other contaminants in drinking-water (WHO, 2008a). The guideline values and the methodology employed to derive them are detailed in a report that is available on the Internet. The guideline values are expressed in units of mass concentration in drinking-water (mg/l) and assume a water consumption rate of 2 litres per day and a body weight of 60 kg. For risk of cancer, the guideline values are equivalent to lifetime exposure that yields an excess lifetime cancer risk of 10^{-5} (or 1 in 10 000). For chemicals that are likely to be present in multiple media, the guideline values account for intake through air, food and soil. In this case, the guideline value is determined based on the fraction of total or aggregate intake expected to occur as a result of a chemical's presence in drinking-water. Consider a case where drinking-water is thought, a priori, to account for one half of all intake of a chemical. Then, the guideline value would be set such that consumption of drinking-water at the prescribed value would account for half of the ADI or TDI for that chemical. Variation in the allocation of the ADI or TDI to water can be an important consideration when considering whether the WHO drinking-water guidelines should be adapted for country use.

4.7.2.2 WHO air quality guidelines

WHO publishes air quality guidelines for ubiquitous pollutants in ambient (i.e. outdoor) air: particulate matter, ozone, nitrogen dioxide and sulfur dioxide (WHO, 2006). Separate guidelines are included for particulate matter less than 2.5 μm ($PM_{2.5}$) and less than 10 μm

(PM_{10}) in aerodynamic diameter.[1] The WHO guidelines are intended for worldwide use but have been developed to support actions to achieve air quality that protects public health in different contexts. Notably, the air quality guidelines are derived from an extensive body of epidemiological studies relating air pollution to its health consequences in human populations. The air quality guidelines for these air pollutants are not based directly upon assumptions about intake rates, body weight and other factors, unlike the drinking-water guidelines described in section 4.7.2.1. Instead, the relationships between ambient air pollution and personal exposure to air pollutants in those studies should be considered in comparison with local circumstances before adopting the guidelines as air quality standards in a country.

4.7.3 Guidance and guideline values from chemical-specific monographs

Media-specific guidelines as well as ADIs, TDIs and other guidance values for specific chemicals are available from the internationally developed comprehensive risk assessment monographs mentioned in section 4.5, including EHCs, CICADs and other documents.

4.7.4 International Toxicity Estimates for Risk (ITER) database

The United States National Library of Medicine maintains the ITER database (ITER, 2010). This database provides a searchable summary of hazard characterization values and risk-based concentrations derived by IARC as well as national agencies, including the United States Agency for Toxic Substances and Disease Registry (ATSDR), the United States Environmental Protection Agency (USEPA), Health Canada, the National Institute for Public Health and the Environment of the Netherlands (RIVM) and independent parties. The database contains non-cancer and cancer risk information for both oral and inhalation exposures. A useful synopsis of the risk information for each chemical and hypertext links to related information are also provided.

4.7.5 Occupational exposure limits (OELs)

OELs are intended for use in the practice of industrial hygiene as standards, guidelines or recommendations in the control of potential workplace health hazards. OELs have not been established by international organizations; however, guideline values are available from a variety of nongovernmental organizations and national authorities. Table 15 provides references to some OELs freely available on the Internet. Not freely available OELs include, for example, the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs) (ACGIH, 2010). Information on national OELs is also available from ILO (2010b).

4.8 Exposure assessment resources

The resources noted in this section include general guidance on exposure assessment as well as detailed information on exposure to a wide variety of specific chemicals. The general guidance resources listed here discuss in detail the concepts that were only briefly summarized in section 3.3.3. The resources on specific chemicals are compendia of chemical

[1] Whereas WHO defines PM_{10} and $PM_{2.5}$ as particulate matter less than 10 µm or 2.5 µm in aerodynamic diameter, most jurisdictions define PM_{10} and $PM_{2.5}$ as particulate matter less than or equal to 10 µm or 2.5 µm in aerodynamic diameter.

profiles that feature information on sources, pathways, routes and typical levels of exposure. A description of each of these resources is provided below, with references that include the Internet address as of the drafting of this document.

Table 15: Examples of freely available national resources for occupational exposure limits (OELs).

OELs	*Organization*	*Reference*
Permissible exposure limits (PELs)	Occupational Safety and Health Administration, United States Department of Labor	OSHA (2010)
Recommended exposure limits (RELs)	National Institute for Occupational Safety and Health, United States Centers for Disease Control and Prevention	NIOSH (2005)
Workplace exposure limits (WELs)	United Kingdom Health and Safety Executive	HSE (2005)

Fundamental principles and approaches for chemicals in specific environmental media and routes of exposure such as food, water and air are set forth in several guidance and EHC documents available from WHO. Key examples of these materials are listed in Table 16.

Table 16: International sources of information on media and routes of exposure.

Topic	*Document title*	*Reference*
Food additives and contaminants	*Principles and methods for the risk assessment of chemicals in food*	FAO/WHO (2009)
Pesticide residues in food	*Principles and methods for the risk assessment of chemicals in food*	FAO/WHO (2009)
Dermal absorption	*Dermal absorption* (EHC 235)	IPCS (2006c)
Drinking-water quality guidelines	*Guidelines for drinking-water quality*, 3rd edition, incorporating first and second addenda	WHO (2008a)
Air quality guidelines	*Air quality guidelines for Europe*, 2nd edition	WHO (2000)
Air quality guidelines	*Air quality guidelines—global update 2005: Particulate matter, ozone, nitrogen dioxide and sulfur dioxide*	WHO (2006)

4.8.1 General guidance on exposure assessment

General guidance on exposure assessment is provided in the international resources listed in Table 17.

In addition, the Office of Pollution Prevention and Toxics of the USEPA has developed several exposure assessment methods, databases and predictive models to help in evaluating what happens to chemicals when they are used and released to the environment; and how workers, the general public and consumers may be exposed to chemicals (USEPA, 2010a).

4.8.2 Emission sources and scenarios

Chemicals can be released to the environment from a variety of sources. These sources include emissions from discrete points, areas or volumes and large geographic areas that may not be possible to quantify precisely. Numerous comprehensive descriptions of different

types of sources of chemical emissions to air and water have been published in the scientific literature.

Table 17: International sources of guidance on exposure assessment.

Document title	*Reference*
Human exposure assessment (EHC 214)	IPCS (2000)
Human exposure assessment: an introduction	Berglund et al. (2001)
Dietary exposure assessment of chemicals in food	FAO/WHO (2008)
Occupational and consumer exposure assessments	OECD (1993)
Principles of characterizing and applying human exposure models (Harmonization Project Document No. 3)	IPCS (2005b)
Biomarkers and risk assessment: concepts and principles (EHC 155)	IPCS (1993a)
Biomarkers in risk assessment: validity and validation (EHC 222)	IPCS (2001b)

Emission scenario documents contain descriptions of sources, production processes, pathways and use patterns of numerous commercial industrial operations with the aim of quantifying the releases of chemicals into water, air, soil or solid waste. They can be used to generate hypotheses about contaminants of concern that may be associated with a particular source, such as a manufacturing operation, laboratory, disposal area or waste site. In addition to contaminants of concern, emission scenario documents frequently provide descriptions of industrial processes and the corresponding points and types of by-product discharges to air, water and land.

OECD has prepared emission scenario documents for approximately 20 industries, including wood preservatives, plastic additives, leather processing, paper mills and many others (OECD, 2010c). These documents are useful for understanding processes that may contribute to emissions of contaminants and support the hazard identification process.

4.8.3 Emission rates

Emission rates are chemical releases from a source expressed as amount per time—for example, grams per second or tonnes per year. As such, emission rates are useful for characterizing the magnitude or strength of emissions associated with a source. In some cases, the emission rate of a substance from a source may be known, perhaps from monitoring or estimates conducted previously. In most cases, however, emission rates are not known. In those situations, an assessor may be able to estimate emission rates from information about the process employed by the source and process-related emission factors published in various reference books and databases.

Peer-reviewed and generally accepted emission factors for numerous processes and sources have been compiled by several organizations (Table 18). The European Monitoring and Evaluation Programme and the European Environment Agency publish emission factors and related information for the evaluation of long-range transboundary air pollutants. Other examples are provided in Table 18. The amount of information on emission factors in countries with developing economies and economies in transition is anticipated to increase, as evidenced by the continually growing record of scientific publications on this topic (Wang et al., 2005; Feng et al., 2009).

Table 18: Widely accepted resources on emissions.

Source	*Topic*	*Reference*
European Monitoring and Evaluation Programme	Emission data for long-range transboundary air pollutants	EMEP (2010)
European Environment Agency	Pollutant emission inventories for stationary and mobile sources	EEA (2009)
National Atmospheric Emissions Inventory	Emission factors database	NAEI (2010)
Intergovernmental Panel on Climate Change (IPCC) Emission Factors Database	Emission factors for greenhouse gases	IPCC (2010)
Clearinghouse for Inventories and Emission Factors	Pollutant emission inventories for stationary and mobile sources	USEPA (2010b)

Default emission factors generally are not applicable to releases from chemical waste sites, storage sites with leaking containers of chemicals and other sources that are not process oriented. Instead, measurements or models can be used to estimate emission rates in those situations. Measurement approaches are detailed and modelling approaches are introduced in EHC 214 (IPCS, 2000).

Chemical emissions from waste sites and related scenarios occur primarily as a result of diffusive processes in which chemicals move from locations of high concentration to locations of low concentration. The rate at which a chemical will diffuse is determined by the physicochemical properties of the substance and environmental conditions, such as temperature. Consider the potential for a semivolatile organic chemical, such as *p*,*p*-dichlorodiphenyldichloroethene, or DDE (a degradation product of *p*,*p*-dichlorodiphenyltrichloroethane, or DDT), to volatize from surface soil to air. Among other factors, volatilization will depend principally upon the vapour pressure of the chemical and the strength of the bond between the chemical and soil. While the details of these techniques are beyond the scope of the Toolkit, readers are referred to some of the primary literature and guidance on this topic. Methods for estimating the partitioning of a chemical between the vapour phase in air and the solid phase in soil have been published in the peer-reviewed scientific literature and books (Jayjock, 1994; Mackay, 2001). In some cases, those methods have been codified in tools and guidance documents, such as EMSOFT: Exposure Model for Soil-Organic Fate and Transport (USEPA, 2010c).

4.8.4 Transport and fate

Chemicals can move through water, air and soil following their release from a source in accordance with their properties and those of the transport media. Numerous tools are available to aid with the transport and fate component of exposure assessment.

For releases to the atmosphere, a number of preferred and recommended models have been identified by international and national organizations. Some of these models are available in the public domain and thus can be accessed by risk assessors around the world. Specialized training, either formal or informal, is possibly required to use these models. Thus, a risk assessor may choose to enlist assistance from a specialist if one of these tools will be used to assess exposure. Two of the most widely used source–receptor or dispersion models are

AERMOD (USEPA, 2010d) and the Atmospheric Dispersion Modeling System (CERC, 2010).

For releases to water, MODFLOW is a public access model that is commonly used to assess the transport and fate of chemicals in aquifers or groundwater (USGS, 2010). MODFLOW can simulate the flow of groundwater and contaminants therein, including the effects of wells, rivers, streams, drains, evaporation and recharge. Like the air models mentioned above, this tool also requires training and practice in order to be applied successfully. A wide range of tools are available for estimating contaminant transport and fate in surface waters. Risk assessors are directed to the WHO *Guidelines for drinking-water quality* for an introduction to those assessment techniques (WHO, 2008a).

In contrast to the tools for assessing exposure in a single medium, such as air or water, some tools can be used for characterizing the distribution of chemical pollutants among multiple environmental media, including surface water, soil, sediment and air, as well as partitioning between the gas, aqueous and solid phases in each of those media. Rather than simulating transport and fate based on atmospheric turbulence, flows of water and other advective processes, these models rely upon physicochemical properties of a substance to predict its distribution among environmental media based on diffusive processes. As a result, the geographic extent of the assessment domain and the initial pollutant concentrations at the boundaries of the domain are important characteristics of the assessment. For these and other reasons, multimedia models of this type typically operate on a regional rather than local scale. The European Union System for the Evaluation of Substances (EUSES) includes a multimedia environmental transport and fate model that was developed specifically for chemical risk assessment (EC, 2010d). The EUSES model, supporting documentation and training materials are available from the EU. EUSES and related multimedia assessment methods are appropriate for screening-level assessments on a regional scale, but are not generally applicable to comprehensive analyses of a specific site or location.

4.8.5 Exposure concentrations

Exposure concentration is the concentration of a chemical in an environmental medium with which a person is in contact. These media include air, water and soil in outdoor and indoor locations frequented by a population, as well as food and consumer products.

Ideally, exposure concentrations will be obtained for media, locations and durations that are representative of potential human contact with a chemical of concern. Therefore, the amount of a chemical in environmental media, food or consumer products that are truly inhaled, ingested or in contact with skin is of primary interest. For example, the concentration of a chemical in the breathing zone of an individual is an example of an ideal exposure concentration, in contrast to the chemical concentration in outdoor or indoor air. Turning to water, chemical concentrations in the actual water used for drinking, bathing and cooking represent ideal exposure concentrations, in contrast to levels in sources of potable water, such as a reservoir or river.

Examples of measurement-based approaches to determination of exposure concentrations are included in the case-studies in sections 5–7. Frequently used modelling approaches for estimating exposure concentrations are introduced in section 4.8.3 and 4.8.4. In reference to section 4.8.4, exposure assessment features in the EUSES model cover the entire life cycle of substances as well as their fate in all environmental compartments at three spatial scales: the

personal scale for consumers and workers, the local scale for humans near point sources and the regional scale for humans exposed as a result of all releases in a larger region. Detailed information on both types of approaches is provided in EHC 214 (IPCS, 2000).

Finally, comprehensive summaries of exposure information for specific chemicals are available in many of the directories of resources and cross-cutting resources identified in sections 4.4 and 4.5. Those resources include exposure concentrations and rates of exposure that are reported in the scientific literature for both occupational and environmental exposure scenarios in various countries and regions of the world.

4.8.6 Exposure factors

Exposure factors are generic or default values that describe contact rates with media, including inhalation rate, drinking-water consumption and food consumption. Exposure factors also include anthropometric features of people, such as body weight and body surface area. Default exposure factors published by WHO are summarized in Table 19.

Table 19: Summary of selected exposure factors published by WHO.

Exposure factor	*Value*	*Reference*
Inhalation rate	22 m^3/day	IPCS (1994)
Drinking-water consumption	2 litres/day	WHO (2008a)
	1.4 litres/day	IPCS (1994)
Body weight	60 kg	WHO (2008a)
	64 kg	IPCS (1994)
Food consumption	Diets for clusters of countries	WHO (2010b)

4.9 Risk characterization resources

Information on risk characterization, the last step of risk assessment, is usually addressed by the documents listed in Tables 9 and 10 of section 4.4.1.

5. DRINKING-WATER CASE-STUDY

5.1 Objective

The objective of this fictional case-study is to demonstrate how the principles and road maps that comprise the Toolkit can be used by a public health or related professional to evaluate potential risks of chemical contaminants in drinking-water as a result of emissions from a discrete or point source. The specific road maps for this scenario are shown in Figures 8–11 below.

While the aim of the case-study is to demonstrate the thinking behind all stages of human health risk assessment, including hazard identification, hazard characterization/guidance or guideline value identification, exposure assessment and risk characterization, the user of the Toolkit should be aware that measuring substances in drinking-water for which drinking-water guidelines exist allows a quick and very first assessment of how big a problem there might be and whether there is a need to pursue this.

5.2 Statement of the problem

A metal finishing facility is located on the bank of the fictional Flowing River in a fictional Country X in Asia. Liquid waste from the plating operations pours from a discharge pipe directly into the river in conjunction with the 24 h per day, 7 days per week operating schedule of the facility. Additional information on the plant operations, such as the rate of production and the content of the liquid waste, is not available. The Flowing River flows directly through the community of Rivertown, which is a short distance downstream of the plating facility. Water from the river is used by the residents of Rivertown for drinking, cooking and bathing. Preliminary research by the official Rivertown Department of Environmental Health (RDEH) has identified cadmium as a by-product of chrome plating operations. To address public health concerns, RDEH undertakes an evaluation of the potential health risks of cadmium releases into the Flowing River.

The questions to be asked are as follows (see also Figure 2):

- What is the identity of the chemical of concern?
- Is the chemical potentially hazardous to humans?
- What properties of the chemical have the potential to cause adverse health effects?
- Do guidance or guideline values from international organizations exist for the chemical?
- What assumptions about exposure and dose are incorporated into guidance or guideline values for the chemical?
- Do those assumptions reflect conditions specific to the local situation?
- In what ways could people come into contact with the chemical?
- How much exposure is likely to occur?
- For how long is exposure likely to occur?
- What metric of exposure is appropriate for characterizing health risks?
- How does the estimated exposure compare with the health-based guidance or guideline values?

5.3 Hazard identification

What is the identity of the chemical of concern?

It is probable that cadmium is one of the hazards and may be the only hazard. However, while carrying out an investigation on cadmium, it is important to seek further information from the company and other local authorities as to what else (e.g. cyanide) might be in the effluent.

In situations where an industrial process or operation is of interest, the assessor should search the emission scenario documents described in section 4.8.2 for information relevant to the current situation. The full-text search feature of the INCHEM database can also be helpful. In addition to these international resources, permits or building plans that may have been filed with local or provincial authorities may also contain useful information about health hazards associated with the metal finishing operation. Also, initiating dialogues with representatives of the facility and other members of the community is an essential step in identifying all contaminants of concern. Finally, collection and analyses of wastewater should be considered in identifying contaminants.

> *Output: Cadmium is identified as the chemical of immediate concern. Other chemicals might also be of concern, including cyanide, and action should be taken to identify these.*

Is cadmium potentially hazardous to humans?

Data on the effects of cadmium can be found by looking in the INCHEM database. Selecting the entry for cadmium brings the user to the ICSC for that chemical. The Chemical Abstracts Service (CAS) number is found in the first row of the card: CAS No. 7440-43-9. Other information contained on the card includes a brief list of acute hazards and symptoms as well as how cadmium is identified in the United Nations (UN) and EU classification schemes. According to the UN classification system for the transport of dangerous goods, cadmium is in UN Hazard Class 6.1: *Poisonous (toxic) substance*. According to the EU system, cadmium is classified as very toxic, with the risk phrases R45 (*May cause cancer*); R26 (*Very toxic by inhalation*); R48/23/25 (*Toxic: danger of serious damage to health by prolonged inhalation and if swallowed*); R62 (*Possible risk of impaired fertility*); R63 (*Possible risk of harm to the unborn child*); and R68 (*Possible risk of irreversible effects*).

Review of the IARC monographs (IARC, 2010) confirms that cadmium has been classified in Group 1: *Carcinogenic to humans*.

> *Output: Knowledge that cadmium is a hazardous chemical and that it has been classified to be very toxic and carcinogenic to humans.*

A road map for the hazard identification step of the drinking-water case-study is shown in Figure 8.

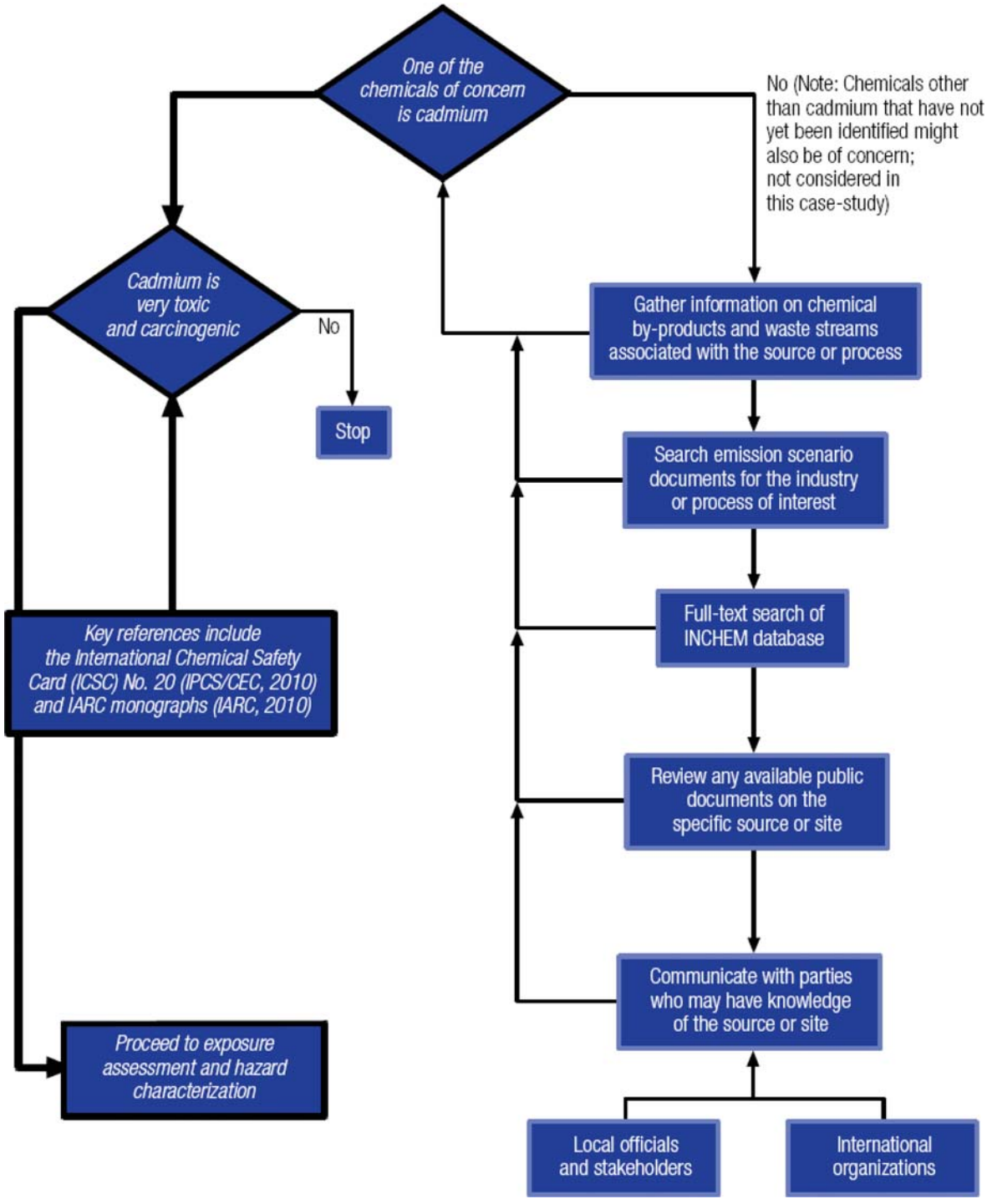


Figure 8: Case-specific road map for hazard identification: drinking-water case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

5.4 Hazard characterization/guidance or guideline value identification

What properties of the chemical have the potential to cause adverse health effects?

Searching the INCHEM database in the previous step brought the user also to the WHO Food Additives Series, No. 52: Cadmium (addendum) (FAO/WHO, 2004) and other documents, including an EHC monograph (IPCS, 1992), that describe the toxicological properties of cadmium.

> *Output: Knowledge about the principal toxic end-points of cadmium, considered to be kidney dysfunction, lung damage, hepatic injury, bone deficiencies, hypertension and cancer, depending on route, dose and duration of exposure, as well as knowledge that cadmium accumulates in the kidney.*

Do health-based guidance or guideline values from international organizations exist for cadmium?

Sources mentioned in section 4.7 provide information on existing guidance and guideline values. JECFA recommends a PTWI for cadmium of 0.007 mg/kg body weight. The WHO *Guidelines for drinking-water quality* contain a guideline value for cadmium of 0.003 mg/l (Table 20). WHO has not published a relevant health-based air quality guideline for cadmium (see also Tables 6 and 7).

Table 20: International guidance and guideline values for cadmium.

Type of value	*Guidance or guideline value*	*Reference*	*URL*
Food guidance value	0.007 mg/kg body weight (PTWI)	FAO/WHO (2010a)	http://apps.who.int/ipsc/database/evaluations/chemical.aspx?chemID=1376
Drinking-water guideline value	0.003 mg/l	WHO (2008a)	http://www.who.int/water_sanitation_health/dwq/GDW12rev1and2.pdf (p. 317)

> *Output: Knowledge about international guidance and guideline values for cadmium in drinking-water and food.*

What assumptions about exposure and dose are incorporated into the WHO drinking-water guideline value for cadmium?

Water is the most important pathway of exposure (see section 5.5); therefore, the WHO drinking-water guideline for cadmium is of main interest. The WHO drinking-water guideline for cadmium is described in section 12.17 of the current edition of the *Guidelines for drinking-water quality* (WHO, 2008a). According to the table of key items presented in that section, the guideline value is based on a default water consumption rate of 2 litres per day, a body weight of 60 kg and an allocation to water of 10% of the PTWI. It is recognized that population average water consumption rates can vary significantly, perhaps by a factor of 2–4, in different parts of the world, particularly where consumers are engaged in manual labour in hot climates. Similarly, typical body weights can also vary among countries or regions, although the range of uncertainty is likely to be less than ±25%. Overall, the range of uncertainty about water consumption rates and body weights is quite small in comparison

with the much larger range in toxicological uncertainty that exists for the vast majority of chemicals. Consequently, the default assumptions for those parameters are likely to be adequate in nearly all situations.

In order to account for the variations in exposure from different sources in different parts of the world, a certain proportion of the ADI, TDI, PTWI, etc., generally between 1% and 80%, is allocated to drinking-water in setting drinking-water guideline values for many chemicals. Where relevant exposure data are available, authorities are encouraged to develop context-specific guideline values that are tailored to local circumstances and conditions. For example, in areas where the intake of a particular contaminant in drinking-water is known to be much greater than that from other sources (e.g. food and air), it may be appropriate to allocate a greater proportion of the ADI, TDI, PTWI, etc., to drinking-water to derive a guideline value more suited to the local conditions.

> *Output: The WHO drinking-water guideline value for cadmium is based on a default water consumption rate of 2 litres per day, a body weight of 60 kg and an allocation to water of 10% of the PTWI.*

Do those assumptions reflect conditions specific to the local situation?

In the case of Rivertown, the RDEH would require detailed information on food consumption patterns, cadmium levels in specific foods and levels of cadmium in air and soil to consider deriving a context-specific drinking-water guideline value for cadmium The water is not used for irrigation of crops, so, in the absence of information on contact rates, body weight, absorption fraction and total exposure to cadmium from the general diet specific to local conditions, the RDEH elects to rely upon the WHO drinking-water guideline value for cadmium of 0.003 mg/l in the risk assessment. This is an appropriate decision, as the WHO drinking-water guideline values account for ingestion through food and are considered, in most cases, sufficient to account for intake of contaminants through inhalation and dermal absorption.

> *Output: The WHO drinking-water guideline value for cadmium of 0.003 mg/l is appropriate to be used under the given local conditions.*

A road map for the hazard characterization step of the drinking-water case-study is shown in Figure 9.

5.5 Exposure assessment

In the context of the risk assessment Toolkit, the goal of the exposure assessment is to obtain an estimate of exposure concentration or rate that can be compared with the appropriate guidance or guideline value. As described in section 3, several combinations of guidance or guideline values and exposure metrics are possible, depending upon the medium (or media) and exposure route(s) that are most appropriate for the situation.

In what ways could people come into contact with the chemical?

The river forms the basis of the water supply to the town, so exposure through drinking-water is likely. Water is also used for cooking and bathing. It is important to consider whether drinking-water consumption is likely to be significantly greater than the 2 litres a day for

adults used by WHO to derive the drinking-water guideline. The water is not used for irrigation, and therefore it is unlikely that food crops are contaminated.

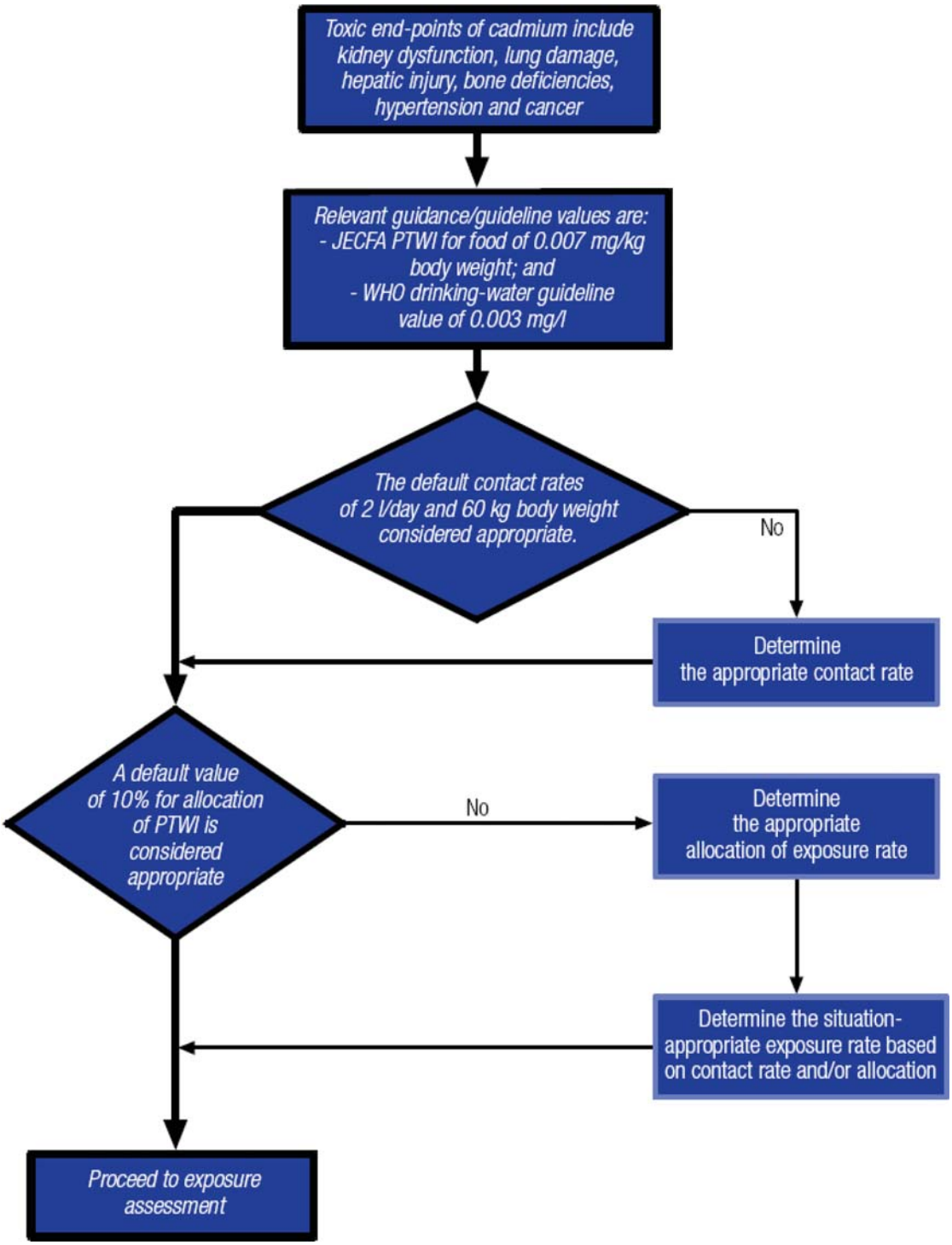


Figure 9: Case-specific road map for hazard characterization/guidance or guideline value identification: drinking-water case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

Output: People come into contact with the chemical through water. Ingestion of drinking-water and water used for cooking and dermal absorption through bathing are the most relevant routes of exposure.

How much exposure is likely to occur?

It is important to obtain further information on the concentration of cadmium (and any other identified contaminants of concern) in order to more accurately assess exposure. Where there is water treatment, it would be appropriate to measure the concentration in water at the water treatment plant after treatment. However, cadmium can also leach from galvanized water supply pipes (usually in buildings), so if such pipes are in use, a sample at a tap in a building using such pipes would be important in judging overall exposure from drinking-water. Crops have not been irrigated, and therefore crop samples are not needed to judge the total exposure to cadmium.

Measurements require that the assessor has access to appropriate protocols and supplies for sampling, storage, transport and analysis of water samples obtained from the river and drinking-water. This also means that there must be access to suitable analytical facilities with an adequate level of expertise and quality assurance, as incorrect analytical data are highly misleading and have led to inappropriate decisions in a number of circumstances. In some cases, it may be appropriate to use models to determine how much of a contaminant will reach a point downstream from a discharge. Models require information on the discharge rate of cadmium through the effluent pipe that extends from the facility to the river.

Guidance on appropriate measurement and modelling methods is provided in several documents and other materials produced by international organizations and countries. In particular, *Guidance on Information Requirements and Chemical Safety Assessment*, prepared in conjunction with the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the EU, provides a detailed discussion of measurement and modelling approaches (ECHA, 2010). Measurement and modelling approaches both require a study design that will allow the assessment question to be answered. General guidance on the design and implementation of exposure investigations is provided in EHC 214 (IPCS, 2000).

Unable to obtain information needed to model the concentration of cadmium in water drawn from the river, the RDEH makes the decision to estimate long-term average exposure concentrations from direct measurements. Information on sampling and analysis methods is available in EHCs and CICADs prepared for specific chemicals. EHC 134 on cadmium (IPCS, 1992) contains introductory information on analytical methods for cadmium, including collection and preparation of samples, separation and concentration, methods for quantitative determination and quality control. Specific methods for sampling water and analysis of cadmium and other metals are available from country resources, such as the USEPA's *Method 1669: Sampling ambient water for trace metals at EPA water quality criteria levels* (USEPA, 1996).

The RDEH collects water samples from three locations on 5 separate days: upstream of the metal finishing facility, downstream of the metal finishing facility and from the tap of the town hall building. The average concentrations of cadmium in the samples obtained from those locations are shown in Table 21.

Table 21: Cadmium concentrations in five samples of water obtained from each of three locations in the vicinity of Rivertown.

Location	*Average concentration (µg/l)*	*Concentration range (µg/l)*
Upstream of facility	<LOD	<LOD–0.2
Downstream of facility	0.4	0.1–1.0
Town hall water	0.3	0.2–0.8

LOD, limit of detection (0.1 µg/l)

The results of the water sampling indicate that concentrations of cadmium downstream of the metal finishing facility are greater than concentrations upstream of the facility. The results also indicate that cadmium concentrations in potable water received from the Flowing River are approximately equal to the levels in the river downstream of the facility.

> *Output: A quantitative estimate of cadmium exposure, with levels greater downstream of the facility compared with upstream and with concentrations in drinking-water approximately equal to the downstream levels.*

For how long is exposure likely to occur?

The assessor has knowledge that the facility routinely operates 24 h per day, 7 days per week. Therefore, long-term average conditions and long-term exposure are of primary interest. The assessor should also consider variation in operations of the facility or flow of the river that could result in transient increases in exposure concentrations.

> *Output: Knowledge that long-term exposure is of concern, with exposure levels that can vary over time as a result of operations of the facility.*

What metric of exposure is appropriate for characterizing health risks?

Having selected the environmental medium (water), exposure route (mainly ingestion) and exposure duration (long-term) of interest, the next step is to determine if an international guidance or guideline value exists that corresponds to those criteria. In this case, data gathering conducted in support of the hazard characterization step revealed that WHO has established a guideline value of 0.003 mg/l for long-term average concentrations of cadmium in drinking-water. The form of the guideline value dictates the form of the exposure estimate required for the risk characterization step. Thus, the risk assessor in this case-study requires an estimate of long-term average concentrations of cadmium in water drawn from the Flowing River in order to proceed to the risk characterization step.

> *Output: Knowledge that a long-term average exposure concentration is needed to perform the risk characterization.*

A road map for the exposure assessment step of the drinking-water case-study is shown in Figure 10.

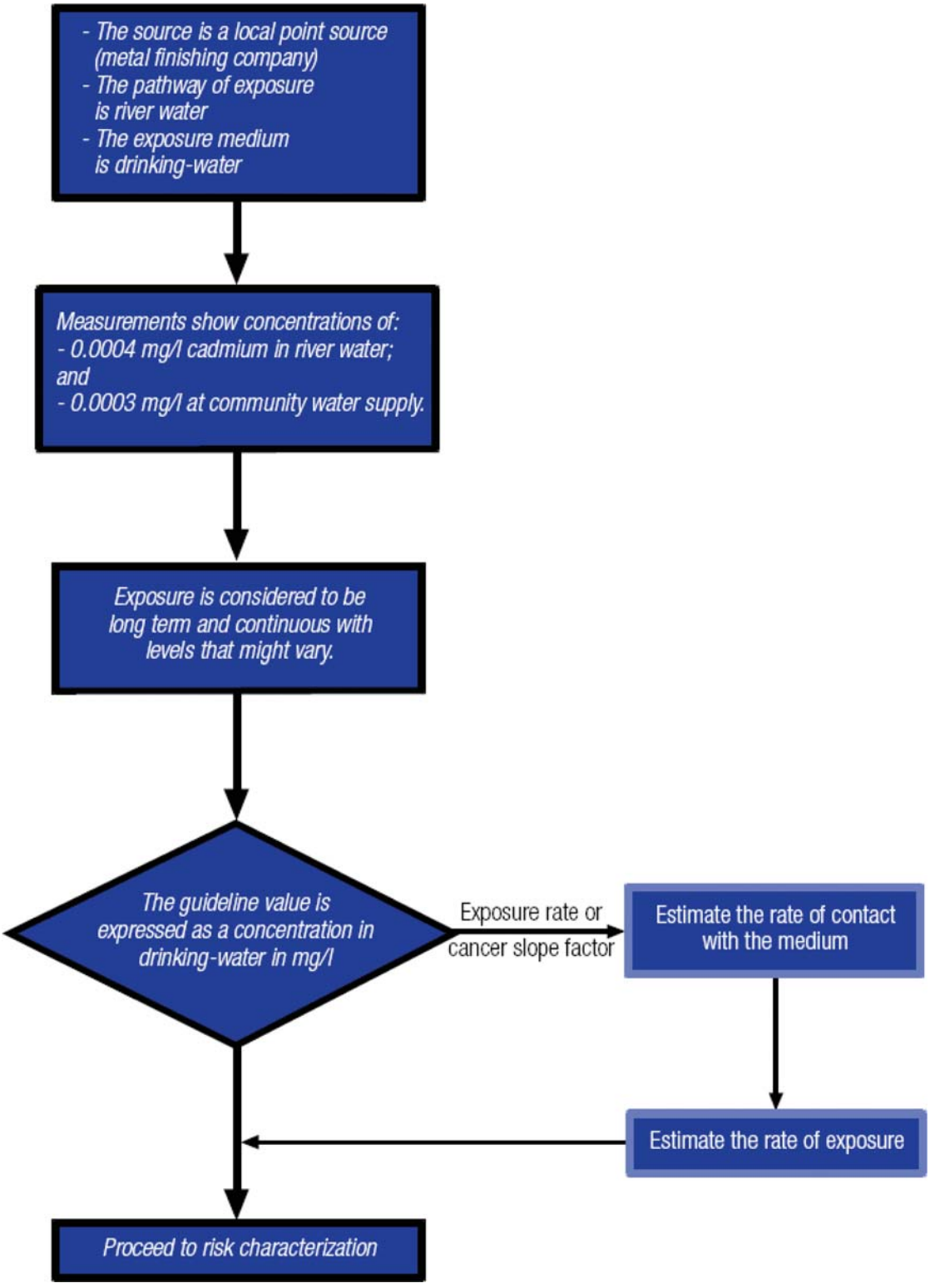


Figure 10: Case-specific road map for exposure assessment: drinking-water case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

5.6 Risk characterization

How does the estimated exposure compare with the guidance or guideline values?

The objective of the risk characterization step is to address the risk assessment question by combining the information gathered on exposure and hazard characterization. As noted in section 3.3.4, health risk can be characterized in various ways. In many cases, risk characterization consists of comparing an estimate of chemical exposure with a guidance or guideline value. The exposure and guidance or guideline value can be expressed as either a concentration or an exposure rate. The exposure and guidance or guideline values should reflect the same averaging time; if not, the assessor should be cognizant of any differences when interpreting the results of the risk characterization.

Where exposure is short term and the guidance or guideline value long term, this provides a more conservative assessment. If the long-term guidance or guideline value is exceeded in short-term exposure, it would be necessary to consider other questions. For example, is exposure from food such that the allocation of the PTWI to water can be increased without exceeding the PTWI? If the exposure of interest is still greater than the PTWI, it is appropriate to examine the derivation of the PTWI to determine if the safety/uncertainty factors are excessively conservative for the situation. For example, an additional factor to allow for extrapolation from medium-term to long-term exposure would not be appropriate if exposure was actually short term.

Referring to the first step in the flow chart shown in Figure 11, the objective of the RDEH was to evaluate potential health risks associated with cadmium releases into the Flowing River. Based upon the available risk-based criteria for cadmium in drinking-water, it is apparent that the assessment involves comparing estimated exposures with a health-based guideline value. In this case, the value is 0.003 mg/l, the WHO guideline value for cadmium in drinking-water. Turning to the exposure metrics, at least two are available: 1) the average concentration of cadmium in drinking-water downstream of the metal finishing facility (0.0004 mg/l) and 2) the average concentration of cadmium in water drawn from the community water supply (0.0003 mg/l). Taking the ratio of the exposure to the guideline value, the hazard quotient is calculated to be approximately 0.1 in this case. Exposures are therefore estimated to be less than the guideline value.

If the concentration in the river was below but close to the guideline value, it would still be appropriate to determine whether there was potential exposure from the plumbing system.

> *Output: The hazard quotient is approximately 0.1 for cadmium in drinking-water. As a result, the cadmium exposures are unlikely to result in any adverse health effects.*

In terms of actions, there is no immediate cause for concern. However, it would be appropriate to consider whether it was feasible to reduce concentrations in the effluent to prevent accumulation of cadmium in sediment that could be mobilized at a later time if conditions change.

A road map for the risk characterization step of the drinking-water case-study is shown in Figure 11.

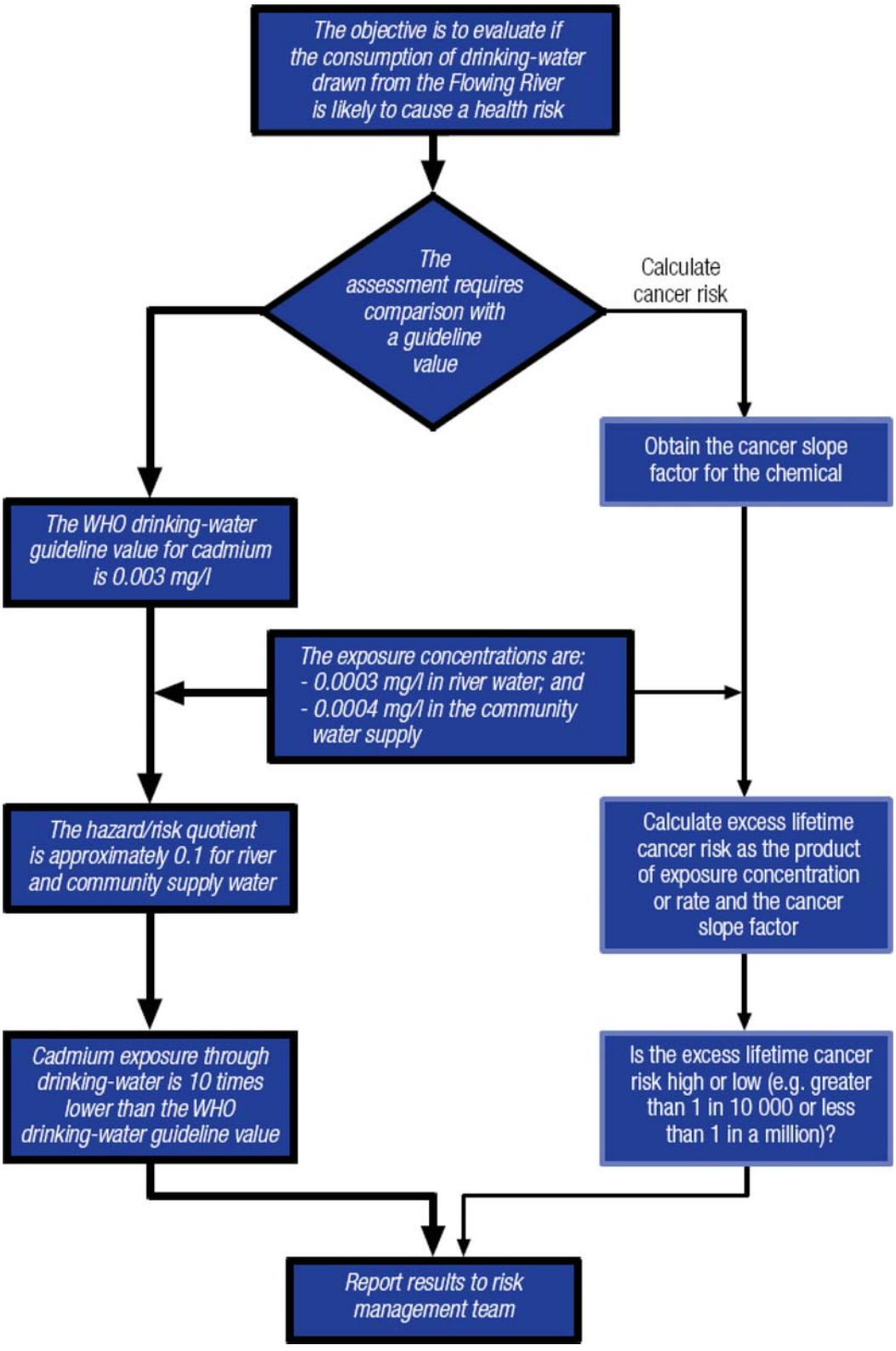


Figure 11: Case-specific road map for risk characterization: drinking-water case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

5.7 Summary

An assessment was conducted of potential health risks associated with ingestion of cadmium introduced into a community water supply as a result of emissions to surface water from a metal finishing facility. Cadmium is reported to accumulate in the kidney, which is also the main target for cadmium toxicity. Consequently, potential health risks of long-term average exposures to cadmium in drinking-water are the primary concern of local authorities. The WHO guideline value for cadmium in drinking-water was selected as the most appropriate guidance or guideline value for evaluation of potential risk. The exposure assessment was based on measurements of cadmium in drinking-water on 5 separate days. Average concentrations of cadmium in river water and drinking-water samples were consistent with contributions from the metal finishing facility, yet were approximately 10 times below the WHO guideline value. This evaluation indicates that risks of adverse health effects from cadmium exposures associated with the facility are relatively low. Authorities should consider obtaining additional plant information and sampling data needed to confirm these findings with exposure periods representative of longer-term average conditions.

6. RESPIRABLE PARTICULATE MATTER (PM_{10}) CASE-STUDY

6.1 Objective

The objective of this case-study is to demonstrate how the principles and road maps of the Toolkit can be used to guide a review of the scientific factors that should be considered in the adoption or amendment of national air quality standards for respirable particulate matter, defined by WHO as aerosols with aerodynamic diameter less than 10 μm (PM_{10}) (see also section 3.2) (WHO, 2006). Specific road maps are shown in Figures 12–14 below.

The questions to be asked are as follows (see also Figure 2):

- What is the identity of the chemical of concern?
- Is the chemical potentially hazardous to humans?
- What properties of the chemical have the potential to cause adverse health effects?
- Do guidance or guideline values from international organizations exist for the chemical?
- What assumptions about exposure and dose are incorporated into guidance or guideline values for the chemical?
- Do those assumptions reflect conditions specific to the local situation?
- In what ways could people come into contact with the chemical?
- For how long is exposure likely to occur?
- What metric of exposure is appropriate for characterizing health risks?

Questions not addressed in this case-study are:

- How much exposure is likely to occur?
- How does the estimated exposure compare with the health-based guidance or guideline values?

PM_{10} was selected for a case-study because of the unique attributes of this ubiquitous and well-studied air pollutant. PM_{10} is a mixture of chemical species, water and biological components and therefore differs from the individual chemical substances considered elsewhere in this document. In addition, epidemiological studies provide strong evidence that health effects occur in human populations at current levels of respirable particulate matter.

6.2 Statement of the problem

Given findings from epidemiological studies and a growing concern about the impacts of ambient respirable particles (or PM_{10}) on health, Country A is interested in setting a national standard to regulate ambient PM_{10} concentrations. The situation is that only limited PM_{10} monitoring data are available in the country and in surrounding countries. Further, there is limited evidence from Country A of associations between increased ambient PM_{10} concentrations and daily mortality, with supporting evidence from other countries in the region.

At this time, the pollutant of interest to Country A is limited to respirable particles (PM_{10}), not its individual components,[1] and the default governmental standard is the WHO air quality guidelines for PM_{10}.

The WHO air quality guidelines were developed based on scientific evidence of the risks posed by PM_{10} pollution to human health. It is important to note that these guidelines are not intended to be fully protective of public health, as there is no identified "safe" concentration of ambient PM_{10}. The guidelines differ from PM_{10} standards set by individual countries, as they were developed for a wide variety of situations across the world and do not take into account individual country characteristics and needs. For individual countries, the WHO guidelines may need to be amended in light of scientific factors, such as PM_{10} sources, populations at risk and geography, and policy-related factors, such as technological feasibility and economic considerations.

6.3 Hazard identification

What is the identity of the chemical of concern?

The hazard identification process for this example is relatively straightforward and follows the flow chart in Figure 12. As shown in this figure, determining the identity of the chemical of interest is the first step in the hazard identification process. In this case, the identity of the chemical is known to be ambient PM_{10}.

> *Output: Identification of PM_{10} as the pollutant of interest.*

Is PM_{10} potentially hazardous to humans?

WHO has evaluated the health effects of particulate matter (PM), including PM_{10}. The evidence on airborne PM and its public health impact is consistent in showing adverse health effects at exposures that are currently experienced by urban populations in both developed and developing countries (WHO, 2006).

> *Output: Knowledge that PM, including PM_{10}, is hazardous to humans at concentrations experienced by urban populations worldwide.*

6.4 Hazard characterization/guidance or guideline value identification

What properties of PM_{10} have the potential to cause adverse health effects?

WHO (2006) reports that the range of health effects caused by PM_{10} is broad, but that effects associated with short-term and long-term exposures are predominantly to the respiratory and cardiovascular systems, with recent scientific studies finding adverse health impacts at short exposures, on the order of 1–4 h. All populations are affected, but susceptibility to the pollutant may vary with health status or age. The risk for various outcomes has been shown

[1] Information about the specific components of PM_{10} may be important to consider for standard-setting purposes, as scientific studies show individual PM_{10} components to have different health risks. Further, for regulatory purposes, the PM_{10} components may provide important information, as they can help to establish appropriate source control strategies.

to increase with exposure, and there is little evidence to suggest a threshold below which no adverse health effects would be anticipated.

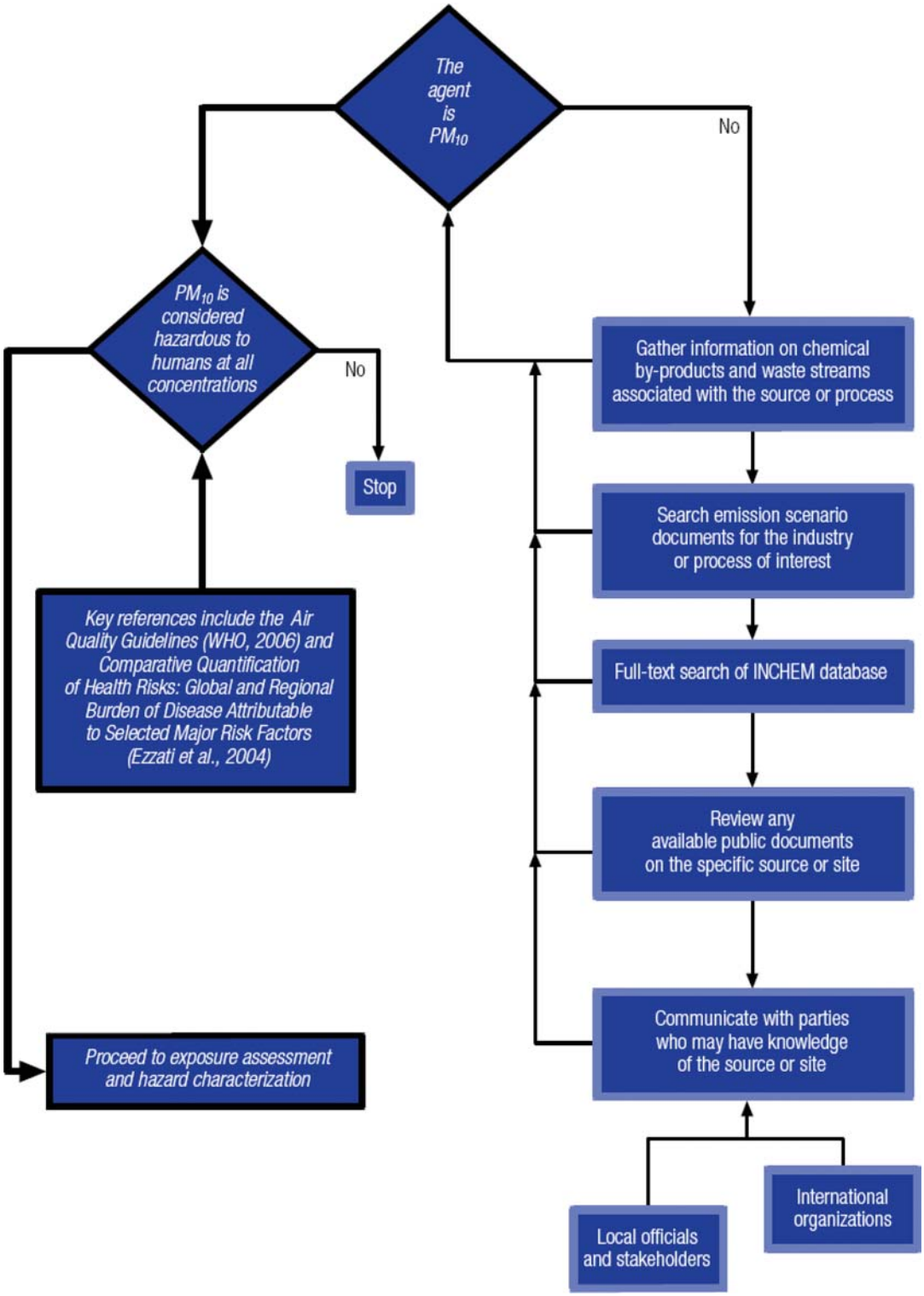


Figure 12: Case-specific road map for hazard identification: particulate matter case-study. Bold lines indicate the flow of information gathering and analysis described in the text.

Output: Description of health hazards for PM_{10} based on results from epidemiological studies.

Do health-based guidance or guideline values from international organizations exist for PM_{10}?

WHO has set international guidelines for ambient PM_{10} of 20 µg/m^3 averaged over a year and 50 µg/m^3 averaged over 24 h (Table 22). These are the lowest levels at which total, cardiopulmonary and lung cancer mortality has been shown to increase in response to long-term exposure to PM.

Table 22: WHO air quality guideline values for PM_{10}.

Type of value	*Guideline value*	*Reference*	*URL*
Annual mean	20 µg/m^3	WHO (2006)	http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf
24-hour mean	50 µg/m^3	WHO (2006)	http://whqlibdoc.who.int/hq/2006/WHO_SDE_PHE_OEH_06.02_eng.pdf

Besides the guideline values, three interim targets are defined for PM_{10}. These have been shown to be achievable with successive and sustained abatement measures. Countries may find these interim targets particularly helpful in gauging progress over time in the difficult process of steadily reducing population exposures to PM, including PM_{10} (WHO, 2006) (Table 23).

Table 23: WHO interim targets for PM_{10}: annual mean concentrations.

Interim target	*PM_{10} concentration*	*Basis for the selected level*
1	70 µg/m^3	This level is associated with about a 15% higher long-term mortality risk relative to the annual air quality guideline mentioned in Table 22.
2	50 µg/m^3	In addition to other health benefits, this level lowers the risk of premature mortality by approximately 6% (2–11%) relative to the interim target-1 level.
3	30 µg/m^3	In addition to other health benefits, this level reduces the mortality risk by approximately 6% (2–11%) relative to the interim target-2 level.

Other countries have set their own PM_{10} standards. For example, the EU has established an annual limit of 40 µg/m^3, with this issue to be revisited in subsequent years (EC, 2010e). Interestingly, standards and guidelines for PM_{10} are somewhat unique, in that they have been established primarily based on findings from epidemiological studies and not toxicological studies.

Output: List of guideline values or standards for PM_{10}.

What assumptions about exposure and dose are incorporated into guideline values for PM_{10}?

As discussed in section 6.5, air quality standards for PM_{10} are expressed as concentrations in ambient air given a specific averaging time and often also specifying the location of

compliance monitors. The WHO air quality guidelines and standards set by the EU, the United States of America (USA) and other countries reflect assumptions about the relative importance of observed health outcomes (e.g. mortality being more important than asthma incidence), population characteristics and activity patterns of the population (e.g. number of potentially susceptible individuals, time spent outside, indoor PM_{10} sources) and source characteristics and locations (e.g. local versus regional sources, location of major PM_{10} sources relative to populations).

> *Output: Knowledge about the health outcomes, population characteristics, activity patterns of the population, pollution source characteristics and locations reflected in the guideline values or standards for PM_{10}.*

Do those assumptions reflect conditions specific to the local conditions?

The relative importance of the assumptions is likely subjective, as are their relevance and applicability to the standard-setting country. If, however, the assumptions are found to be appropriate for the standard-setting country as well, then risk assessors may decide to adopt the PM_{10} guideline set by WHO or standard set by another governmental group or country. Otherwise, risk assessors may want to seek additional information to identify hazard characterization information applicable to their country. This information can be obtained from a variety of sources, including 1) a review of the scientific literature for PM_{10}, with specific emphasis on studies from Country A or surrounding countries, 2) PM_{10} standards for Country A or other countries and 3) measurements or estimates of background PM_{10} concentrations, which can include PM_{10} that originates from anthropogenic sources outside Country A. A road map for the hazard characterization step is shown in Figure 13.

> *Output: Selection of the appropriate PM_{10} guideline value or standard for specific exposure averaging times.*

6.5 Exposure assessment

In what ways could people come into contact with PM_{10}?

In this case-study, the assessor knows that PM_{10} is present in ambient air. Therefore, air is the environmental medium of interest, with inhalation being the only route of exposure. The frequency of exposure is likely to be constant: people may be exposed to ambient PM_{10} even when inside, as ambient PM_{10} can readily enter homes and other buildings. Although the level of exposure may differ inside compared with outside, epidemiological studies are generally based on ambient concentrations. As a result, risks estimated by these studies intrinsically take into account the building types and activity patterns of their study populations. As these factors can differ substantially by country and even city, Country A should consider giving more weight to risk estimates obtained from epidemiological studies conducted in populations with activity patterns and housing stock that are similar to those in Country A.

> *Output: Identification of air as the relevant environmental medium, inhalation as the exposure route and exposure frequency as constant. Also, qualitative determination of the importance of housing stock and activity patterns in evaluating PM_{10} exposures.*

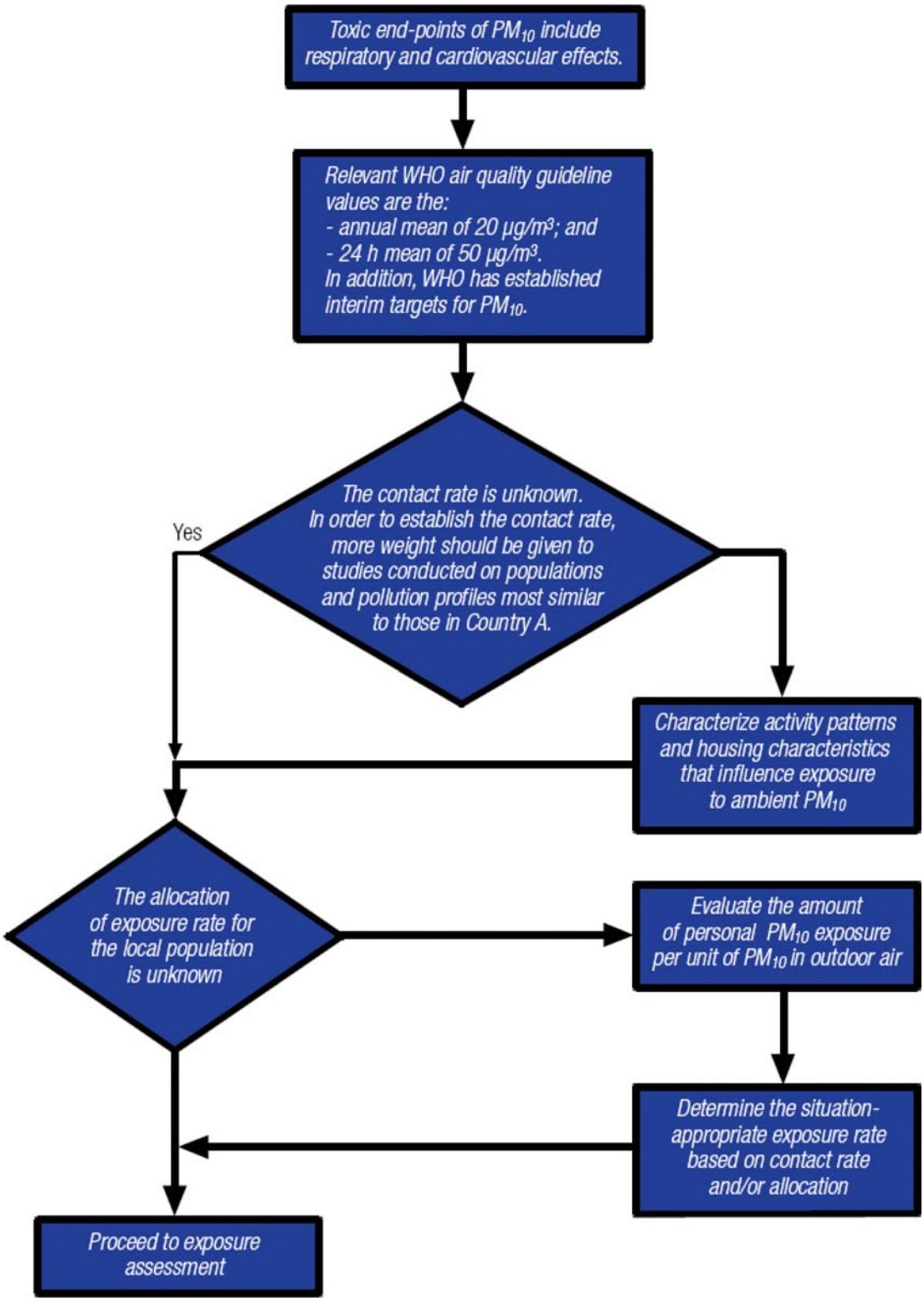


Figure 13: Case-specific road map for hazard characterization/guidance or guideline value identification: particulate matter case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

For how long is exposure likely to occur?

Decisions about the appropriate averaging time for the PM_{10} standard are more complicated, as consideration should be paid not only to the exposure averaging time (e.g. year, day, hour or minute), but also to how concentrations for this averaging time will be calculated and from which measurements and monitoring sites. Exposure averaging times will generally be based on findings from epidemiological studies, as these studies are the basis of existing PM_{10} standards and guidelines. As reflected in the WHO annual and daily air quality guidelines, health effect studies conducted in countries across the world have shown both acute and chronic adverse effects to be associated with exposure to PM_{10} in ambient air, suggesting that both a short-term and a long-term standard are appropriate. To address acute adverse effects, WHO set air quality guidelines based on a 24 h averaging time, whereas WHO addressed chronic effects using an annual average guideline. To determine the appropriate averaging time for a PM_{10} standard, countries can rely on the WHO air quality guidelines or on standards set by other countries with similar populations, source profiles and topography. In addition, a variety of other resources may be useful, including 1) PM_{10} monitoring data that show the relationship between annual and daily concentrations and 2) findings from health studies that identify the exposure windows of concern, taking into account country-specific factors, such as geography, sources and their location, and the country's inhabitants.

> *Output: Determination of the appropriate averaging times for an ambient PM_{10} standard, including an evaluation of the importance of separate standards for daily and yearly mean PM_{10} concentrations.*

What metric of exposure is appropriate for characterizing health risks?

Once the appropriate averaging time is selected, the method used to calculate the exposure averaging time and the location of the compliance monitors must be determined. In terms of exposure averaging time, the WHO guidelines average data across 1 year for the annual concentration limit for PM_{10} and across 1 day for the 24 h limit. In contrast, the annual PM_{10} standard in the USA is based on the 3-year average of the weighted annual mean PM_{10} concentrations from single or multiple monitors representing population exposure. Similarly, the daily standard in the USA is based on the 3-year average of the 98th percentile of 24 h concentrations at each monitor representing population exposure. The calculations for the USA are intended to de-emphasize years or days with unusually high concentrations.

The final component of a PM_{10} standard is generally the location of the compliance monitors, which are the monitors from which concentrations will be obtained to determine whether the PM_{10} standard is met or violated. Specification of the compliance monitor locations is generally a key component of a PM_{10} standard, as it will help determine the stringency of the PM_{10} standard and may cause emissions from certain PM_{10} sources to have more impact on standard compliance than others. Possible locations for compliance monitors could include urban settings where people live, rural areas or near roadways or sources; alternatively, concentrations from monitors located across the country could be averaged.

> *Output: Specification of 1) the calculation used to estimate PM_{10} concentrations for the specified exposure averaging times to allow comparisons with the PM_{10} standard and 2) the location and number of compliance monitors.*

The question on *How much exposure is likely to occur?* has not been addressed in this case-study because of a lack of monitoring data. A road map for the exposure assessment step, as applied in this case-study, is shown in Figure 14.

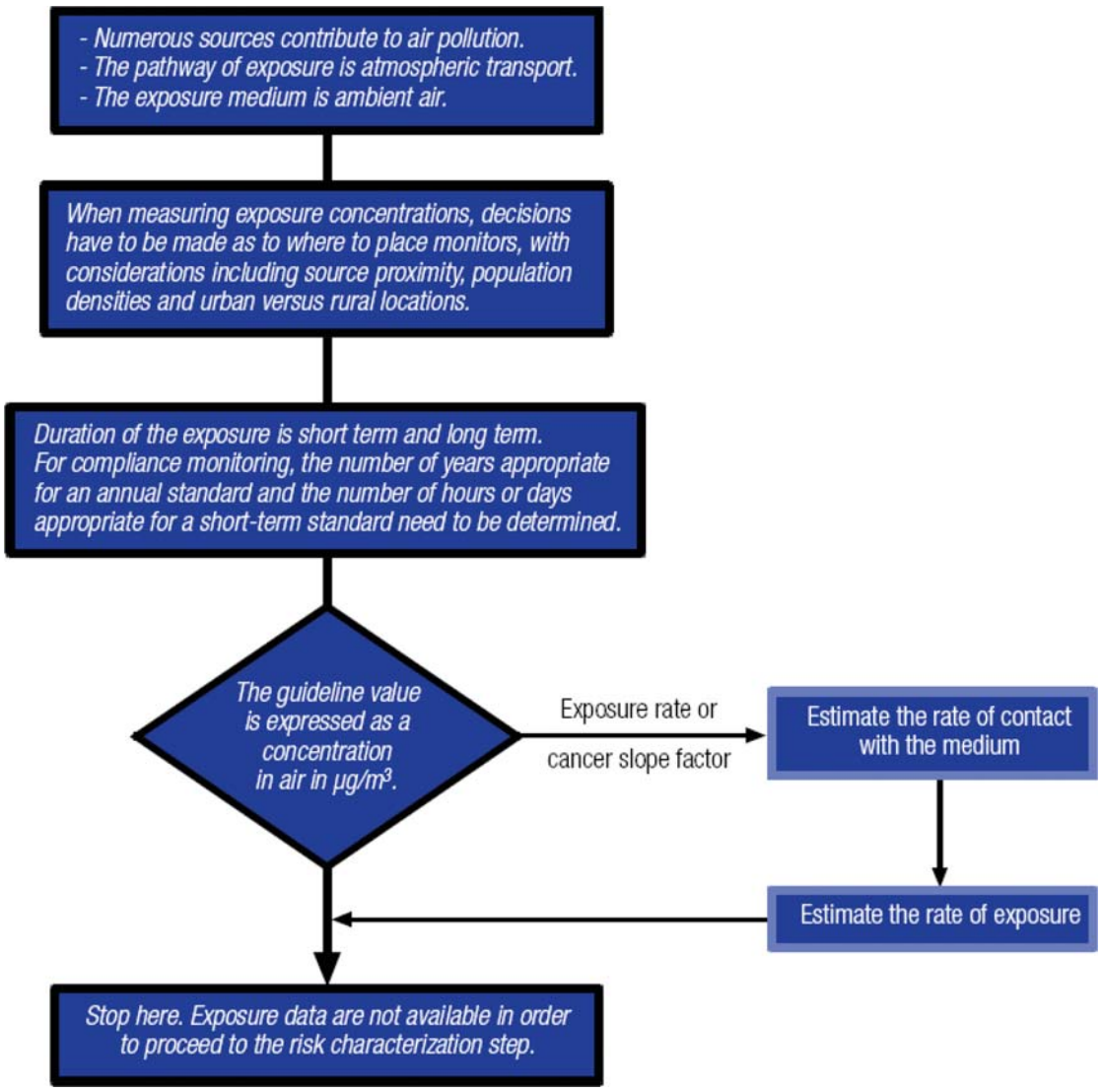


Figure 14: Case-specific road map for exposure assessment: particulate matter case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

6.6 Risk characterization

Because of the fact that exposure information is not available, the question on *How does the estimated exposure compare with the health-based guidance or guideline values?*—and therefore the risk characterization step—is not necessary for this example.

6.7 Summary

Principles and road maps of the Toolkit were used to guide the review of scientific factors to be considered when adopting or amending international available guidance or guideline values or national standards for respirable particulate matter (PM_{10}) for local/national conditions. The range of health effects of PM_{10} is broad, but the effects associated with short-term and long-term exposures are predominantly to the respiratory and cardiovascular systems, with recent scientific studies finding adverse health impacts at short exposures, on the order of 1–4 h. All populations are affected, but susceptibility to the pollutant may vary with health status or age. WHO has set international air quality guidelines for ambient PM_{10} of 20 $\mu g/m^3$ averaged over a year and 50 $\mu g/m^3$ averaged over 24 h. Knowledge about the health outcomes, population characteristics, activity patterns of the population, pollution source characteristics and locations is needed to adopt or amend existing international guidelines or national standards. In addition, the case-study discussed averaging time of a local standard and the method used to calculate the exposure averaging time and the location of the compliance monitors.

7. PESTICIDE CASE-STUDY

7.1 Objective

In making decisions on the use of chemicals, many countries take into account risk assessments completed by other countries or by international organizations. In doing so, these countries are faced with several challenges, one of the most difficult of which is the assessment of whether and how the original risk evaluation, including the exposure assessment, is relevant to their own conditions and situations. This assessment must be made before a prior risk evaluation can be used as the basis for national decision-making.

The objective of this fictional case-study is to illustrate how the Toolkit can be used to guide a review of the factors that would need to be considered in using a risk evaluation conducted in one country as the basis for regulatory decision-making in a second country.

7.2 Statement of the problem

In a central African country (Country B) with a population of approximately 12 million, public health officials have observed cases of poisoning in workers using a methyl parathion formulation to control insects in vegetable fields. In order to protect human health, the country considers a regulatory action to severely restrict uses of methyl parathion and conducts a risk assessment of methyl parathion to support such an action. Because risk assessment data specific for their country are not available, risk assessors decide to rely on international data and observations to evaluate the health risks from methyl parathion use in their country and, from this evaluation, to decide whether methyl parathion use should be restricted.

The questions to be asked are as follows (see also Figure 2):

- What is the identity of the chemical of concern?
- Is the chemical potentially hazardous to humans?
- What properties of the chemical have the potential to cause adverse health effects?
- Do guidance or guideline values from international organizations exist for the chemical?
- What assumptions about exposure and dose are incorporated into guidance or guideline values for the chemical?
- Do those assumptions reflect conditions specific to the local situation?
- In what ways could people come into contact with the chemical?
- How much exposure is likely to occur?
- For how long is exposure likely to occur?
- What metric of exposure is appropriate for characterizing health risks?
- How does the estimated exposure compare with the health-based guidance or guideline values?

7.3 Hazard identification

What is the identity of the chemical (or formulation) of concern?

A primary source of information on methyl parathion formulations could be a pesticide registry within the country, if, in fact, a registration process existed. In the absence of a registry, information on methyl parathion formulations may be obtained from a variety of sources, such as industrial permits, import/export records, survey results administered by the Ministry of Agriculture or Ministry of the Interior, surveys of wholesale or retail agricultural supply companies and, finally, owners or managers of agricultural properties.

Information on formulations of methyl parathion is also available from sources outside of the country. The HSDB (see section 4.6.6), for example, provides information on the presence of methyl parathion in technical-grade products and numerous ready-to-use products. The technical-grade products include pure methyl parathion as a solid and an 80% solution of methyl parathion in xylene. Ready-to-use products appear to be 2% methyl parathion available as dusts, emulsifiable concentrates, ultra-low-volume liquids and wettable powders.

In addition to the codified chemical identity information available from the HSDB, interviews with insecticide applicators and observations of application procedures made by personnel of the Department of Environmental Health (DEH) in Country B indicate that wettable powders and emulsifiable concentrates of methyl parathion are the primary forms of methyl parathion used in the country. The DEH noted the product names Kilex Parathion and Metaphos during their inspections and recorded that the labels indicated 2% methyl parathion concentrations.

> *Output: Wettable powders and emulsifiable concentrates are the primary forms of methyl parathion used in the country. Applied products contain a 2% methyl parathion concentration.*

Is the chemical (or formulation) potentially hazardous to humans?

The toxicological properties of methyl parathion have been classified by numerous international and national agencies, including WHO, the UN and the EU:

- WHO Recommended Classification of Pesticides by Hazard: Category 1a (*Extremely hazardous*) (WHO, 2005)
- IARC: Group 3 (*Not classifiable as to its carcinogenicity to humans*) (IARC, 2010)
- UN Recommendations for the Transport of Dangerous Goods: Hazard Class 6.1 (*Poisonous (toxic) substance*) (UNECE, 2010b)
- EU System for Classification and Labelling: T+ (*Very toxic*) with the following risk phrases concerning toxicity (EC, 2010b):
  - R24 (*Toxic in contact with skin*)
  - R26/28 (*Very toxic by inhalation and if swallowed*)
  - R48/22 (*Harmful: danger of serious damage to health by prolonged exposure if swallowed*)

> *Output: Methyl parathion is very toxic to humans when inhaled and ingested and when in contact with skin.*

What properties of the chemical (or formulation) have the potential to cause adverse health effects?

Toxicological information is available from EHC 145 on methyl parathion (IPCS, 1993c), the JMPR monograph on the toxicological evaluation of methyl parathion (listed there as parathion-methyl) (WHO, 1996) and the HSDB (2010). As noted in these documents, exposure to methyl parathion at sufficiently high concentrations can result in severe or fatal poisoning, primarily through damage to the peripheral and central nervous systems. Symptoms of poisoning may appear almost immediately (e.g. a few minutes) after exposure. When exposures occur through skin contact, the severity of poisoning symptoms may increase over more than 1 day and may last several days. Exposures to methyl parathion may also cause eye or skin irritation and may adversely affect health in ways that are not clinically apparent—for example, by decreasing blood cholinesterase activities or by increasing chromosomal aberrations. Methyl parathion is readily absorbed via all routes of exposure (oral, dermal, inhalation). Once absorbed, methyl parathion is rapidly distributed to the tissues, with the liver being the primary organ of metabolism and detoxification. Methyl parathion and its metabolic products are eliminated primarily through urine.

> *Output: Exposure can result in severe or fatal poisoning, primarily through damage to the peripheral and central nervous systems. Symptoms of poisoning may appear almost immediately (e.g. a few minutes) after exposure.*

A road map for the hazard identification step of the pesticide case-study is shown in Figure 15.

7.4 Hazard characterization/guidance or guideline value identification

Do guidance or guideline values from international organizations exist for the chemical?

Health-based guidance values available from international resources are listed below:

- In 1995, JMPR re-evaluated methyl parathion and set an ADI of 0–0.003 mg/kg body weight and an ARfD of 0.03 mg/kg body weight (WHO, 1996; IPCS, 2010a).

- The Codex Alimentarius Commission established MRLs for methyl parathion for a variety of food commodities (in milligrams of methyl parathion per kilogram of food item), including apples (0.2 mg/kg), dry beans (0.05 mg/kg), head cabbages (0.05 mg/kg), dried grapes (1 mg/kg), grapes (0.5 mg/kg), nectarines (0.3 mg/kg), peaches (0.3 mg/kg), dry peas (0.3 mg/kg), potatoes (0.05 mg/kg) and sugar beets (0.05 mg/kg) (FAO/WHO, 2010b).

- An OEL of 0.2 mg/m^3 as an 8 h time-weighted average concentration for air has been established by the ACGIH. The OEL can be accessed via the ICSC (IPCS/CEC, 2010).

As a note, a formal WHO drinking-water guideline value for methyl parathion has not been established. In fact, health-based value of 9 µg/l was derived (for guidance purposes), and as this value is much greater than concentrations likely to be found in water, no formal guideline value was deemed necessary (WHO, 2008a). WHO has not published an air quality guideline for methyl parathion.

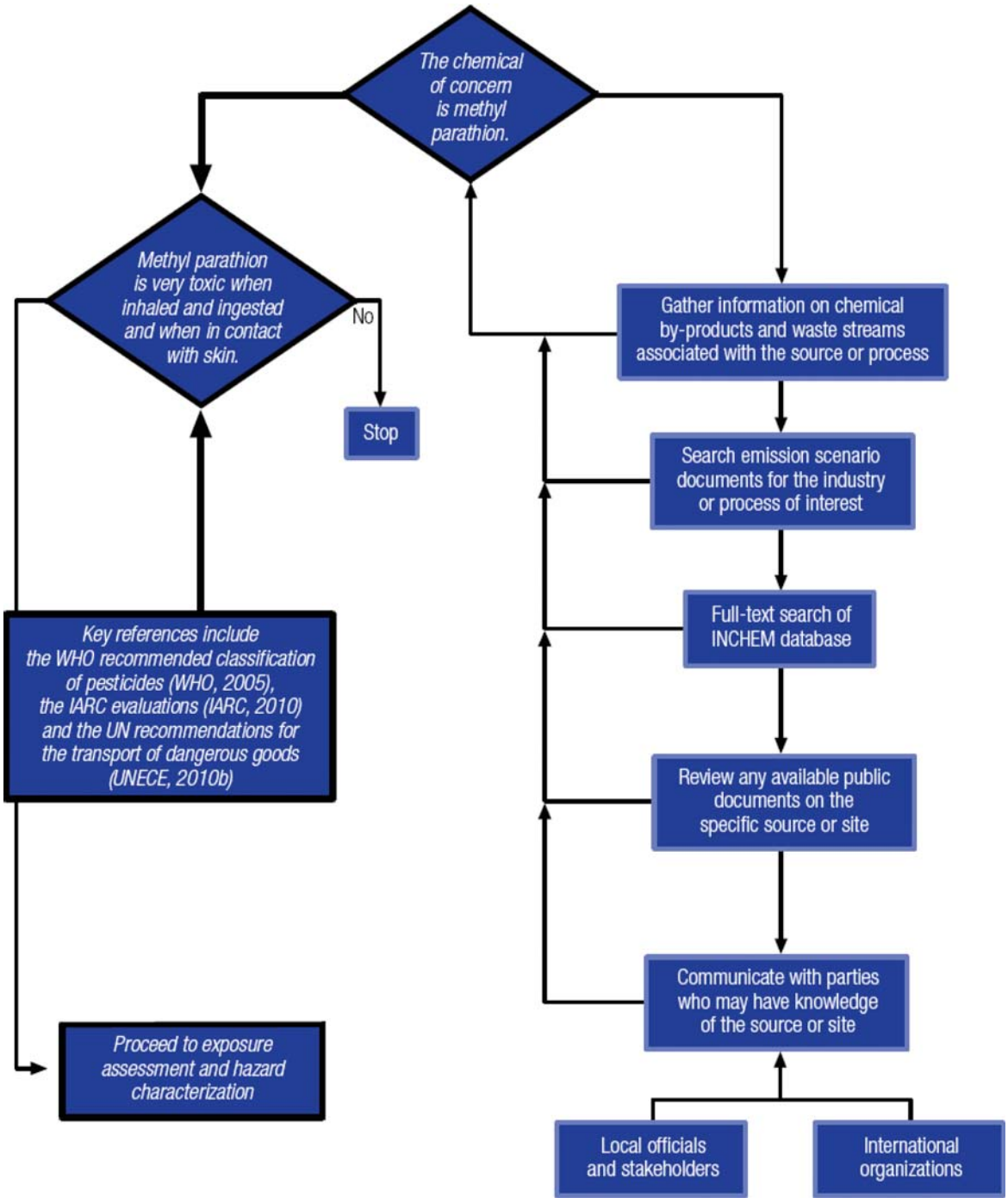


Figure 15: Case-specific road map for hazard identification: pesticide case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

Output: JMPR established an ADI (0–0.003 mg/kg body weight) and an ARfD (0.03 mg/kg body weight) for oral intake (considering mainly food intake). In addition, the Codex Alimentarius Commission established MRLs for a variety of food commodities. An OEL has been established by an American organization. A health-based value of 0.009 mg/l for methyl parathion in drinking-water was derived by WHO for guidance purposes only.

What assumptions about exposure and dose are incorporated into guidance or guideline values for the chemical, and do those assumptions reflect conditions specific to the local situation?

As described in section 7.5, applicators of methyl parathion are anticipated to have the greatest exposure among the population of the country. In the absence of information on contact rates, body weight, absorption fraction and total exposure to methyl parathion specific to local conditions, the DEH elects to rely upon the guidance/guideline values provided above in this section.

A road map for the hazard characterization step of the pesticide case-study is shown in Figure 16.

7.5 Exposure assessment

In what ways could people come into contact with the chemical?

The risk assessor gathered information from within the country that showed that the methyl parathion in the country was primarily applied to vegetable fields using rotary disc sprayers carried on the backs of workers. Through field visits and interviews with agricultural workers, DEH found that workers were not informed about the health risks of methyl parathion and its formulations, nor do they wear personal protective equipment (PPE) during the preparation of the formulation or during the spraying campaigns. The corresponding routes of exposure of workers are expected to be dermal absorption, inhalation and ingestion. Short-term exposures of workers are expected to occur during application, whereas short-term, medium-term and long-term exposures may occur after application until the commodity is harvested. Further, interviews with local medical professionals at local health facilities revealed that an increasing number of patients show neurological symptoms during spraying campaigns. As an official disease surveillance system is not in place, the exact number, distribution and cause of poisonings are not known.

From international information sources—EHC 145 on methyl parathion (IPCS, 1993c) and the HSDB (2010)—the risk assessor learns that methyl parathion is thermally unstable, relatively insoluble in water, poorly soluble in petroleum ether and mineral oils, but soluble in most organic solvents. Important exposure routes include skin contact and, to a lesser degree, inhalation for workers and inhalation and ingestion of contaminated food for the general public. Methyl parathion exposures of workers generally result from both proper use and misuse (or misapplication) of the pesticide during agricultural or forestry practices.

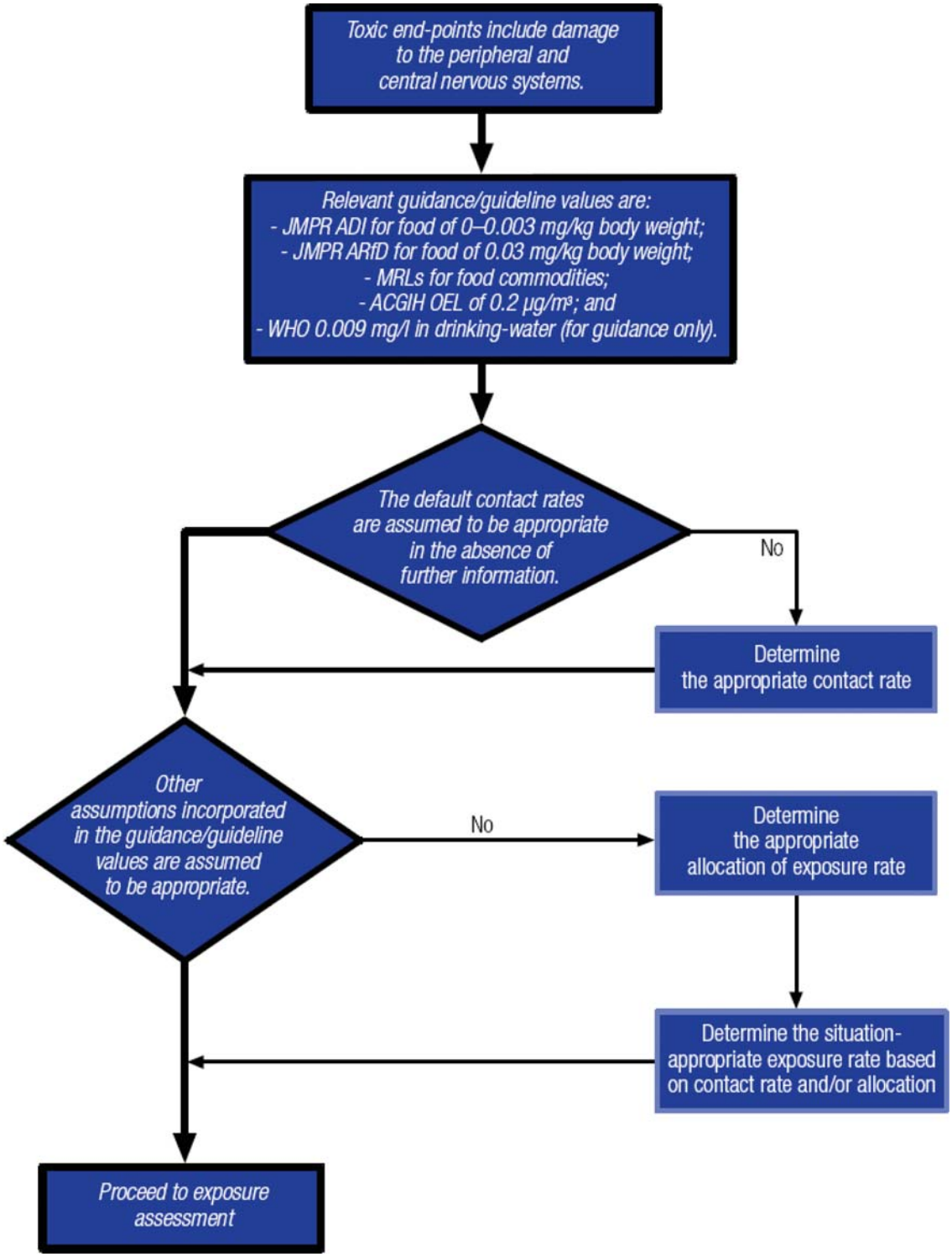


Figure 16: Case-specific road map for hazard characterization/guidance or guideline value identification: pesticide case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

Although occupational exposure studies have not been conducted in the country, information from other countries demonstrates the potential for elevated exposure to methyl parathion among applicators. The HSDB provides information that can be used in support of an exposure assessment. For example, as noted above, the HSDB provides information about critical methyl parathion exposure pathways. Of these critical pathways, the greatest danger to workers exposed to methyl parathion is from skin contact, which may occur during or after its application or where it is formulated. Occupational exposure to methyl parathion may also occur through other pathways, such as inhalation of spray mists. As listed in the HSDB, occupations with potential exposure to methyl parathion include aerial application personnel, area cleanup crews, bagging machine operators, basic manufacturing employees, laundry haulers, drum fillers, drum reconditioning personnel, dump personnel, field checkers, fieldworkers (e.g. exposed to residues on crops and foliage), flag persons, ground applicator vehicle drivers, janitorial personnel, laundry workers, maintenance personnel, mixer and blender operators, refuse haulers, tractor tank loaders, truck loaders and warehouse personnel. In production plants, average air levels are less than 0.1 mg/m^3, with maximum levels of 0.2 mg/m^3. For workers checking cotton for insect damage, dermal exposures are estimated to be 0.7 mg/h. For formulators, median levels of methyl parathion on their non-washed body parts range between 510 and 9200 ng, compared with a range of 74–345 ng for formulators who wash after work.

For the general population, exposures to methyl parathion may occur via inhalation of ambient air and ingestion of contaminated food. The general population is not expected to be exposed to meaningful levels of methyl parathion in drinking-water. Inhalation exposures of the general population are likely to be greatest for populations living near agricultural applications.

> *Output: Methyl parathion is applied to vegetable fields using rotary disc sprayers carried on the backs of workers. Workers are not aware of the health risks of methyl parathion, nor do they wear PPE when preparing formulations and during spraying campaigns. Therefore, the greatest danger to workers exposed to methyl parathion is from skin contact, which may occur during or after its application or where it is formulated. Suspected cases of poisoning during spraying campaigns confirm possible exposure to methyl parathion. The international literature confirms these exposure pathways and routes for workers working with methyl parathion. General population exposure is possible through food, but not confirmed.*

How much exposure is likely to occur?

In the absence of exposure information from Country B, the DEH conducted a literature search that revealed that a non-African country recently assessed the health risks of methyl parathion in order to support regulatory action. The DEH in the African country convened a small, multidisciplinary workshop (involving health, occupational, pesticide, agricultural, environmental and other experts) to evaluate and discuss the relevance of the other country's findings for the African country. Discussions were organized along a template. The template and results are presented in Table 24.

Table 24: Relevance of study findings to an African country: template.

Study element	*Local condition*	*Other country*
1. Is the form in which the pesticide was used at the local level similar to those in the exposure assessment undertaken at the international level or in another country?		
(i) Has the same formulation been used (e.g. liquid, powder, granule, etc.; concentration of active ingredient(s))?	2% ready-to-use product	Wettable powder
(ii) What are the contaminants that should be considered?	Unknown	None
2. Is the pesticide/formulation(s) applied in the same way? Do similar environmental conditions apply?		
Are the use patterns the same, including:		
- Type of use (agriculture, non-agriculture, public health, disinfectant, etc.)?	Agriculture, vegetables	Agriculture, vegetables
- Environment of use (greenhouse, field, indoor, etc.)?	Open field	Open field
- Environmental conditions (temperature, type of soil, etc.)?	Tropical climate	Moderate climate
- Rate, frequency and period of application?	Six times a year	Twice a year
- Application equipment (backpack sprayer, air blast sprayer, etc.)?	Rotary disc sprayer	Different back sprayers
- Transportation, dissemination and storage?	Uncontrolled	Very controlled (follow GHS, trained drivers, controlled dissemination, etc.)
3. Are similar pesticide management measures in place?		
(i) Are workers trained? Do they know about risks?	Generally, not	Yes, training programmes are in place
(ii) Is PPE available and used?	Usually not	Yes
(iii) Are occupational standards in place?	No	Yes
3. Are similar health impacts observed?		
(i) Are workers poisoned, and what are the signs and symptoms?	Believed to be common; neurological symptoms	Seldom; surveillance system in place
(ii) Has the pesticide been detected in environmental media or food?	Unknown	Low levels in some crops; not detected in air or surface water
(iii) Is the public exposed to the pesticide?	Unknown	Little via food

Study element	Local condition	Other country
(iv) Are there signs of intoxication in the general population?	Unknown	No; surveillance system in place
4. Others		
NA	NA	NA

The meeting concluded that the exposure conditions as described in the study of the other country do not apply to the situation in Africa. Striking differences included the literacy of workers about the health risks of methyl parathion and the use of PPE, as well as the pesticide management system, which was functioning in the non-African country, and the small number of poisoned worker cases reported in the other country by the existing disease surveillance system and local poison centres.

> *Output: Compared with another country that has management measures in place, the African country seems to experience much higher exposure.*

A road map for the exposure assessment step of the pesticide case-study is shown in Figure 17.

For how long is exposure likely to occur?

Short-term exposures of workers are expected to occur during application, whereas short-term, medium-term and long-term exposures may occur mainly through skin contact after application until the commodity is harvested. For the general population, short-term, medium-term and long-term exposures to methyl parathion may occur via ingestion of contaminated food and by inhalation of ambient air. The general population is not expected to be exposed to meaningful levels of methyl parathion in drinking-water. Inhalation exposures of the general population are likely to be greatest for populations living near agricultural applications.

> *Output: Knowledge that exposure can be short term, medium term and long term for workers as well as the general population.*

What metric of exposure is appropriate for characterizing health risks?

As described in section 7.4, guidance/guideline values are expressed in mg/kg body weight (ADI and ARfD), mg/kg of food item (MRLs), mg/l for drinking-water and mg/m^3 (OEL).

> *Output: Knowledge that if exposure has been modelled or measured, it should be expressed as an exposure rate (mg/kg body weight) and/or as an exposure concentration (mg/kg of food item, mg/m^3 in air or mg/l in drinking-water).*

7.6 Risk characterization

How does the estimated exposure compare with the health-based guidance or guideline values?

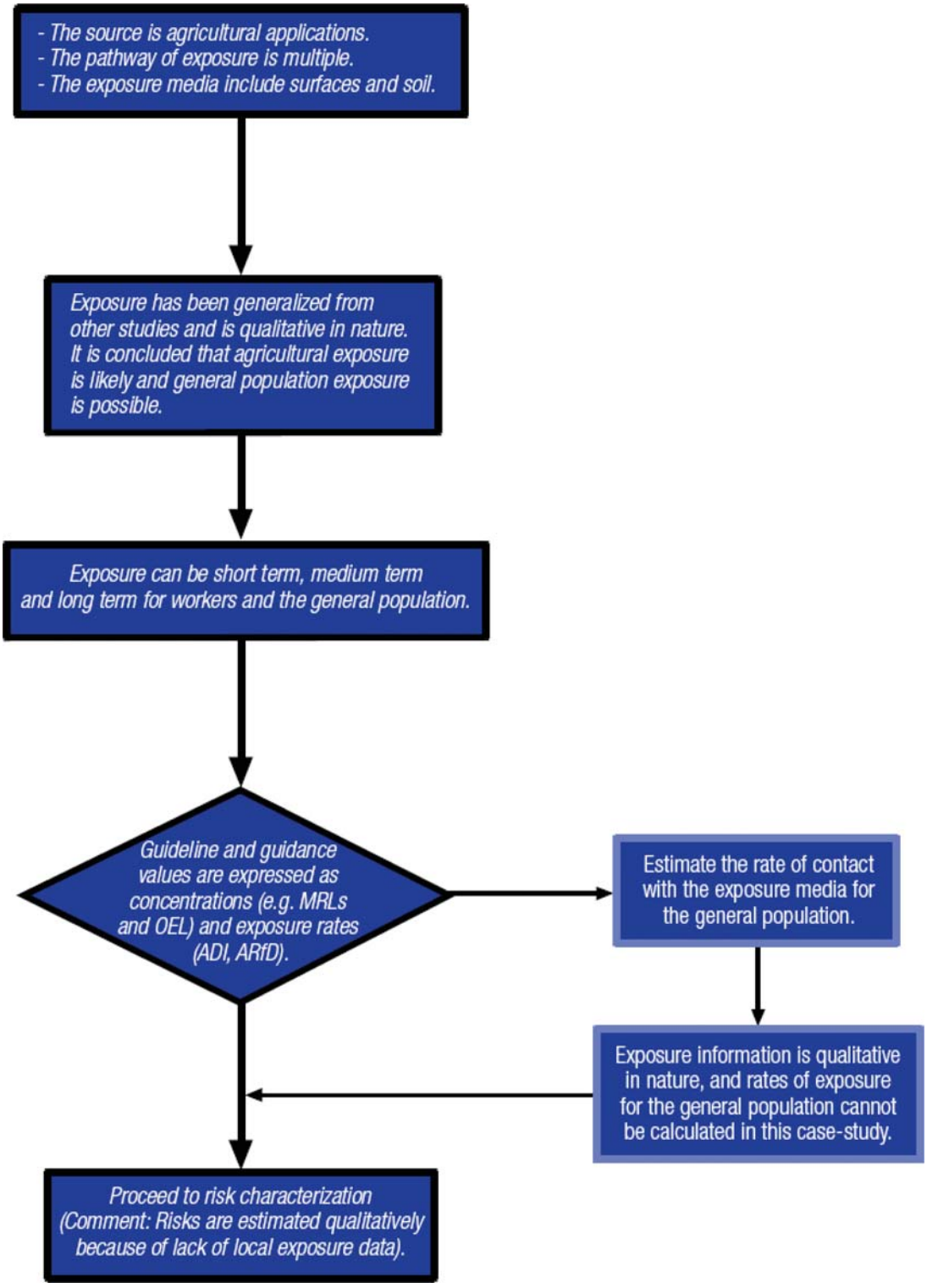


Figure 17: Case-specific road map for exposure assessment: pesticide case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

The above question cannot be answered, because the DEH has not come up with a measure of exposure, either exposure rate or exposure concentration. However, the DEH believes that the potential for exposure to workers is high, based on studies in other areas, as summarized in section 7.5. Upon initial consideration, the absence of exposure information could be interpreted as precluding a risk assessment. However, a qualitative assessment is possible by generalizing from empirical information available from other locations. To minimize exposure among occupational populations, other countries recommend that workers use PPE, including respirators, gloves, tight fabric or polyvinyl chloride overalls, rubber gloves, rubber boots and goggles, as discussed in the HSDB. Further, the signalmen for aerial dusting operations must wear a hat and cape made of polyvinyl chloride or a fabric impregnated with a water repellent.

Information compiled in the HSDB also includes other necessary protective equipment, including eyewash fountains and showers or other facilities to quickly drench the body in the immediate work areas where exposures may occur. Additional protective measures include segregation of contaminated protective clothing to prevent personal contact by personnel who handle, dispose of or clean the clothing. Quality assurance procedures must be implemented to ascertain the completeness of the cleaning procedures before the decontaminated protective clothing is returned for reuse by the workers. Contaminated clothing should not be taken home at end of shift, but should remain at the employee's place of work for cleaning.

The African country does not have the infrastructure needed to ensure appropriate training and implementation of occupational health and safety measures in agricultural operations. Without a management system for protecting workers from excessive exposure to methyl parathion, the DEH concludes that risks to human health are likely to be unacceptable under current conditions and considers restricting methyl parathion use.

A road map for the risk characterization step of the pesticide case-study is shown in Figure 18.

7.7 Summary

A case-study of methyl parathion was used to illustrate how principles, road maps and resources contained in the Toolkit can be used to facilitate the use of risk assessments and information available in international sources and their extrapolation to the conditions prevailing at the national level as a basis for national decision-making on chemicals. References to online databases compiled in the Toolkit were provided, and the electronic links contained in those references provide direct access to information.

The case-study demonstrated how qualitative information on chemical use in a country can be related to empirical information on exposures and risks developed in other countries or settings through the use of bridging principles that consider use patterns, formulations and risk mitigation measures.

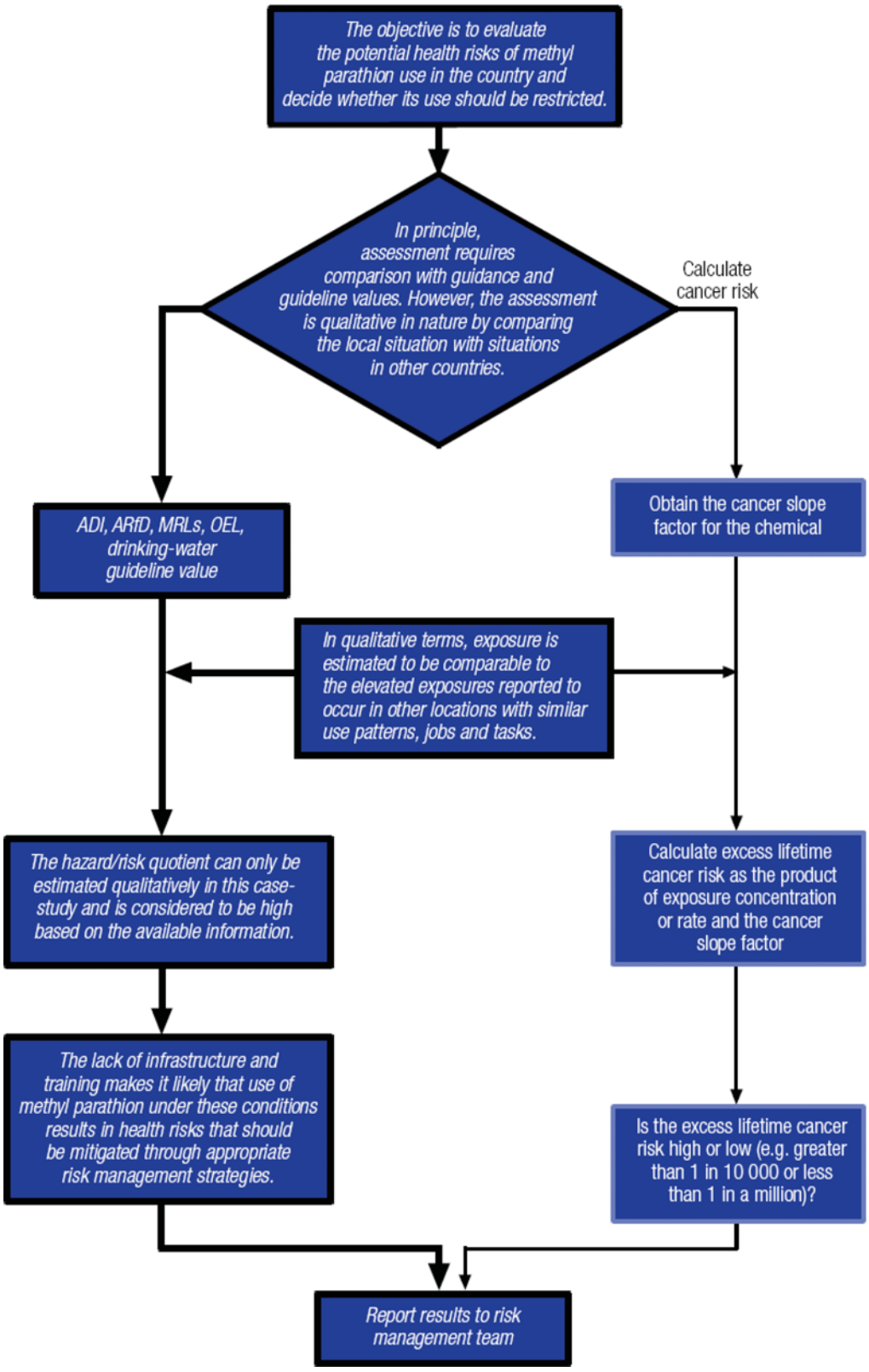


Figure 18: Case-specific road map for risk characterization: pesticide case-study.
Bold lines indicate the flow of information gathering and analysis described in the text.

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