World Health Organization

Harmonization Project Document No. 8

WHO Human Health Risk Assessment Toolkit

CHEMICAL HAZARDS

Second Edition

IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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

IPCS
INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

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PREFACE

The production and use of chemicals are increasing worldwide. According to the UNEP publication "Global Chemicals Outlook II" (UNEP 2019) the production capacity of the global chemical industry almost doubled between 2000 and 2017, from about 1.2 to 2.3 billion tonnes. It was also noted in that report that production of chemicals was projected to continue growing rapidly in emerging economies.

The World Health Organization (WHO) has estimated that 24% of global deaths are due to modifiable environmental factors, including exposure to toxic chemicals (Preventing disease through healthy environments, WHO 2019). The estimated burden of disease attributable to chemicals (from a limited selection of chemicals where sufficient data are available and hence an underestimate of the total) was 1.6 million lives and 45 million disability-adjusted life years lost based on 2016 data. Lead exposure, for example, accounts for 2.5% of cardiovascular diseases, 1.7% of chronic kidney diseases and 30% of idiopathic intellectual disability. Unintentional poisonings kill an estimated 78,000 people per year, in particular children and young adults, and cancer and lung disease attributable to exposure to occupational carcinogens were responsible for more than 300,000 deaths (The public health impact of chemicals: knowns and unknowns – data addendum for 2016, WHO 2018).

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 national levels. The toolkit provides roadmaps 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 to raise awareness and promote 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 the Organisation for Economic Co-operation and Development (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.

Since the publication of the first edition in 2010, the toolkit has been acknowledged for the role it has played in providing assistance with chemical risk assessments (UNEP, 2019). In the period since 2010 there have been a number of new developments in chemical risk assessment methodologies, new tools and new WHO publications. This revised edition of the toolkit is intended to incorporate information about these new developments in methodologies, and to keep references and links to the information sources up to date.

WHO continues to hope that the toolkit will have wide application, especially in developing countries and countries with economies in transition. It is hoped that, in all 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, will be 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.

UNEP (2019) – Global Chemicals Outlook II. Nairobi: United Nations Environment Programme; 2019 https://wedocs.unep.org/handle/20.500.11822/28113
WHO (2018) – The public health impact of chemicals: knowns and unknowns – data addendum for 2016. Geneva: World Health Organization; 2018 https://apps.who.int/iris/rest/bitstreams/916484/retrieve
WHO (2019) – Preventing disease through healthy environments – updated 2016 data tables. Geneva: World Health Organization; 2019 https://www.who.int/quantifying_ehimpacts/publications/Updated-2016-data-tables_Preventing_disease_Deaths_DALYs_PAFs_Sept_2019_rev.xlsx

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 (https://www.who.int/activities/harmonizing-global-approaches-to-chemical-risk-assessment). 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 and 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: China, Malaysia and Thailand. 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 and 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 and 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 Subdivision, 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 learned 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 of Great Britain and Northern Ireland), 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; 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), with technical and linguistic editing by Ms M. Sheffer (Ottawa, Canada).

Update for the second edition

The toolkit was updated during 2019–2020 to incorporate new developments in chemical risk assessment methodologies and tools since the first edition was published in 2010. This included an update of the references and links in the main body text of the toolkit. The case studies published in the first edition in 2010 were not updated but were moved to annexes in the document along with separate reference lists.

The update of the toolkit was prepared by Ms K. Hughes (consultant, Canada). The draft updated toolkit underwent invited peer review from international experts during June and July 2020. Comments were received from the following: Dr A. Beronius (Karolinska Institutet, Sweden), Dr R. Fitzgerald (University of Basel, Switzerland), Dr A. Hanberg (Karolinska Institutet, Sweden), Dr Y. Hirabayashi (National Institute of Health Sciences, Japan), Dr A. Hirose (National Institute of Health Sciences, Japan), Dr G. Kass (European Food Safety Authority, Italy), Dr G. Kowalczyk (consultant, United Kingdom), Dr B. Meek (University of Ottawa, Canada), Dr J. Nicolas (Ministry for Primary Industries, New Zealand), Dr L. Perharič (National Institute of Public Health, Slovenia), Dr T. Vermeire (RIVM, Netherlands), Dr M. Wilks (University of Basel, Switzerland) and Dr J. Zilliacus (Karolinska Institutet, Sweden).

Following peer review, the draft toolkit was finalized by Ms K. Hughes taking into account comments received during peer review.

The updated toolkit was edited by Mr J. Dawson (Nairobi, Kenya).

Dr R. Brown (Chemical Safety and Health Unit, Department of Environment, Climate Change and Health, WHO) served as the responsible officer for the update of the 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 China, Malaysia and Thailand and provided invaluable comments from their experience to further the development of the toolkit.

ABBREVIATIONS

ADI	acceptable daily intake
ALOHA	Areal Locations of Hazardous Atmospheres
AOP	Adverse Outcome Pathway
ARfD	acute reference dose
BE	biomonitoring equivalent
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
CAS	Chemical Abstracts Service
CICAD	Concise International Chemical Assessment Document
CSAF	chemical-specific adjustment factor
DDE	*p,p*-dichlorodiphenyldichloroethane
DDT	*p,p*-dichlorodiphenyltrichloroethane
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EHC	Environmental Health Criteria
EPA	Environmental Protection Agency
EU	European Union
EuroMix	European Test and Risk Assessment Strategies for Mixtures
EUSES	European Union System for the Evaluation of Substances
FAO	Food and Agriculture Organization of the United Nations
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
ICSC	International Chemical Safety Card
ILO	International Labour Organization
IPCHEM	Information Platform for Chemical Monitoring
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System

JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
MOA	Mode of Action
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
PBTK	physiologically based toxicokinetic model
PM	particulate matter
POD	Point of Departure
PPE	personal protective equipment
PTMI	provisional tolerable monthly intake
PTWI	provisional tolerable weekly intake
QSAR	quantitative structure–activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RfD	reference dose
RIVM	National Institute for Public Health and the Environment (Netherlands)
SF	slope factor
SIDS	Screening Information Dataset for High Production Volume Chemicals
TC	tolerable concentration
TDI	tolerable daily intake
TRA	Targeted Risk Assessment
TTC	threshold of toxicological concern
UN	United Nations
UNEP	United Nations Environment Programme
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 substance (henceforth generally referred to as a "chemical" in this toolkit).

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 the relationships between exposure, dose and adverse effects. Acquisition of information appropriate to an exposure 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 (a) identify and acquire the information needed to assess chemical hazards, exposures and risks; and (b) 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 situations that are relevant to the management of risks for public health. For example, the 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 or management decision. Specific examples of risk assessment are described in the case studies presented in the annexes. Users of the toolkit may also find it helpful to consult a glossary of key terminology used in chemical risk assessment published by the International Programme on Chemical Safety *(1)*.

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 (for example, public health and environmental, scientific or engineering professionals) and making decisions on whether to take action to manage environmental risks (for example, 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 conceptual framework for a preventive, risk-based approach to managing water quality is presented in the WHO *Guidelines for drinking-water quality (2)*, along with a range of supporting information. In addition, the Organisation for Economic Co-operation and Development (OECD) has developed Internet-based resources for environmental risk assessment in parallel with the toolkit *(3)*. 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 chemicals *(4)*.

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 *(3)*. 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, this toolkit:

- provides roadmaps for conducting chemical risk assessments;
- identifies information that must be gathered to complete an assessment;
- provides references, including internet 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 roadmap that describes how to conduct a chemical risk assessment and interpret its results using publicly available resources from international organizations. The roadmap 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 the annexes 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 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 that 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 (such as air) or food published by an international

organization. This toolkit focuses on lower tiers of chemical risk assessment that involve similar 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 and some brief descriptions of more resource-intensive methodologies, such as hazard characterization of new chemicals or new health outcomes associated with an existing chemical, to provide additional or background information on tools and approaches incorporated into higher-tiered assessments, such as derivation of existing guidance or guideline values. In those cases, a quantitative evaluation of toxicity based on laboratory animal models or epidemiological studies may be required. This 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 hazard 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 (5)*.

It is recognized that humans are usually exposed to several different chemicals at the same time. While methodologies for assessing combined exposures to multiple chemicals have been developed and continue to evolve (see section 5.7), this toolkit focuses on approaches to assessing risks associated with exposure to individual chemicals.

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 these may also be helpful or where there are gaps in international sources) of information useful for conducting chemical risk assessments (section 4);
- information about evolving approaches and methodologies and anticipated future developments in chemical risk assessment methodology (section 5).

The annexes contain case studies that illustrate how the toolkit can be used to address a human health risk assessment question.

Reference lists, including URLs for most of the information resources, are also provided.

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 *(1)*. 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 associated with 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: (a) hazard identification, (b) hazard characterization, (c) exposure assessment and (d) risk characterization *(1)*. 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 *(6)*. A detailed description of risk assessment can also be found in Chapter 2 of EHC 240 *(7)* and in a number of general publications on this topic.

Table 1. Paradigm for risk assessment, including problem formulation

Step	Description	Content
Problem formulation	Establishes the scope and objective of the assessment and the degree of uncertainty acceptable	Defining the question Prior knowledge Time and resources required Nature of desired assessment output Analysis plan
Hazard identification	Identifies the type and nature of adverse health effects	Human studies Animal-based toxicology studies In vitro toxicology studies Structure–activity studies Other predictive technologies
Hazard characterization	Qualitative or quantitative description of inherent properties of an agent having the potential to cause adverse health effects	Selection of critical data sets Modes/mechanisms of action Kinetic variability Dynamic variability Dose/exposure–response for critical effects
Exposure assessment	Evaluation of the exposure situation of the (sub) population identified in problem formulation to a particular agent (e.g. concentration or amount)	Characteristics of population exposed Sources Magnitude Frequency Duration Route
Risk characterization	Advice for decision-making	Qualitative statements or recommendations or quantitative guidance or risk estimates Nature and severity of effects Probability of effects Health-based guidance Populations of concern Uncertainties

Source: Adapted from EHC 239 *(6)*.

Risk assessors should be aware that their outputs 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 exposure sources, human exposures and adverse health effects. A modified version of the environmental health chain published originally in EHC 214 *(8)* is illustrated in Figure 1. The chain of events depicted in Figure 1 is an "environmental health paradigm": a simplified representation of the key steps between exposure to toxic agents 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. In addition to risk assessment, effective chemical risk management also includes other aspects such as risk perception and socioeconomic considerations; all of these components should be reflected in effective risk communication.

2.2 Uses of human health risk assessments of chemicals

Human health risk assessments of chemicals can be performed to evaluate exposures to any chemical found in air, soil, water, food, consumer or other products (henceforth referred to more generally as "products" in this toolkit), or other materials. These assessments could relate to past or current exposures (retrospective) or potential future exposures (prospective). 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. Chemical risk assessments rely on scientific understanding of chemical behaviour, exposure, dose and toxicity. In general terms, risk depends on the following factors:

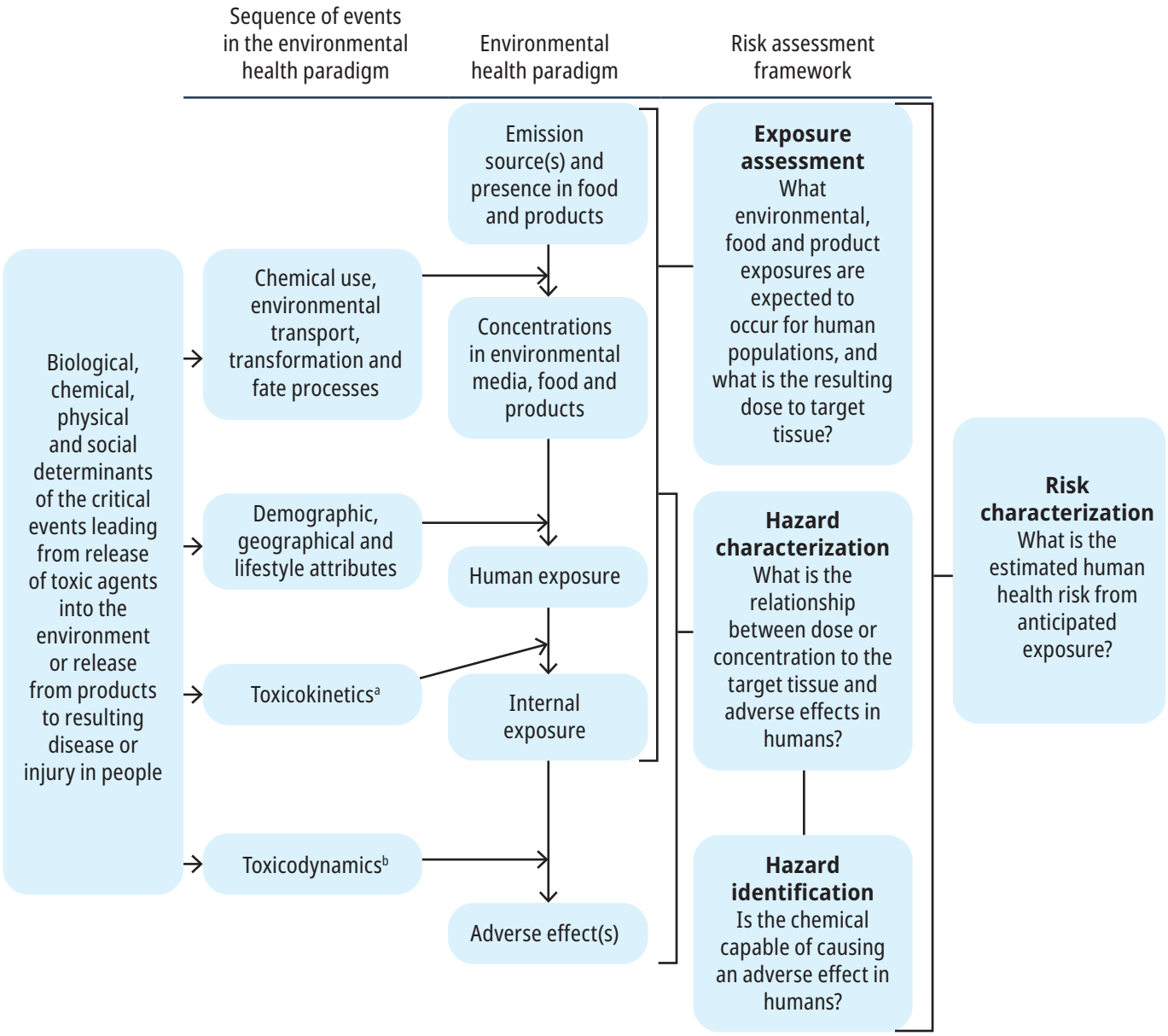
- the amount of a chemical present in an environmental medium (such as soil, water or air), food and/or a product;
- the amount of contact (exposure) a person has with the chemical in the medium;
- how the body processes the chemical (toxicokinetics);
- the toxicity of the chemical.

Obtaining information on these factors is the basis or foundation of most chemical risk assessments. As these data are not always available, estimates or judgements may be necessary for 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?
- Should this chemical be authorized for the proposed use(s)?
- What, if any, limits on chemical exposure should be established in occupational settings, in 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



a. Toxicokinetics: what the body does to the agent. The process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues and the elimination of the substances and their metabolites from the body *(9)*.
b. Toxicodynamics: what the agent does to the body. The process of interaction of chemical substances with the target sites and the subsequent reactions leading to adverse effects *(9)*.
Source: Adapted from Sexton et al. *(10)*; IPCS *(8)*.

3. DESCRIPTION OF THE TOOLKIT

The *WHO human health risk assessment toolkit: chemical hazards* follows the traditional risk assessment paradigm and guides the reader through the various components of the paradigm in an applied manner. 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. Three practical aspects of the toolkit that are intended to facilitate its use – (a) the presentation of the risk paradigm as a roadmap, (b) the introduction of a tiered approach based on the attributes of the assessment question and the available data, and (c) the provision of sources of information on aspects on risk assessment – are described below. These brief descriptions are followed by generic roadmaps for components of risk assessment: hazard identification, hazard characterization (including guidance value and guideline value identification), exposure assessment, and risk characterization.

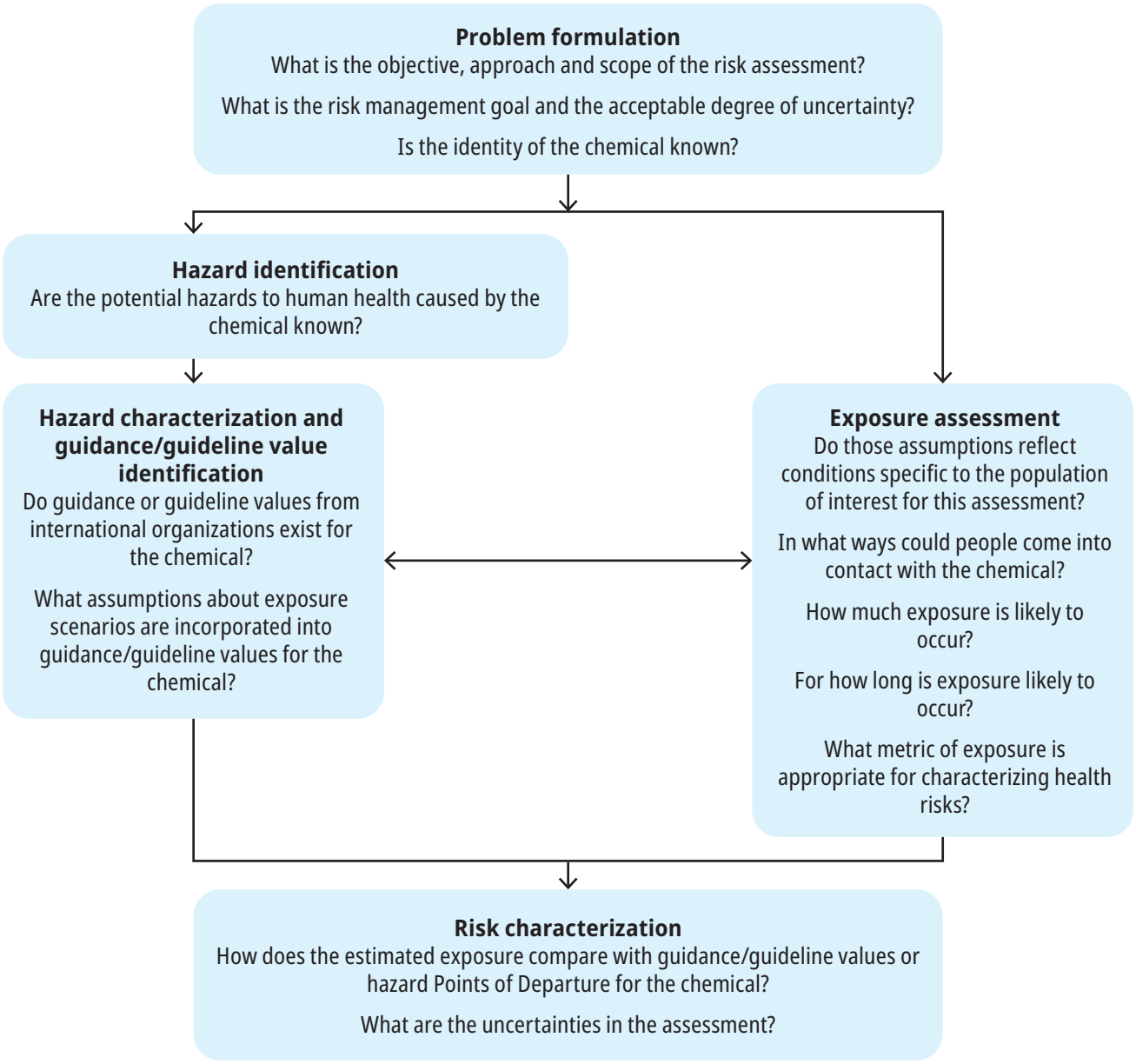
The terminology used in the toolkit is generally in line with the definitions and practice established through the WHO/International Programme on Chemical Safety (IPCS) in numerous publications. Throughout this document, frequent reference is made to guidance values and guideline values. The reader should note that WHO is not entirely consistent in the usage of these terms and that, for the purpose of the toolkit, guidance values refers to those values developed entirely from health-based toxicological and epidemiological information, such as the acceptable daily intake (ADI) and tolerable daily intake (TDI) (or reference dose (RfD), the term used by some institutions), whereas guideline values, such as those for concentrations in air or water, are derived after allocation of the guidance value or reference dose among the different possible media (routes) of exposure. The reader is referred to subsection 3.3.3 for further information on guidance and guideline values.

3.1 The toolkit as a roadmap

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 the 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 roadmap that extends from problem formulation to risk characterization (Figure 2). Each step in the roadmap is represented by a set of questions that an assessor can follow to identify information and resources that are appropriate for estimating risk. A generic roadmap 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 higher-tier de novo assessment of risk conducted for a new chemical, proposed use or health end-point, or for full reassessment of a previously assessed chemical. However, information on some of the tools and approaches applied in higher-tier assessments are included herein for additional information.

Figure 2. Generic roadmap for chemical risk assessment in the context of the toolkit following the conventional risk assessment paradigm



As shown in Figure 2, a chemical risk assessment starts with the problem formulation. Problem formulation is a process that considers the need for and the purpose of the assessment, the scope and the depth of assessment that is needed, the time and resources available and the overall risk management goal *(7, 11)*. Problem formulation identifies the focus of the assessment (for example, a single chemical or a group of chemicals[1] and the identity of the chemical(s)) and what degree of uncertainty is acceptable (that is, what degree of certainty is needed to meet the overall goal), and guides adoption of an approach that is appropriate to the situation (for example, whether there a need to provide guidance to risk managers in an emergency situation such as a spill, or whether a more comprehensive assessment is desired). Problem formulation is iterative and should be revisited as more knowledge is acquired and the focus refined as required. Communication between risk assessors and risk managers, along with other interested parties, is an important aspect of problem formulation, to ensure that a risk assessment meets the needs and expectations of risk managers and stakeholders.

The purpose of the hazard identification step (subsection 3.3.2) is to determine 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, though it is recognized that exposure assessment may occur prior to or concurrent with hazard identification. Hazard characterization/guidance or guideline value identification (subsection 3.3.3) is used to obtain a guidance or guideline value for the chemical that matches the anticipated route and duration of exposure (for example, 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 (subsection 3.3.4) is used to determine the most likely routes, pathways, duration, frequency and intensity of exposure to the identified chemical. Information obtained in these two steps must be compared during 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 are combined to yield a statement of risk. As described in subsection 3.3.5, 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 pesticide case study in Annex 3 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 formulate the risk assessment problem, identify the hazard, characterize the hazard, assess the exposure and characterize the risk. Output anticipated from answering the questions is shown in Table 2.

1 Although the descriptions of the various steps of the risk assessment process included in this toolkit generally refer to assessment of individual chemicals, assessments of groups or classes of substances follow the same basic process.

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

Question	Output
Problem formulation	
What is the objective, approach and scope of the risk assessment?	Clear idea of the objective and scope of the assessment, the resources available and the approach to be followed
What is the risk management goal and the acceptable degree of uncertainty?	Clear vision of what is needed to achieve the risk management goal
Is the identity of the chemical known?	Clear identification of chemical in question through Chemical Abstracts Service (CAS) registry number
Hazard identification	
Are the potential hazards to human health caused by the chemical known?	Description of health hazards obtained from internationally available information
Hazard characterization/guidance or guideline value identification	
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 scenarios 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 population of interest for this assessment?	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 and quantitative description of the relevant media, exposure conditions 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 or hazard Points of Departure (PODs) for the chemical? What are the uncertainties in the assessment?	A quantitative or qualitative statement of non-cancer or cancer risk and a description of uncertainties

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, and societal acceptability of 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.

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

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 the occupational health risks of using the chemical under current conditions are unacceptable. 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 Annex 3 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 respirable particulate matter case study presented in Annex 2 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 micrometres (μm) in aerodynamic diameter, or PM_{10}[2]) 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 *(12)*. The evaluation is qualitative in this example, but nonetheless involves a more rigorous analysis than a Tier 1 risk assessment.

2 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

Tier[a]	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 measurements 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. It should also be noted that, for Tiers 1 to 3, existing hazard data evaluations developed by international sources can be updated in order to include more recent available information.

Tier 3 (modelling or field-based level) risk assessments involve quantitative characterization of exposure conditions through a measurement or modelling campaign, but are otherwise 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 Tier 3 requires generation or gathering of new exposure information, whereas Tier 2 does not. The drinking-water case study presented in Annex 1 is an example of a Tier 3 risk assessment.

Tier 4 (de novo) risk assessments apply to chemicals or chemical forms whose toxicological properties have not been evaluated previously, as well as to consideration of new routes of exposure to existing chemicals. They are unique in that they may involve the review of original data or the generation of new information concerning the hazardous properties of a chemical, as well as measurement or modelling approaches for the quantitative assessment of exposure that is specific to local conditions. Tier 4 assessments are generally 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 roadmaps

3.3.1 Problem formulation: chemical identification

Given sufficient time and resources, the surest way to identify chemicals that are the focus of the risk assessment is sample collection and chemical analysis. However, this generally requires preliminary identification of the chemical of interest, as the appropriate collection and laboratory analysis methods 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 compromise the entire chemical identification step.

In some cases, it may be important to identify the specific form or nature of the chemical of interest, as the health risks of the different forms may vary. Examples could include individual isomers of the chemical, its physical state (which could influence routes of exposure), or whether the assessment might focus on a commercial formulation or its active ingredient.

Chemicals can be identified from a number of internal and external information sources (see Figure 3). For workplace settings, internal sources include company documents and people who work with the chemical, such as 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 or product packaging, on the associated chemical safety card or material safety data sheet or on a list of chemicals used in the industrial process. For general population exposures, the chemical may also be listed as an ingredient in the packaging of products or have been included in local air or water quality measurement programmes. The same information sources 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 to 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 subsection 4.8.3 for information relevant to the current situation. Emission scenario documents published by OECD *(13)* 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 chemicals 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 Chemicals Agency publishes emission scenario documents in support of risk assessments for new and existing substances *(14)*. The emission scenario documents describe environmental releases for different industrial categories and biocidal products.

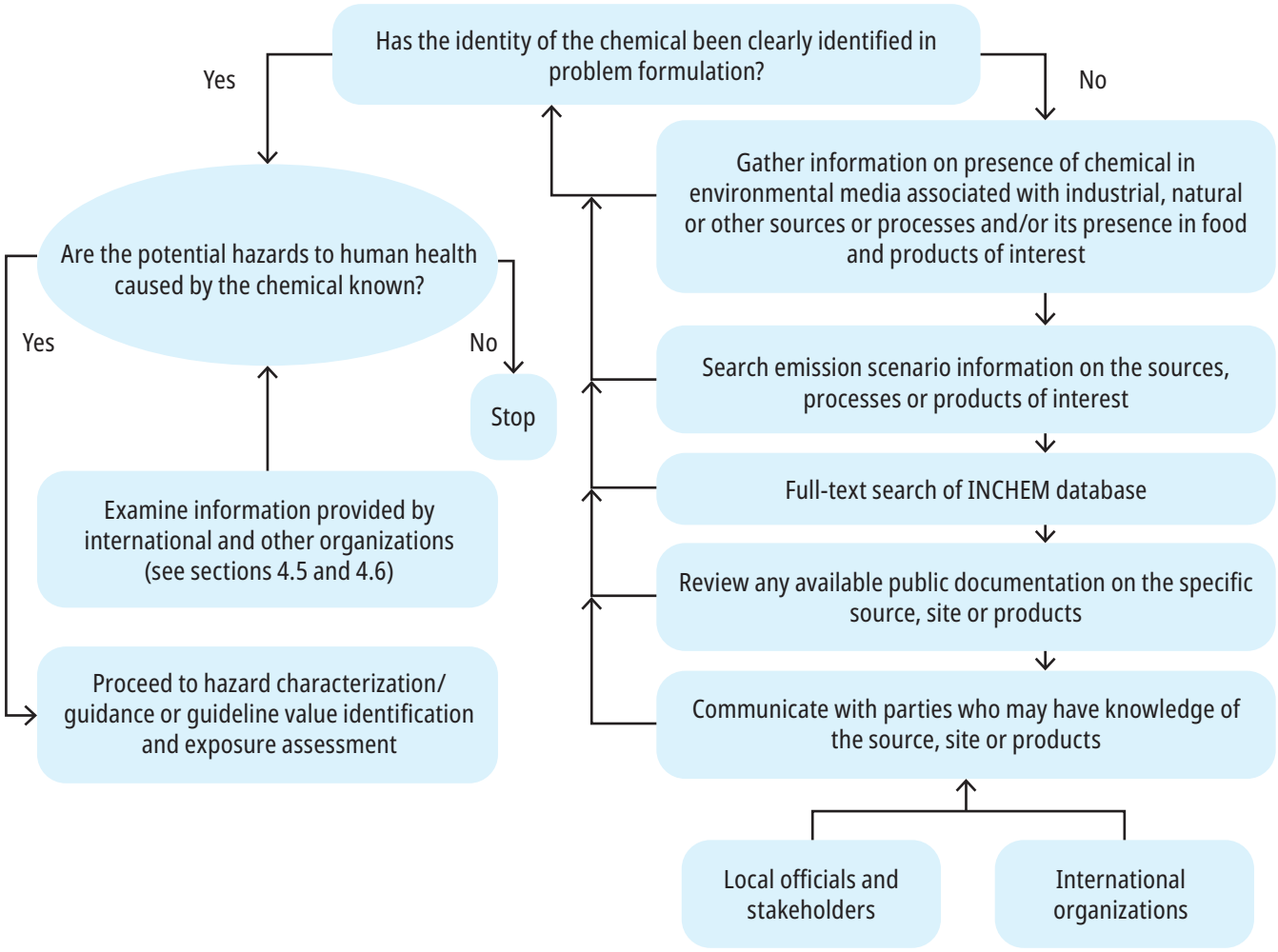
With respect to identification of chemicals in products, where product ingredient lists may not be available, a potential source of information may be EHC 242 on dermal exposure *(15)*, which provides examples of some chemicals that may be present in a range of occupational scenarios or products. A comprehensive source of information on chemicals present in a wide range of products is the Chemicals and Products Database of the United States Environmental Protection Agency (EPA), which is searchable online using the CompTox Chemicals Dashboard *(16)*.

A full-text search feature of the INCHEM database *(17)* (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 chemicals of concern.

3.3.2 Hazard identification

Hazard identification is generally the first step in a risk assessment following problem formulation (possibly at the same time as exposure assessment) and is the process used to determine whether exposure to this chemical has the potential to harm human health. For the purposes of the toolkit, hazard identification involves 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.

Figure 3. Generic roadmap for chemical and hazard identification in the context of the toolkit



For Tier 1 to 3 assessments, once a chemical is identified, the potential hazards of the chemical can be determined from international reviews of 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 the human health hazards that they pose, such as irritation and sensitization, or neurological, developmental, reproductive, 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 health hazards of a chemical have not yet been identified, the reader is referred to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) *(18)*. The GHS was initiated by international organizations in recognition of the varying criteria for determination of hazardous chemicals among countries and the extensive global trade of chemicals. The GHS includes (a) harmonized criteria for classifying chemicals and mixtures[3] according to their health, environmental and physical hazards; and (b) harmonized hazard communication elements,

3 The term "mixtures" in the context of GHS relates primarily to chemicals in products, whereas "mixtures" toxicology is more concerned with co-exposures to multiple chemicals.

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 (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	GHS categories or subcategories[a]
Acute toxicity	1 to 5
Skin corrosion or irritation	1 to 3
Serious eye damage or irritation	1, 2A, 2B
Respiratory sensitizer	1A, 1B
Skin sensitizer	1A, 1B
Germ cell mutagenicity	1A, 1B, 2
Carcinogenicity	1A, 1B, 2
Toxic to reproduction	1A, 1B, 2
Effects on or via lactation	1
Specific organ toxicity (acute exposure)	1 to 3
Specific organ toxicity (repeated exposure)	1, 2
Aspiration hazard	1, 2

[a] Note that use of subcategories is not obligatory in application of the GHS system.

The weight of evidence for carcinogenic effects of a chemical in humans is another important feature of hazard identification. In addition to the GHS system of classification for carcinogenicity, the International Agency for Research on Cancer (IARC) *(19)* categorizes chemicals and other agents into one of five categories based on the strength of evidence of carcinogenicity:

- 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 the IARC can be found in the Preamble that is included in each monograph published by the agency. The Preamble is periodically updated *(20)*.

3.3.3 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 potential of the chemical to cause adverse health effects as a result of exposure. An adverse effect is defined as a change in the morphology, physiology, growth, development, reproduction or lifespan of an organism, system or (sub)population (or their progeny) that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences (definition adapted from reference *(1)*). To discriminate between adverse and non-adverse effects, consideration should be given to whether the observed effect is an adaptive or trivial response, transient or reversible, of minor magnitude or frequency, a specific response of an organ or system, or secondary to general toxicity *(21)*.

Note, however, that for 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 (for example, vitamin A).

Quantitative hazard characterization often consists of a dose–response assessment, including identification of a Point of Departure for health effects in critical studies, such as:

- no observed adverse effect level (NOAEL);
- no observed effect level (NOEL);
- lowest observed adverse effect level (LOAEL);
- lowest observed effect level (LOEL);
- benchmark dose lower confidence limit (BMDL), which is the lower confidence limit of the benchmark dose (BMD), the dose associated with a predefined degree of adverse response;
- cancer potency factor (slope factor from the dose–response curve).

With the application of uncertainty factors to account for interspecies and intraspecies (interindividual) variability, data quality and other uncertainties (see subsection 3.3.3.1), this information is used to develop guidance values, such as the TDI, ADI and acute reference dose (ARfD) (see subsection 3.3.3.1 and Tables 5 and 6). Human exposure factors, such as intake rates (see subsection 4.8.2 and Table 17), are then considered to develop guideline values for chemicals in specific media such as air, water and food (see subsection 3.3.3.2 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 (such as 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 (such as 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 (the concepts in Figure 4 (such as contact rate) are described in detail in subsection 3.3.3.3).

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

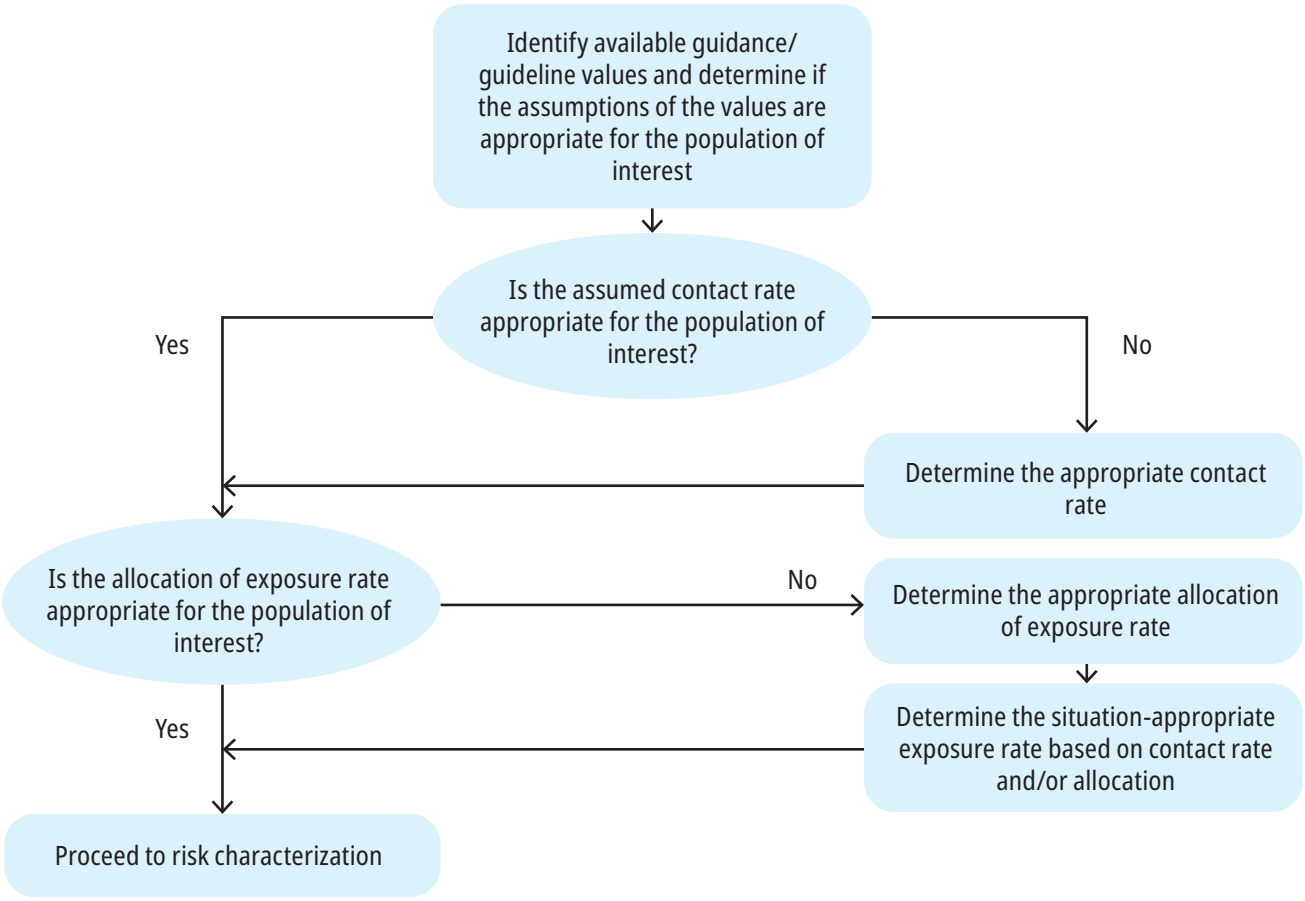
— guidance values developed entirely from toxicological and epidemiological information ("health-based guidance values"), such as the ADI and TDI, which provide an estimate of the amount of a chemical that can be taken in orally (mainly by food and drinking-water) or by inhalation or dermal contact by a person without appreciable health risk, or a tolerable concentration (TC), which relates to a concentration in air similarly considered to be without appreciable health risk (see also Tables 5 and 6 in subsection 3.3.3.1 below);

— 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 (for example, the WHO *Guidelines for drinking-water quality*). Alternatively, they may be based on agricultural practices and climate scenarios, 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 subsections. 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 (see annexes).

In addition to guidance or guideline values developed by international organizations, many countries have developed national quality standards for chemicals in media (for example, food, water, air and 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 chemical that are unlikely to produce adverse effects or characterizes the potency of carcinogens (for example, by establishing BMDLs or 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 (such as a national air quality standard), consideration must be given to the relevant socioeconomic factors. A national air quality standard, for example, might be numerically 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 roadmap for hazard characterization/guidance or guideline value identification in the context of the toolkit



3.3.3.1 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. A range of increasingly complex tools and approaches and higher-tiered assessments may be used by international organizations to derive health-based guidance values based on the results of these studies. The WHO Harmonization Project Document No. 2 on chemical-specific adjustment factors (CSAF) provides a detailed description of the extrapolation of the results from laboratory-based toxicology studies from experimental animals to humans *(22)*. The use of CSAF was reviewed by WHO after ten years (*23*). Extrapolation across studies, species, routes and dose levels may also be aided by the use of physiologically based pharmacokinetic (PBPK) modelling *(24)*. The relevance of the effects observed in experimental species to humans can be evaluated with the WHO/IPCS Framework on Mode of Action/Species Concordance Analysis, which lays out a biologically plausible series of key events that lead to an adverse effect *(11)*, as shown in Figure 5. (Mode of Action analyses can, in turn, be informed by existing Adverse Outcome Pathways – see section 5.4.) In other cases, observations of effects in human populations characterized with epidemiological methods are the basis of guidance value development. Even if the human data are insufficient to be used to quantitatively assess risk, they may support the evaluation of the relevance of observations in animal studies or identify important data gaps not addressed by the animal data.

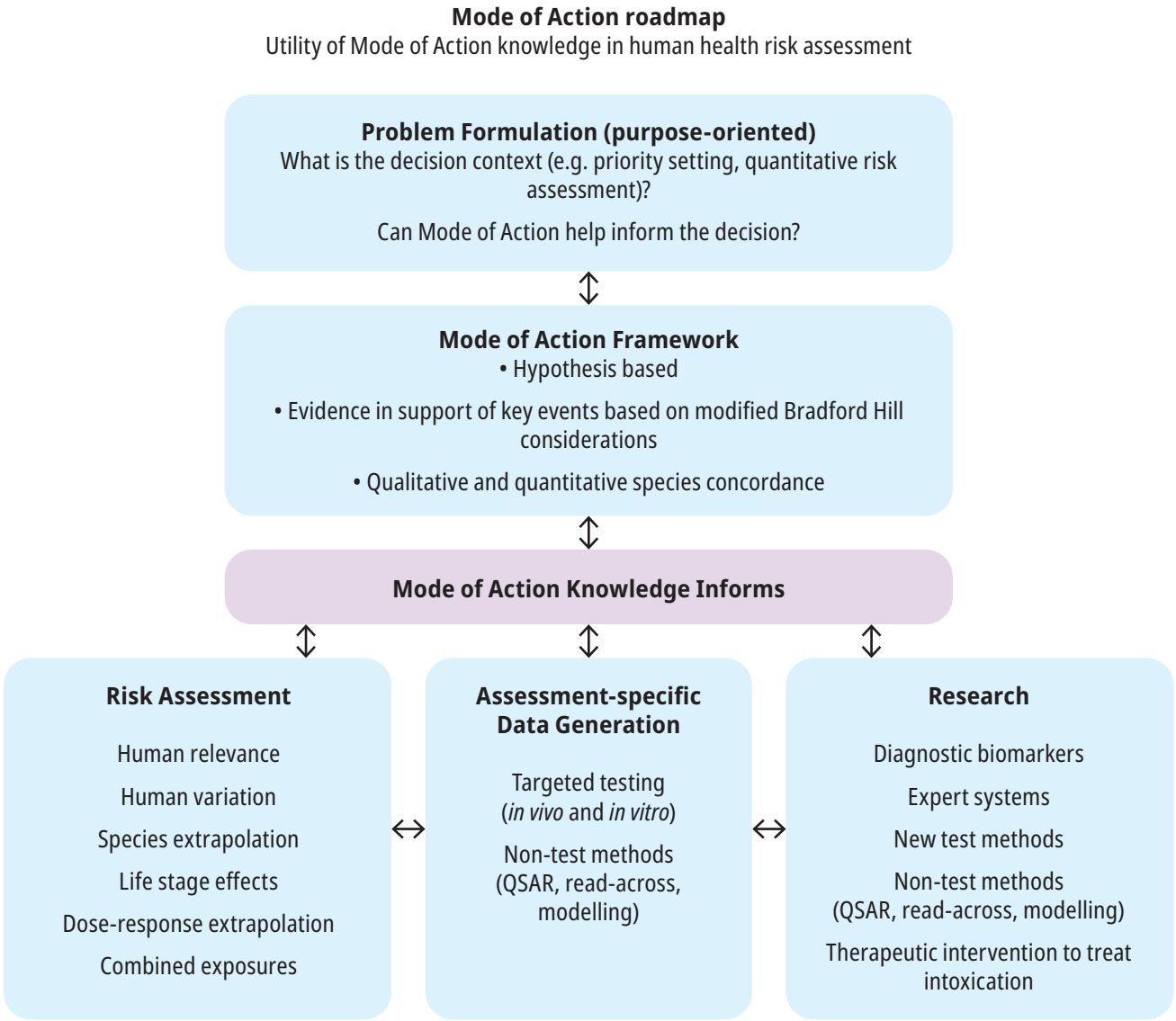
Table 5. Guidance and other values commonly used in chemical evaluations

Type of outcome	Term (units)[a]	Abbreviation	Definition
Non-cancer, including laboratory animal carcinogens determined to not be relevant to humans	Tolerable concentration (mg/m^3)	TC	An estimate of the amount of a chemical 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 For products, these values would be estimates of the dermal, oral or inhalation exposure to a chemical from products over a specified duration without appreciable health risk
	Tolerable daily intake (mg/kg body weight per day)	TDI	
	Provisional[b] tolerable weekly intake (mg/kg body weight per week)	PTWI	
	Provisional[b] 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 chemical, normally in food or drinking-water, that can be ingested in a period of 24 hours 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 $([\mu g/m^3]^{-1})$		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 $([\mu g/L]^{-1})$		
Cancer and non-cancer effects	Benchmark dose (mg/kg body weight per day)	BMD	Amount of contaminant derived from epidemiological studies or studies in experimental animals associated with a predefined incidence of adverse effect (e.g. 5% or 10%). This value is usually expressed as the lower confidence limit of the BMD, or BMDL

[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] Note that it is being considered that the term "provisional" be phased out (25).

Figure 5. Mode of Action roadmap illustrating the use of mode of action knowledge in human health risk assessment



Note: The extent of analysis is tailored to the issue under consideration through iterative analysis and consultation among the assessment, management and research communities.
Source: From Meek el al. *(11)*.

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. The dose of some known or suspected genotoxic human carcinogenic chemicals is assumed to have a relationship with risk of cancer, and some level of risk is assumed to occur at any level of exposure (so-called non-threshold carcinogens). However, for some other carcinogens, sufficient information may be available to confidently determine that the Mode of Action involves a non-genotoxic key event for which a threshold of exposure can be characterized (so-called threshold carcinogens).

2. For adverse effects other than non-threshold cancer, there is a threshold level of exposure below which adverse effects are unlikely to occur (that is, the probability is considered to be very low or negligible).

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 or exposure scenarios 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.

As noted above, for chemicals positive in experimental animal carcinogenicity studies, available information on Mode of Action is assessed in order to consider human relevance *(11)*. For chemicals that are treated as potential non-threshold human carcinogens, the risk of cancer is characterized as the response (for example, incidence of tumours) in relation to the dose. Dose–response data from epidemiological studies may also be used for hazard characterization if exposure is adequately characterized; this avoids the need for interspecies comparisons and extrapolation over many orders of magnitude from the high doses usually employed in animal studies to more human-relevant exposures.

Two methods for characterizing carcinogenic potency of a chemical are available: (a) calculation of the slope of the line fit to the dose–response data to derive the increase in cancer risk per unit dose (the slope factor approach); and (b) modelling of the dose–response relationship to identify a predefined level of carcinogenic response (the BMD approach).

In the slope factor approach, the carcinogenic potency of a chemical is characterized as the slope of a line fitted 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 fitted to dose–response data from cancer bioassay studies in laboratory animals *(6)*. 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 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 $(mg/kg\ body\ weight\ per\ day)^{-1}$. 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 $(\mu g/m^3)^{-1}$ or $(\mu g/L)^{-1}$, respectively. These slope factors can be used to derive health-based guidance values or guideline values for a given level of risk (see subsection 3.3.5).

In the BMD approach, a suite of dose–response models is used to calculate the dose for a biologically relevant predetermined level of response, called the benchmark response (BMR), such as a 5% or 10%

cancer incidence in animal studies. Information about where to obtain BMD models (software packages) and instructions for their use are provided in Chapter 5 of EHC 240 *(25)*. BMDs or, more typically, 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 subsection 3.3.5.2). This approach is currently preferred by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) where possible and appropriate, because all of the dose–response data are taken into account *(25)*.

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 (that is, there is sufficient support for a threshold of exposure for carcinogenicity), health-based guidance values are characterized as thresholds of exposure below which adverse effects are considered unlikely to occur. Reference doses 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 (for example, ADIs have been developed for pesticides by JMPR and for food additives by JECFA), TDI, PTWI, PTMI (developed for food contaminants by JECFA) and ARfD (for example, developed for pesticides by JMPR) (see also subsections 4.5.1 and 4.5.2). These reference values are estimates of the amount of a chemical 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). For airborne chemicals, the guidance value is often expressed as a tolerable concentration (TC), with units of milligrams or micrograms per cubic metre of air.

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

Guidance values	Sources/references
Acceptable daily intake (ADI)	INCHEM *(17)* WHO food safety databases *(26)* OECD eChemPortal *(27)*
Acute reference dose (ARfD)	
Tolerable daily intake (TDI)	
Provisional tolerable weekly intake (PTWI)	
Provisional tolerable monthly intake (PTMI)	

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 (the term generally used in this toolkit, though these factors are 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:

- differences between experimental animal species and humans (interspecies differences) and the application of laboratory animal test results to humans;[4]
- susceptible members of human populations (intraspecies or interindividual variability);
- extrapolation of laboratory animal bioassay tests conducted over short periods of time (for example, weeks or months) to exposures of interest over longer periods of time (for example, years) or to adjust for experimental frequency to human-relevant frequency (for example, intermittent to continuous exposure); these concepts are separate from the time course of adverse effects that can immediately follow exposure or result from cumulative or continuous exposure;
- other aspects, such as insufficiency of the database or steepness of the dose–response curve.

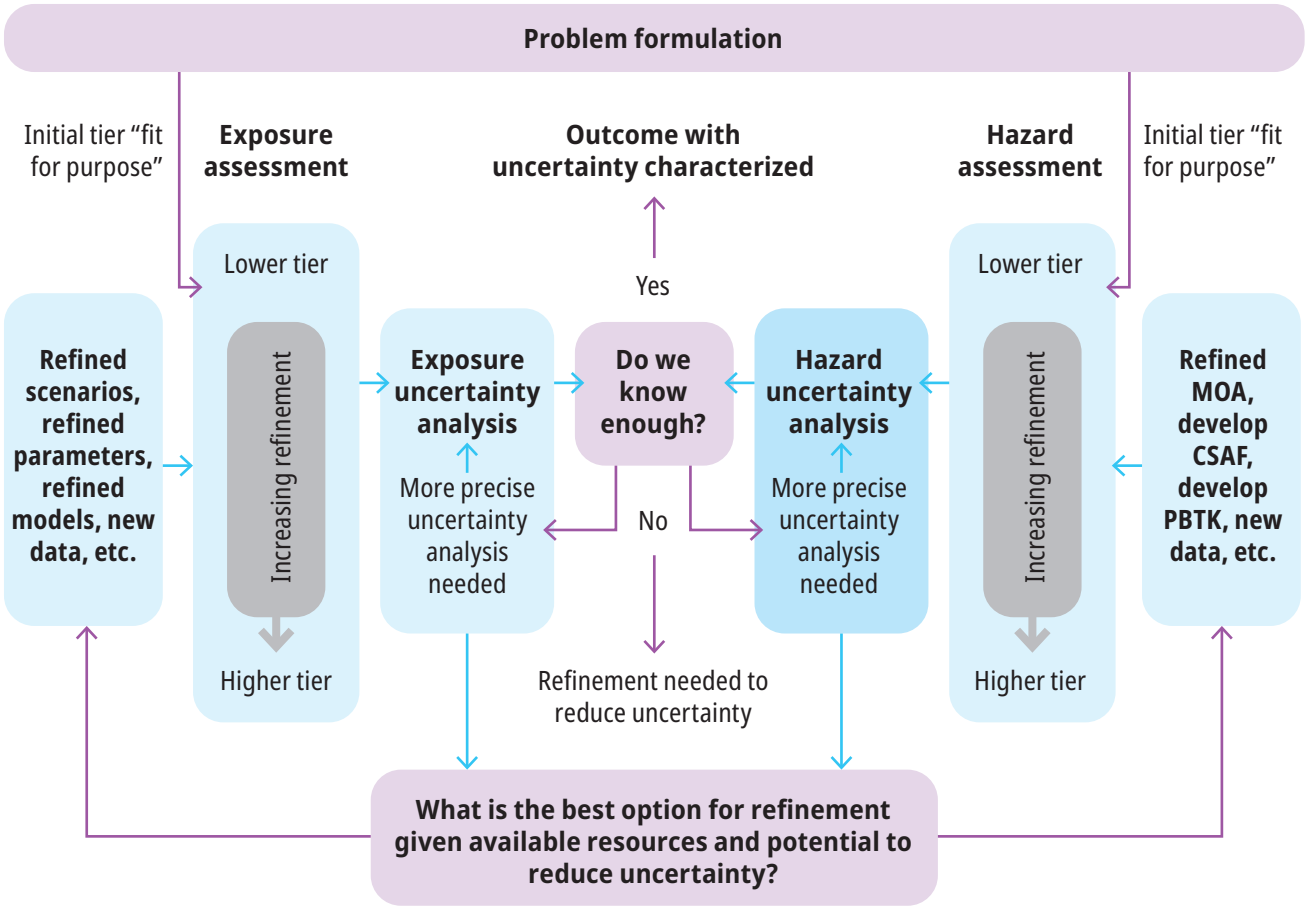
Hazard characterization will involve uncertainties associated with extrapolating results from studies to the population of interest. Though it adds an element of complexity, addressing the uncertainty quantitatively where possible can lead to a more complete risk assessment, improved risk communication and more informed decision-making.

Guidance on how to quantitatively address uncertainty in hazard characterization is also available in the WHO Harmonization Project Document No. 11 *(9)* and supporting documentation *(28)*. The framework outlined in this guidance involves characterization of individual sources of uncertainty (associated with Point of Departure, study population or study design versus target population, and human variability) and combining these uncertainties using increasingly complex approaches (Figure 6):

- a non-probabilistic approach (where the individual lower and upper bounds for each hazard characterization aspect are combined by multiplication);
- an approximate probabilistic approach (where uncertainty distributions are combined probabilistically, assuming that all uncertainties can be described as independent lognormal probability distributions);
- a full probabilistic approach (where uncertainty distributions are combined probabilistically, generally through Monte Carlo simulations, and are not restricted to independent log-normal probability distributions).

4 Note that some institutions do not apply uncertainty factors for inter- and intraspecies differences for genotoxic carcinogens, assuming that linear extrapolation is already a conservative approach.

Figure 6. Tiered approach in risk assessment including uncertainty analysis with reference to pertinent WHO/IPCS guidance



Source: IPCS *(9)*

A simple, easy-to-use spreadsheet tool, APROBA, is provided with WHO Harmonization Project Document No. 11 *(9)* for the application of the approximate probabilistic approach. The outcome is expressed in terms of ranges or probability distributions rather than as single (often considered to be conservative) values as developed using a deterministic approach. Estimates of the relative contributions from the various aspects to the overall uncertainties are useful for identifying the greatest sources of uncertainty and showing for which aspects additional information would be most effective in reducing the overall uncertainty. The APROBA tool can also assist in the application of a non-probabilistic approach.

Some of the authors of the APROBA tool extended the tool further (APROBA-Plus) to combine the output from the probabilistic hazard characterization with probabilistic exposure estimates to rapidly characterize risk and its uncertainty, adding balanced transparency in regard to uncertainties. APROBA-Plus can inform risk management measures or assist in prioritizing refinements in a higher-tier assessment *(29)*. Several case studies are presented in supplementary materials to this publication.

3.3.3.2 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) exposure to a chemical from all routes and pathways (see subsection 3.3.4). In contrast, the media-specific guideline values 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 WHO drinking-water guidelines are primarily health-based and do attempt to account for exposure through other media. However, the FAO/WHO maximum residue limits (MRLs) and maximum limits (MLs) are not direct public health limits, but instead reflect agricultural or veterinary practices, climate scenarios, and technical and economic feasibility, and they are normally set at levels well below amounts that might lead to an adverse health effect.

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 subsection 3.3.5 and illustrated in the case studies presented in the annexes.

Table 7. Sources of media-specific guideline values for chemicals developed by international organizations

Guidelines	Organization and reference
Drinking-water quality guideline values	WHO *(2)*
Air quality guidelines	WHO Regional Office for Europe *(12, 30-32)*
Indoor air quality guidelines	WHO *(33)* WHO Regional Office for Europe *(12, 34)*
Maximum residue limits (MRLs) of pesticides in food	FAO/WHO *(35)*
Maximum limits (MLs) of contaminants in food	FAO/WHO *(26)*

Media-specific guideline values (for example, 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 regard to their activity and dietary patterns and demographics, and the exposure averaging times, among other considerations.

More specifically, media-specific guideline values typically incorporate a number of assumptions about exposure, including contact rate, body weight, absorption fraction and allocation of total intake (see also subsection 4.8.2 and Table 17).

3.3.3.3 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 subsection 3.3.5 and the case studies that appear in the annexes. Contact rates related to different means of contact, as shown in Figure 8 in subsection 3.3.4.1, refer to assumptions about rates of water consumption, inhalation, food consumption and other forms of contact with environmental media, food and products. Default values are typically used for those contact rates (see Table 17 in subsection 4.8.2). 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 (such as drinking-water, air or 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 (such as 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. For more information on some of the methods used by these organizations in establishing guidelines, readers are referred to:

- *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits* (EHC 170) *(36)*;
- *Principles for modelling dose–response for the risk assessment of chemicals* (EHC 239) *(6)*;
- *Principles and methods for the risk assessment of chemicals in food* (EHC 240) *(7).*

Other sources of helpful information are described in section 4.

3.3.4 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 or dermal) and duration (short-term, medium-term or 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.

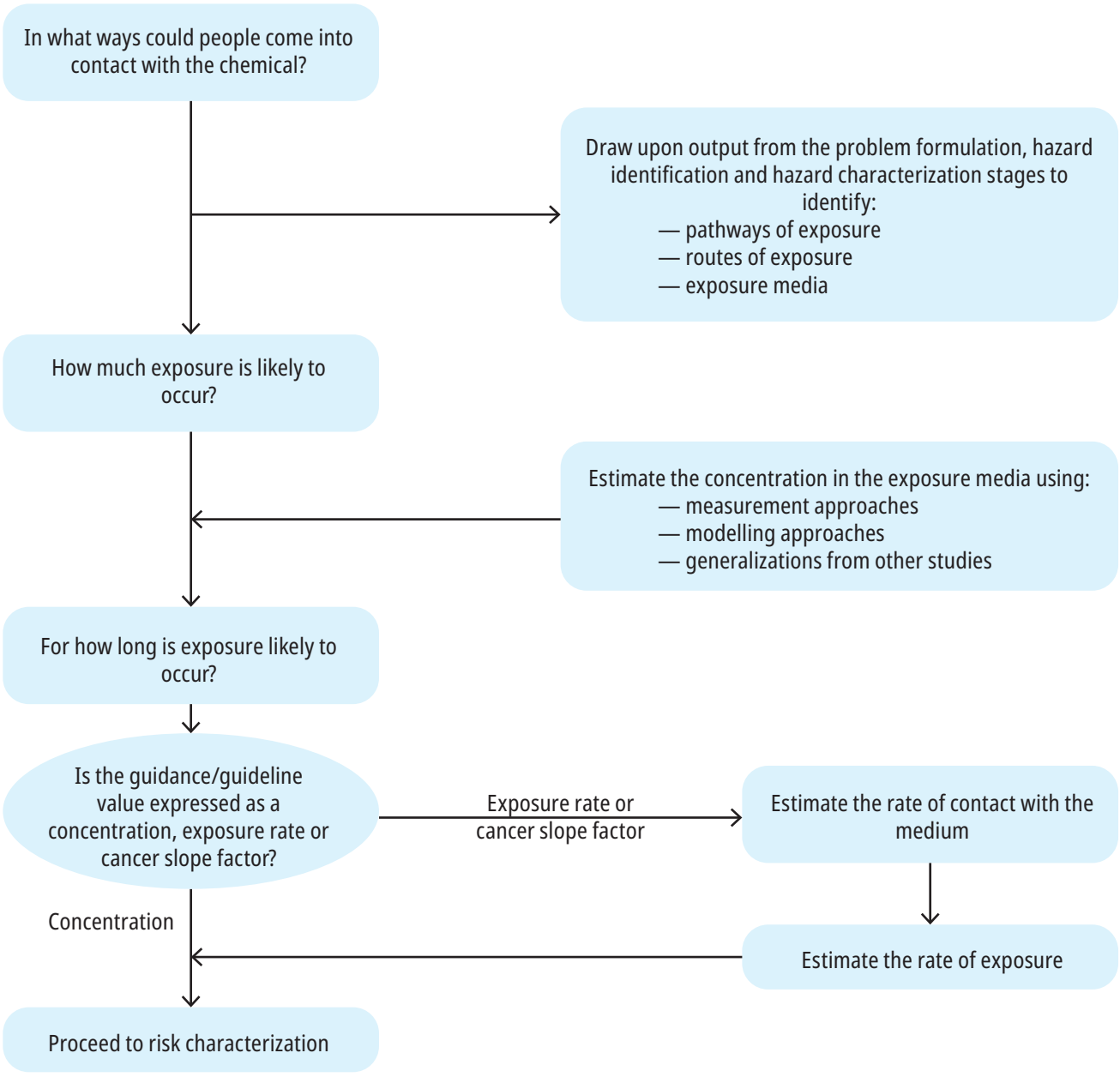
The exposure concentration is the concentration of a chemical in a medium with which a person is in contact. These media include air, water and soil in outdoor and indoor locations frequented by a population. Other media include food and products with which people come in contact. Ideally, exposure

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 7, 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 media expected to contain the chemical
- the appropriate duration and frequency of exposure.

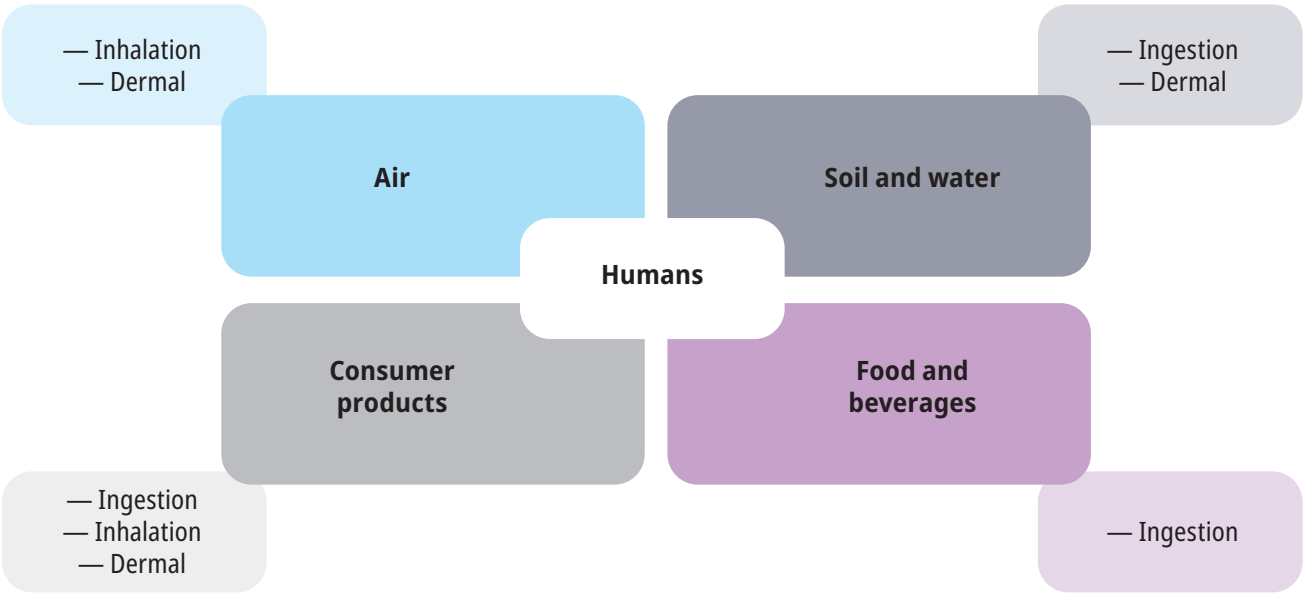
Figure 7. Generic roadmap for exposure assessment in the context of the toolkit



3.3.4.1 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 8). These exposures may occur in occupational or community (that is, 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, soil or products 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, dusts, particulates or fibres. 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 of the chemical or products in which it is present.

Figure 8. Possible exposure media and corresponding means of contact



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 or chloroform, information about the chemical properties and behaviour can point to environmental media, locations, foodstuffs or products 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 (for example, 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.

3.3.4.2 Estimating exposures: modelling or measurement approaches

While data on exposure concentrations in personal air, ingested media such as drinking-water and food, and media contacting the skin (including products) 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 light of this limitation, risk assessments, especially screening-level risk assessments, are often based upon incomplete data on chemical concentrations in media that are relatively easy to access, such as outdoor air, indoor air, surface water, outdoor soil and commonly used products. Chemical concentration data can be determined from measurement campaigns or modelling efforts.

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 not entirely representative of the exposure scenario of interest. Measurements, on the other hand, generally provide the most accurate and relevant data, but are the most time and resource intensive, precluding their use for many risk assessments. Exposure models may be used to provide estimates of exposure from a range of sources. A summary of exposure measurement and generalization methods is given in EHC 214 *(8)*. Other sources of helpful information are described in section 4.

(a) Exposure models

Exposure models generally require information about the concentration of a chemical in a medium or product, the period of time over which individuals are in contact with the chemical and the route of the contact (dermal, inhalation and/or ingestion). Chemical concentrations can be measured or can be estimated from chemical usage, data from previous investigations or product composition information. As described in section 4.8, concentrations in specific environmental 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. Similarly, models have been developed to estimate exposures to chemicals through use of products. Given the complexity of many of these models, some may require specialized training on running the models, while for many models, extensive information on how to use them is available online; see, for example, the United States EPA ExpoBox *(37)* and ConsExpo Web from the National Institute for Public Health and the Environment (RIVM) of the Netherlands *(38, 39)*. In order to select the appropriate model, information about the geographical and temporal extent of the chemical exposures of interest or the nature and intended use of the products in which the chemicals are present, and the exposed populations of interest, should be obtained or otherwise determined.

To estimate exposures, concentration estimates in media provided by models can be used, together with information about chemical contact, including who is exposed and the frequency and duration of their exposure. Depending on the route of contact, information on physiological parameters such as body surface area, area of the exposed skin, degree of dermal or gastrointestinal absorption, inhalation rate and inhalation volume for various populations and circumstances (rest or activity) may also be required. Models that estimate direct exposure to chemicals in products incorporate information on product use patterns and product composition. Information about chemical contact can be obtained using a variety of techniques, including questionnaires or enquiries 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, soil or

products can be estimated using mathematical equations. A summary of principles for characterizing and applying human exposure models is given in IPCS Harmonization Project Document No. 3 *(40)*. Other helpful information on conducting exposure assessments is indicated in section 4.8. Guidance on how to address uncertainty and data quality in exposure assessments is also available from WHO Harmonization Project Document No. 6 *(41)*. A range of publications on exposure assessment is also available through OECD *(42)*.

(b) Exposure measurements

Exposure concentrations in media 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 relevant environmental media (such as air, water or soil), food or products. Exposure measurements are intended to match the actual media, location, duration and use 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 *(8)*. Often, the cost of the measurement method is proportional 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 apply 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. By contrast, 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. The problem formulation stage in the risk assessment process can serve to identify which particular subpopulation is the focus of the exposure assessment. An example of a measurement-based approach to determine exposure concentrations is included in the drinking water case study in Annex 1. With respect to exposures to chemicals in products, exposure measurements would apply specifically to the subgroup of the population using the products.

3.3.4.3 Duration and frequency 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 (as well as cancer), 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.

Exposure to chemicals may be of shorter duration on an intermittent basis, such as during use of products or application of pesticides. In these situations, it is important to consider the frequency of exposure as well as duration. The ConsExpo models developed by RIVM incorporate frequency of event in estimating exposure and provide default values for a range of product uses *(39)*. Likewise, information on incorporation of frequency is provided in the generic scenarios for estimating exposure to vector control agents *(43)*.

3.3.4.4 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 subsection 3.3.3).

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, food and products. 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); a shorter period of time may be considered for situations where the exposure may be infrequent or occurs over only a limited duration (for example, a brief exposure to a chemical in a household cleaning product). Approaches to assessment for shorter-term exposures to chemicals are illustrated in the generic risk assessment models developed by WHO for insecticides *(43)*. 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, ingests or has dermal contact with that medium, divided by a representative body weight. For dermal exposures, the area of skin contact is also considered.

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

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

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 and is related to the situation identified in problem formulation.

However, for some chemicals in products, such as for volatile substances migrating from toys, the air concentration in the room in which the product is used is determined by the concentration in the product, the migration rate and the breathing space or room volume.

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.

3.3.4.5 Biomonitoring

Besides the above-described traditional exposure assessment, the use of biological monitoring (generally referred to as biomonitoring) is another method with which to evaluate human exposure to a chemical. Biological monitoring of exposure is considered a measure of internal dose, whereas exposure describes the contact with a chemical at the boundary between an individual (for example, skin, mouth or nostrils) and the environment, food or product.

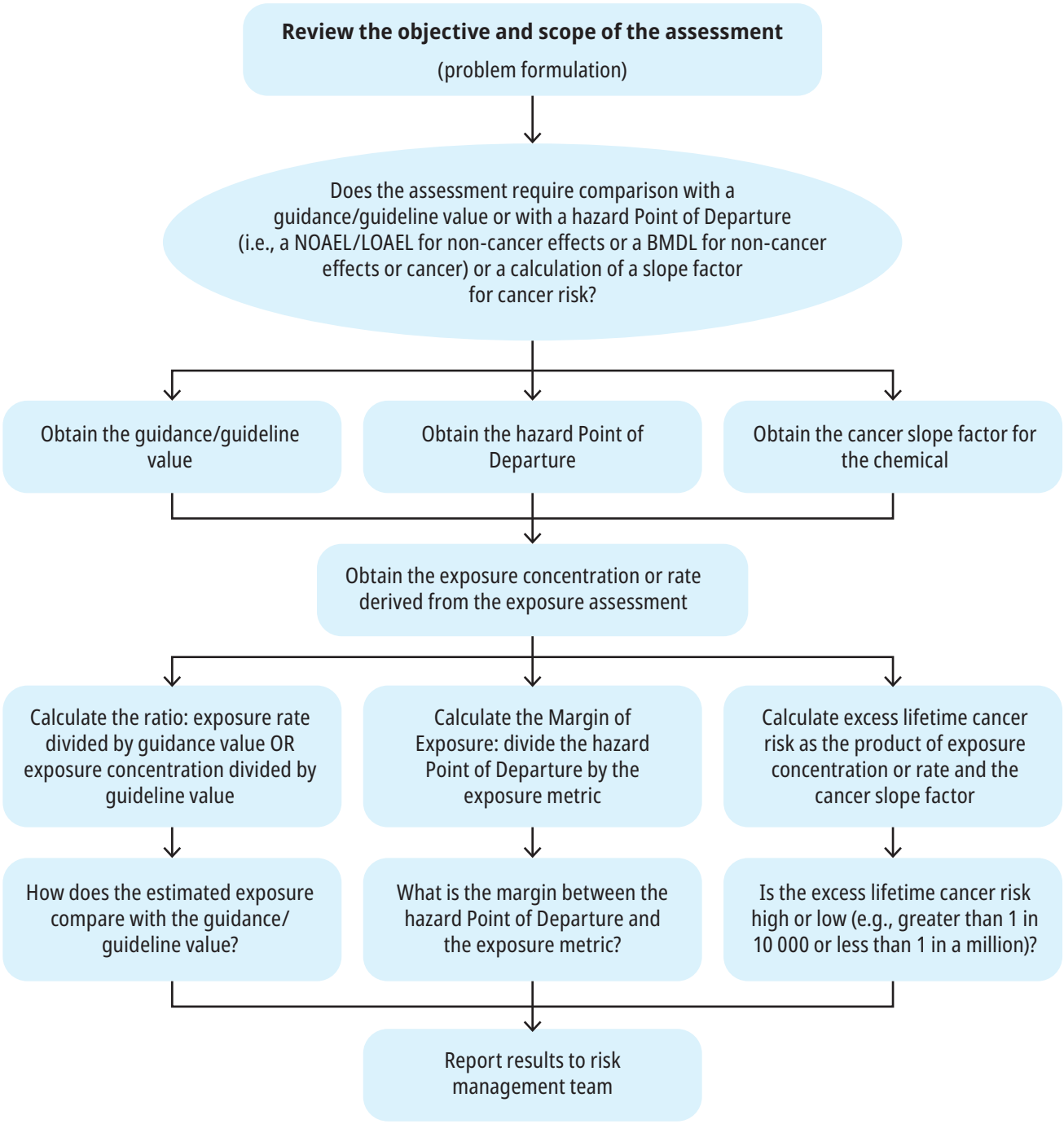
Numerous biological media are available for use in exposure assessment. Selection of sampling media depends on the contaminant of interest, the pattern of exposure, the timing of exposure, the population studied, ease of collection and storage, and participant burden. Biological monitoring is frequently 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 biomonitoring studies include faeces, nasal lavage, tears, sputum, semen, cord blood and buccal cells, which can be feasible means for population exposure characterization. For some chemicals, biomonitoring has been conducted over periods of several years, permitting a better understanding of geographical and temporal trends, such as those for mercury *(44)*. Further information on biomonitoring is available in various IPCS and WHO publications *(8, 45–47)* (see also Table 16 in section 4.8).

To assist in interpreting the results of biomonitoring in a public health context, biomonitoring equivalents (BEs) have been developed for several chemicals. BEs are estimates of the concentration of a chemical or its metabolite in a biological medium that is consistent with an existing exposure guidance value such as a tolerable daily intake or reference dose. BEs for various chemicals are available in *Human biomonitoring: facts and figures (47)*, as well as in the open scientific literature.

3.3.5 Risk characterization

The last step of a chemical risk assessment – the risk characterization – is typically a quantitative statement about the comparison of estimated exposure to the most appropriate health-based guidance value, media-specific quality guideline value or other hazard characterization value, such as the cancer slope factor or a Point of Departure (for example, a NOAEL/LOAEL or BMDL) (Figure 9).

Figure 9. Generic roadmap for risk characterization in the context of the toolkit



3.3.5.1 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. For chemicals that are considered to be "threshold chemicals" (that is, chemicals for which there is believed to be a threshold of exposure or dose for induction of effects; see subsections 3.3.3.1 and 3.3.3.2), the guidance or guideline value may be based on an exposure concentration or rate below which adverse effects are considered to be unlikely.

For chemicals that have the potential to result in non-cancer effects, risk is frequently characterized as the ratio of the appropriate exposure rate (for example, the average daily, weekly or 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 (such as the WHO air quality guideline or the WHO drinking-water quality guideline value) may also be used to assess risk. The ratio is obtained by dividing the exposure rate or concentration by the guidance value or reference concentration. A ratio of less than 1 indicates that the chemical exposure is less than the reference concentration 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 reference concentration for risk of an adverse effect. Conversely, a ratio of greater than 1 indicates that the exposure is greater than the reference concentration 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 other 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 (such as 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.

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 chemicals, guidance or guideline values are often exposure concentrations or rates that correspond to levels of risk that have been determined to be very low and may be tolerable. For instance, the WHO drinking-water guideline for benzene was based on extrapolation of modelled excess lifetime risk for leukaemia of 1 in 100 000 estimated from epidemiological studies involving inhalation exposure *(48, 49)* (see subsection 3.3.5.2 for more on estimation of cancer risk). Further, in some cases, a level of exposure associated with low levels of risk may not be achievable using control measures available at the time. For example, the WHO drinking-water guideline for arsenic is considered provisional in light of practical difficulties in removing it from drinking-water *(50)*.

3.3.5.2 Margin of exposure approach

The margin of exposure approach involves the comparison of a metric of exposure to a Point of Departure for adverse effects (such as a NOAEL or BMDL). This approach can be used for both cancer and non-cancer effects. The margin of exposure (often abbreviated as MOE) is unitless and is not an absolute value but provides guidance to risk managers of how close human exposures are to those anticipated to produce a measurable effect in experimental animals or humans. For example, the NOAEL for a non-cancer effect such as reproductive toxicity can be compared to an estimate of exposure to a chemical in a medium or during use of a product; similarly, the BMDL for a defined incidence of tumours in a cancer bioassay can be compared to a metric of exposure. JMPR and JECFA use the margin of exposure approach

when assessing presumed genotoxic carcinogens and sometimes in cases where data are inadequate for establishing guidance or guideline values. JECFA also applies the margin of exposure approach in the evaluation of additives used in infant formulas. The margin of exposure approach can be used to prioritize different contaminants, providing that a consistent approach has been adopted *(51)*.

In interpretation of a margin of exposure (such as in determination of whether the margin is adequately protective of the population), considerations that need to be taken into account are similar to those used in selection of appropriate uncertainty factors in the establishment of a guidance or guideline value, including human variability, interspecies differences, the nature and severity of the effect that is the basis of the Point of Departure and the steepness of the dose–response curve, and database uncertainties (for example, have all potentially relevant end-points been assessed). In general, a higher margin of exposure is desirable for more serious effects such as cancer, or for when there are more uncertainties in the risk assessment.

3.3.5.3 Estimation of cancer risk using the slope factor approach

For chemicals that may exert a carcinogenic effect, the risk characterization is sometimes 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 excess cancer associated with a given level of exposure averaged over a lifetime. To estimate cancer risk in environmental media, the slope factor determined from dose–response modelling, expressed in the appropriate units for relevant media (the "unit risk" or the estimated number of cases of a cancer associated with a unit of exposure), is compared to measured or estimated concentrations in those media, with the risk increasing proportionately with exposure (for example, a twofold increase in exposure would be estimated to be associated with a doubling in the number of projected cases in a population). Slope factors can be used to provide guidance for risk management. For example, a target concentration of a chemical in drinking-water that would be associated with a 1 in 100 000 ($1x10^{-5}$) excess risk for a chemical with a unit risk of $5x10^{-5}$ $(\mu g/L)^{-1}$ would be 0.2 µg/L, while the target for an excess risk of 1 in 1 000 000 ($1x10^{-6}$) would be 0.02 µg/L.

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 described in the annexes of this document 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, including 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 risk assessment guidance or data that are more specific to the populations and geographical 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.

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 and guidance or guideline value resources
- exposure assessment resources
- 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 as well as other international and national institutions. 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.

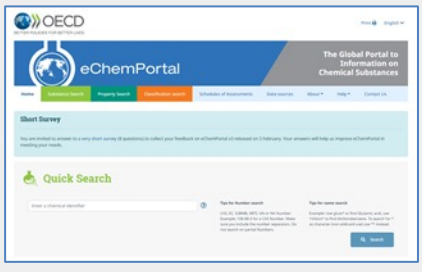
The chemical-specific resources identified in section 4.5 contain detailed summaries on numerous aspects of hundreds of chemicals that are widespread in commerce and have hazardous properties. In addition to information on hazard characterization, exposure assessment and risk characterization, these 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
Sponsor	WHO/IPCS *(17)*	OECD *(27)*
Description	A compilation of internationally peer reviewed information from a number of international organizations whose goal is to assist in the sound management of chemicals	OECD, United Nations Environment Programme (UNEP), WHO, European Chemicals Agency (ECHA) and national databases on physical-chemical properties, ecotoxicity, environmental fate and behaviour and toxicity; also GHS classifications
URL	http://www.inchem.org/	https://www.oecd.org/env/ehs/risk-assessment/echemportalglobalportaltoinformationonchemicalsubstances.htm
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 exposure to chemicals, as well as chemical incidents.

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

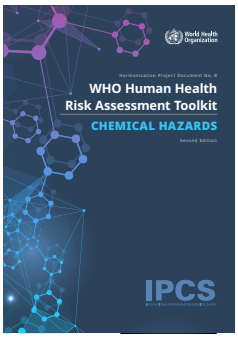
Document title	Reference
Principles for the assessment of risks to human health from exposure to chemicals (EHC 210)	IPCS *(52)*
Human exposure assessment (EHC 214)	IPCS *(8)*
Principles and methods for the risk assessment of chemicals in food (EHC 240)	IPCS *(7)*
Principles and methods for the assessment of risk from essential trace elements (EHC 228)	IPCS *(53)*
Elemental speciation in human health risk assessment (EHC 234)	IPCS *(54)*

The European Food Safety Authority (EFSA) has also published several guidance and other assessment methodology documents that define the scientific rationale for evaluations and important scientific considerations such as data needs and formats, study design requirements and reporting standards. These offer cross-cutting guidance on broader assessment principles and other methodologies, including approaches and procedures, "state-of-the-science" reviews of international assessment best practices, and reviews of new and developing assessment tools *(55).* Similarly, ECHA has published guidance on conducting human health risk assessments for registrants *(56).*

The United States EPA has also developed numerous guidance materials on a range of risk assessment topics, including assessment of cancer and several non-cancer end-points (such as developmental toxicity, neurotoxicity and mutagenicity), for individual chemicals and groups of chemicals that are made available through the Integrated Risk Information System (IRIS) (see United States EPA *(57)* for basic information about IRIS and links to the range of guidance and tools therein). Other helpful guidance documents in IRIS relate to quantitative characterization of hazard and interspecies extrapolation.

The IRIS assessments have increasingly applied the concept of systematic review in consideration of scientific information, using an objective and transparent approach for analysing and synthesizing data, with the aim of minimizing bias. WHO is in the process of developing a framework for application of systematic review methods in chemical risk assessment (see section 5.1). Likewise, WHO has published the *WHO Handbook for guideline development*, which provides guidance on the process behind

establishment of WHO guidelines (see section 4.7) *(58)*. It is anticipated that such methodologies will be further developed and elaborated in future efforts to assess chemical risks to health in a transparent and consistent manner.



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, along with key publications where the original authors have extended the tools further, are provided in Table 10 (this toolkit was originally published as No. 8 in that series).

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 *(1)*
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 *(22)*
Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance	Bhat et al. *(23)*
Principles of characterizing and applying human exposure models (Harmonization Project Document No. 3)	IPCS *(40)*
New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis (update to Harmonization Project Document No. 4, Parts 1 and 2) (59)	Meek et al. *(11)*
Skin sensitization in chemical risk assessment (Harmonization Project Document No. 5)	IPCS *(60)*
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 *(41)*
Assessment of combined exposures to multiple chemicals: report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment (Harmonization Project Document No.7)	IPCS *(61)*
Risk assessment of combined exposures to multiple chemicals: a WHO/IPCS framework	Meek et al. *(62)*
Chemical mixtures in source water and drinking-water	WHO *(63)*
Characterization and application of physiologically based pharmacokinetic models in risk assessment (Harmonization Project Document No. 9)	IPCS *(24)*

Document title	Reference
Case study illustrating the WHO/IPCS guidance on characterization and application of physiologically based pharmacokinetic models in risk assessment	Meek et al. *(64)*
Guidance for immunotoxicity risk assessment for chemicals (Harmonization Project Document No. 10)	IPCS *(65)*
Guidance document on evaluating and expressing uncertainty in hazard characterization, second edition (Harmonization Project Document No. 11)	IPCS *(9)*
A unified probabilistic framework for dose–response assessment of human health effects	Chiu and Slob (28)
APROBA-Plus: a probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances	Bokkers et al. *(29)*

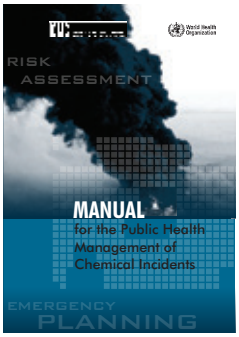
4.4.2 Resources on susceptible populations

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 (such as 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 *(66)*
Principles for evaluating health risks from chemicals during infancy and early childhood: the need for a special approach (EHC 59)	IPCS *(67)*
Principles for evaluating chemical effects on the aged population (EHC 144)	IPCS *(68)*
Principles for evaluating health risks in children associated with exposure to chemicals (EHC 237)	IPCS *(69)*
Summary of principles for evaluating health risks in children associated with exposure to chemicals	WHO *(70)*
Identifying important life stages for monitoring and assessing risks from exposures to environmental contaminants: results of a World Health Organization review	Cohen Hubal et al. *(71)*

4.4.3 Risk assessment for chemical incidents



Risk assessment also plays a crucial role in managing chemical incidents such as accidental industrial releases, natural events or deliberate mass poisonings. The WHO *Manual for the public health management of chemical incidents (72)* provides a comprehensive overview of the principles and roles of public health in the management of chemical incidents and emergencies, including prevention, planning and preparedness, detection and alert, response and recovery. The risk assessment component of this type of incident is necessarily conducted over a very short period of time (usually hours), referred to as "rapid risk assessment". WHO guidance is available on rapid risk assessment of acute public health risks from all types of hazard, including multisectoral links in these types of incidents *(73)*. The key steps of a rapid risk assessment are the same as those included in the toolkit, namely problem formulation, hazard identification, hazard characterization, exposure assessment and risk characterization. Many of the resources mentioned in the toolkit can be consulted for a rapid risk assessment, along with predictive exposure modelling tools such as the Areal Locations of Hazardous Atmospheres (ALOHA®), a programme designed by the United States EPA specifically for use in responding to chemical releases that result in toxic gas dispersions, fires, and explosions *(74)*.

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

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) is an international expert scientific group that is administered jointly by FAO and WHO *(75)*. The values set by JMPR are published in a searchable database *(26)*. JMPR consists of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, and 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 and ARfDs of the pesticides under consideration (see also subsection 3.3.3.1).

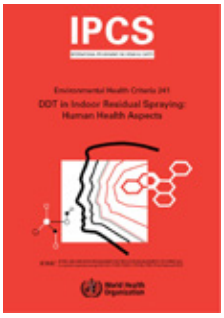
WHO and FAO have jointly developed an International Code of Conduct on Pesticide Management *(76)*. The Code provides standards of conduct and serves as a point of reference in relation to sound pesticide life cycle management practices, in particular for government authorities and the pesticide industry.

4.5.2 JECFA monographs

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an international expert scientific committee that is administered jointly by FAO and WHO. It has been meeting since 1956 to evaluate the safety of food additives, contaminants, naturally occurring toxicants and residues of veterinary drugs in food. JECFA has evaluated more than 2600 food additives, approximately 50 contaminants and naturally occurring toxicants, and the residues of approximately 75 veterinary drugs (as of 2016) *(77)*. A searchable database is maintained that contains summaries of all evaluations *(26)*. 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 subsections 3.3.3.1 and 4.7.1.2).

4.5.3 EHC monographs

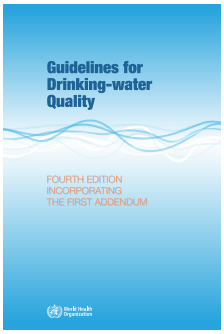


WHO has published EHC monographs on over 220 chemicals, each of which contains a detailed summary of the sources, pathways and routes of exposure to each chemical *(78)*. Ranges of exposure reported in the scientific literature for multiple exposure sources are also presented in the monographs. As such, the EHC monographs are valuable for helping investigators prioritize exposure media and routes as part of a risk assessment.

4.5.4 CICADs

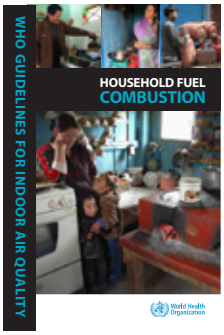
The Concise International Chemical Assessment Documents (CICADs), published by WHO, join the EHC monographs as authoritative sources of information on risk assessment of chemicals *(79)*. In addition to hazard characterization of a chemical, CICADs contain information on sources of human exposure; environmental 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, soil, food and products, 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 (see also subsection 4.7.2.1). For many of these, guideline values are derived. All of these can be accessed through WHO publications *(2)* and also via an online resource *(80)*

4.5.6 Air quality guidelines



WHO sets recommended limits for concentrations of key harmful air pollutants both outdoors and inside buildings and homes, based on a global synthesis of scientific evidence (see also subsection 4.7.2.2). WHO guidelines cover annual and daily concentrations of fine particulates, nitrogen dioxide, sulfur dioxide, carbon monoxide and ozone *(12)*. Guidelines also cover indoor mould and dampness *(34)*. Most recently, WHO *Guidelines for indoor air quality: household fuel combustion* set limits on emissions from cooking and heating stoves, as well as recommendations regarding clean fuel use *(33)*.

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 *(5)*.

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 and other sources (Table 12). Likewise, OECD has published a series of guidance documents and case studies on how to test for and assess different kinds of toxic effects *(81)*, such as endocrine disruption *(82)*.

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 *(83)*
Principles and methods for the assessment of nephrotoxicity associated with exposure to chemicals (EHC 119)	IPCS *(84)*
Principles and methods for assessing direct immunotoxicity associated with exposure to chemicals (EHC 180)	IPCS *(85)*
Principles and methods for assessing allergic hypersensitization associated with exposure to chemicals (EHC 212)	IPCS *(86)*
Principles for evaluating health risks to reproduction associated with exposure to chemicals (EHC 225)	IPCS *(87)*
Principles and methods for assessing autoimmunity associated with exposure to chemicals (EHC 236)	IPCS *(88)*
Guidance for immunotoxicity risk assessment for chemicals (Harmonization Project Document No. 10)	IPCS *(65)*
The WHO recommended classification of pesticides by hazard and guidelines to classification 2019	WHO *(89)*
Pesticide registration toolkit: identification of HHPs	FAO *(90)*

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 Dataset for High Production Volume Chemicals	Detailed	No
WHO Recommended Classification of Pesticides by Hazard	Summary	Yes
United Nations Recommendations on the Transport of Dangerous Goods	Summary	Yes
IARC monographs	Detailed	Yes
Hazardous Substances Data Bank	Detailed	No
European Union Classification and Labelling System	Detailed	Yes
ECHA substance evaluation reports	Detailed	Yes
ECHA Infocards	Summary	Yes
European Union risk assessment reports	Detailed	No
International Chemical Control Toolkit	Detailed	Yes
EFSA OpenFoodTox chemical hazards database	Summary	No

4.6.1 International Chemical Safety Cards

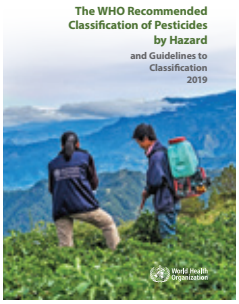
International Chemical Safety Cards (ICSCs) contain a brief summary of essential information on chemicals that was developed cooperatively by IPCS and the International Labour Organization *(91)*. In addition to potential health and environmental hazards, each ICSC also contains a description of fire and explosion hazards and preventive measures, as well as appropriate responses to a spill, packaging and labelling information, guidance on personal protection, and storage conditions. Basic physical, chemical and hazardous properties of chemicals are also summarized in a standard format on each ICSC. GHS classifications *(18)* are also indicated on many ICSCs. The ICSCs are available in multiple languages.

4.6.2 Screening Information Dataset for High Production Volume Chemicals

The OECD 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, along with the major conclusions of the hazard assessment *(92)*. 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 (that is, the risk of a single exposure or multiple exposures over a relatively short period of time) *(89)*. 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. Since 2009, the acute toxicity hazard categories from the GHS have been used as the starting point for determining a revised classification scheme, replacing the guide points originally proposed in 1975.

4.6.4 United Nations Recommendations on the Transport of Dangerous Goods

The United Nations Recommendations on 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 chemicals and materials, the exigencies of modern transport systems and, above all, the requirement to ensure the safety of people, property and the environment *(93)*. Goods, including chemicals, are classified according to hazard class. The recommendations are harmonized with the GHS *(18)*.

4.6.5 IARC monographs

IARC has published summaries and evaluations of the evidence of carcinogenicity of chemicals since its inception in 1969 *(19)*. 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, is a detailed listing of peer-reviewed toxicological data for over 5800 chemicals, including information on human health effects, emergency medical treatment, physicochemical properties, metabolism, toxicology and laboratory methods. It is accessed by searching for the chemical in the United States National Institutes of Health PubChem database *(94)*. Unlike the ICSCs (see subsection 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 Union (EU) Classification and Labelling System

Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures of the EU (commonly referred to as the "CLP Regulation) entered into force on 20 January 2009 and is based on the GHS *(18)*. Since 2015, the regulation is the only legislation in force in the EU for classification and labelling of substances and mixtures.

An online version of the Classification and Labelling Inventory of the European Chemicals Agency (ECHA) is available *(95)*. This "C&L Inventory" is a database that contains classification and labelling information on notified and registered chemicals on the EU market according to their toxicological properties, as well as harmonized classifications where they have been established in the EU for health hazards of highest concern (carcinogenicity, mutagenicity and reproductive toxicity). It should be noted that the C&L Inventory shows information that has been submitted to ECHA by manufacturers and importers but, apart from EU harmonized classifications, ECHA does not review or verify the accuracy of the information.

4.6.8 ECHA substance evaluation reports

As part of the implementation of the regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), comprehensive substance evaluations are prepared by EU Member States under the coordination of ECHA. Substance evaluation aims to clarify whether a chemical that has been identified as being of potential concern poses an actual risk to human health and/or the environment, based on information submitted by registrants and any additional clarifying information requested *(96)*. These reports contain information related to clarifying the risk of particular concern but also include information on other aspects. The ECHA REACH database *(97)* provides comprehensive information on chemicals.

4.6.9 ECHA Infocards

ECHA Infocards provide a first-tier tool for disseminating information on chemicals from ECHA's database. Infocards present key information on chemical identification, hazard classification and labelling, properties of concern, a summary of the most relevant regulatory activities in the EU, how to safely use the chemical, and where and how the chemical is used, along with other helpful information such as guidance on where to find more detailed information *(97)*. Information is displayed automatically on Infocards based on data submitted to ECHA by manufacturers and importers, and does not undergo review or verification by ECHA. The quality and correctness of the information is the responsibility of the data submitter, not ECHA.

4.6.10 EU risk assessment reports

Before REACH came into force, comprehensive risk assessment reports were prepared by Member States and published by the Joint Research Centre of the European Commission. Several of these assessments are now available on the ECHA website *(98)* and on the EU Publications Office website *(99)*. These reports evaluated environmental risks as well as risks to human health from occupational, consumer and environmental exposures to chemicals.

4.6.11 International Chemical Control Toolkit

Another source of hazard information is provided by the International Chemical Control toolkit of the International Labour Organization *(100)*, 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.

4.6.12 EFSA OpenFoodTox chemical hazards database

The EFSA OpenFoodTox *(101)* is a structured database that summarizes the outcomes of hazard identification and characterization for human health (all regulated products, including substances used in feed and food, and contaminants), as well as for animal health (feed additives, pesticides and contaminants) and the environment (feed additives and pesticides). The database provides open-source information on the substance characterization, links to EFSA's related output, background European legislation, and a summary of the critical toxicological end-points and reference values.

4.7 Hazard characterization/guidance or guideline value resources

As mentioned in subsection 3.3.3, 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 (for example, exposure duration and allocation of total exposure among routes of exposure).

WHO has published a *Handbook for guideline development (58)*, which provides step-by-step guidance on how to plan, develop and publish a WHO guideline. The handbook covers the methods, processes and procedures for producing a document that meets WHO standards for guidelines (WHO publications containing recommendations for clinical practice or public health policy). It does not provide detailed technical guidance on many of the steps; this can be obtained from the references in the handbook. The principles of the methods underlying WHO guidelines are that they should be based on a review of all the relevant evidence in a systematic process that evaluates the evidence in ways that minimize the risk of bias and evaluate the quality of the evidence using a framework such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) (see section 5.1). Evaluations of the health effects of chemicals are increasingly adopting systematic review principles, a trend that is likely to continue in the future (see section 5.1).

The resources noted in subsections 4.7.1–4.7.3 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. As described in subsection 3.3.5, 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. Points of Departure (such as BMDLs or NOAELs) presented in some of these resources can also be used to derive margins of exposure (MOEs) to provide guidance to risk managers. In addition, this section provides an example of a national resource that provides similar information from national assessments (the United States EPA IRIS database). Finally, the section provides examples of national resources of occupational exposure limits (OELs).

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 *(102)*
Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits (EHC 170)	IPCS *(36)*
Principles for modelling dose–response for the risk assessment of chemicals (EHC 239)	IPCS *(6)*
Principles and methods for the risk assessment of chemicals in food (EHC 240)	IPCS *(7)*
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 *(22)*
Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience: increasing utility and facilitating regulatory acceptance	Bhat et al. *(23)*
New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis (update to Harmonization Project Document No. 4, Parts 1 and 2 (59))	Meek et al. *(11)*

OECD also coordinates projects to help identify the health hazards associated with exposure to chemicals or groups of chemicals using predictive technologies such as the quantitative structure–activity relationship (QSAR) through the OECD QSAR Toolbox *(103)* and gain better understanding of the biological pathways by which they are induced (Adverse Outcome Pathways) *(104)*, which can be useful in a higher-tier assessment.

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 the WHO food safety databases *(26)*. Additional information is available in Tables 5 and 6 and subsection 3.3.3.1.

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 subsection 3.3.3.1). These values are also available on the WHO food safety databases *(26)*.

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. The guideline values, as well as supporting information and the methodology employed to derive the guideline values, are published *(2)*. 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 100 000). 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 factor when considering whether the WHO drinking-water guidelines should be adapted for country use.

The methodology used to develop WHO drinking-water guidelines is being adapted to systematically review the evidence available for the health effects of chemicals, in line with the WHO *Handbook for guideline development (58)*.

While the WHO drinking-water guidelines are based on the hazard characterization, it should be noted that other factors may also be taken into consideration in derivation of the guidelines, including treatment technologies, analytical capabilities and feasibility.

4.7.2.2 WHO air quality guidelines

Air pollution from both outdoor and indoor sources represents the single largest environmental risk to health globally *(32)*. WHO publishes air quality guidelines for ubiquitous pollutants in ambient (outdoor) air – particulate matter, ozone, nitrogen dioxide and sulfur dioxide *(12)* – and other commonly encountered pollutants. 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 subsection 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.

WHO has also developed guidelines for indoor air quality for a number of indoor pollutants, including chemicals, biological contaminants and those derived from household fuel consumption *(31, 33, 34)*.

WHO has recently undertaken an update of the air quality guidelines, a process that will involve systematic review of the enormous amount of new relevant scientific evidence. The process will apply the procedures outlined in the WHO *Handbook for guideline development (58)* and will use evidence-based methods for assessing the quality of the body of evidence.

4.7.3 Guidance and guideline values from chemical-specific monographs

Media-specific guidelines, as well as ADIs, TDIs and other guidance and guideline 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.

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.

4.7.4 Integrated Risk Information System

The United States EPA maintains an online database that contains chronic toxicity values for more than 500 chemicals, groups of chemicals or mixtures *(105)*. The database contains reference concentrations (RfC) or reference doses (RfD), which are derived from a NOAEL, LOAEL, or benchmark concentration or dose, with uncertainty factors generally applied to reflect limitations of the data used. For cancer, the IRIS database contains qualitative descriptors as well as oral slope factors and inhalation unit risks. This source contains national information provided by the United States Government. Other sources of national information may also be available and should be consulted where applicable.

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. The EU provides OELs for a range of workplace chemicals, based on scientific advice from ECHA (previously provided by the Scientific Committee for Occupational Exposure Limits to Chemical Agents (SCOEL)). The EU OELs, along with several available national OELs, are available on the free GESTIS Substance Database, hosted by the Institute for Occupational Safety and Health of the German Social Accident Insurance *(106)*. Not freely available OELs include, for example, the threshold limit values (TLVs) of the American Conference of Governmental Industrial Hygienists *(107)*.

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 subsection 3.3.4. The resources on specific chemicals are compendia of chemical 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.

Fundamental principles and approaches for chemicals in specific environmental media and routes of exposure such as food, water and air are set out in several guidance and EHC documents available from WHO. Key examples of these materials are listed in Table 15.

Table 15. 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 (EHC 240)	IPCS *(7)*
Pesticide residues in food	Principles and methods for the risk assessment of chemicals in food (EHC 240)	IPCS *(7)*
Dermal absorption	Dermal absorption (EHC 235)	IPCS *(108)*
Drinking-water quality guidelines	Guidelines for drinking-water quality: fourth edition, incorporating the first addendum	WHO *(2)*

Topic	Document title	Reference
Air quality guidelines	Air quality guidelines for Europe, second edition	WHO Regional Office for Europe *(30)*
Air quality guidelines	Air quality guidelines – global update 2005: particulate matter, ozone, nitrogen dioxide and sulfur dioxide	WHO Regional Office for Europe *(12)*
Indoor air quality guidelines	WHO guidelines for indoor air quality: selected pollutants	WHO Regional Office for Europe *(31)*

4.8.1 General guidance on exposure assessment

General guidance on exposure assessment is provided in the international resources listed in Table 16. Information about some examples of other tools that are available from sources other than international organizations are shown in the following list.

Other tools available for exposure assessment (not international resources)

- The United States EPA provides a list of a range of tools and databases to assist in conducting exposure assessments for human health risk assessment and ecological assessment, pulled from the EPA ExpoBox and EPA EcoBox websites, respectively *(109)*. The EPA ExpoBox provides links to guidance documents, databases, models, reference materials, and other related resources for exposure assessment for six "tool sets", including approaches, media, routes, tiers and types, life stages and populations, and chemical classes *(37)*.

- The Environmental Modeling Community of Practice of the United States EPA 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 *(110)*.

- The National Institute for Public Health and the Environment of the Netherlands (RIVM) has developed a suite of helpful models called ConsExpo *(39)* to assist in assessing exposure to chemicals in products, in particular for spray products, with an emphasis on consumer products (see subsection 4.8.2 for further details).

- Institutions in the United Kingdom have developed a range of models to estimate exposure to chemicals, including for contaminated soil (Contaminated Land Exposure Assessment tool) *(111)* and for registration of pesticides *(112)*.

- The European Centre for Ecotoxicology and Toxicology of Chemicals *(113)* has developed a Targeted Risk Assessment (TRA) tool to calculate exposures for workers, consumers and the environment. The TRA tool is used extensively in the European Union to prepare chemical safety reports submitted under the REACH regulations.

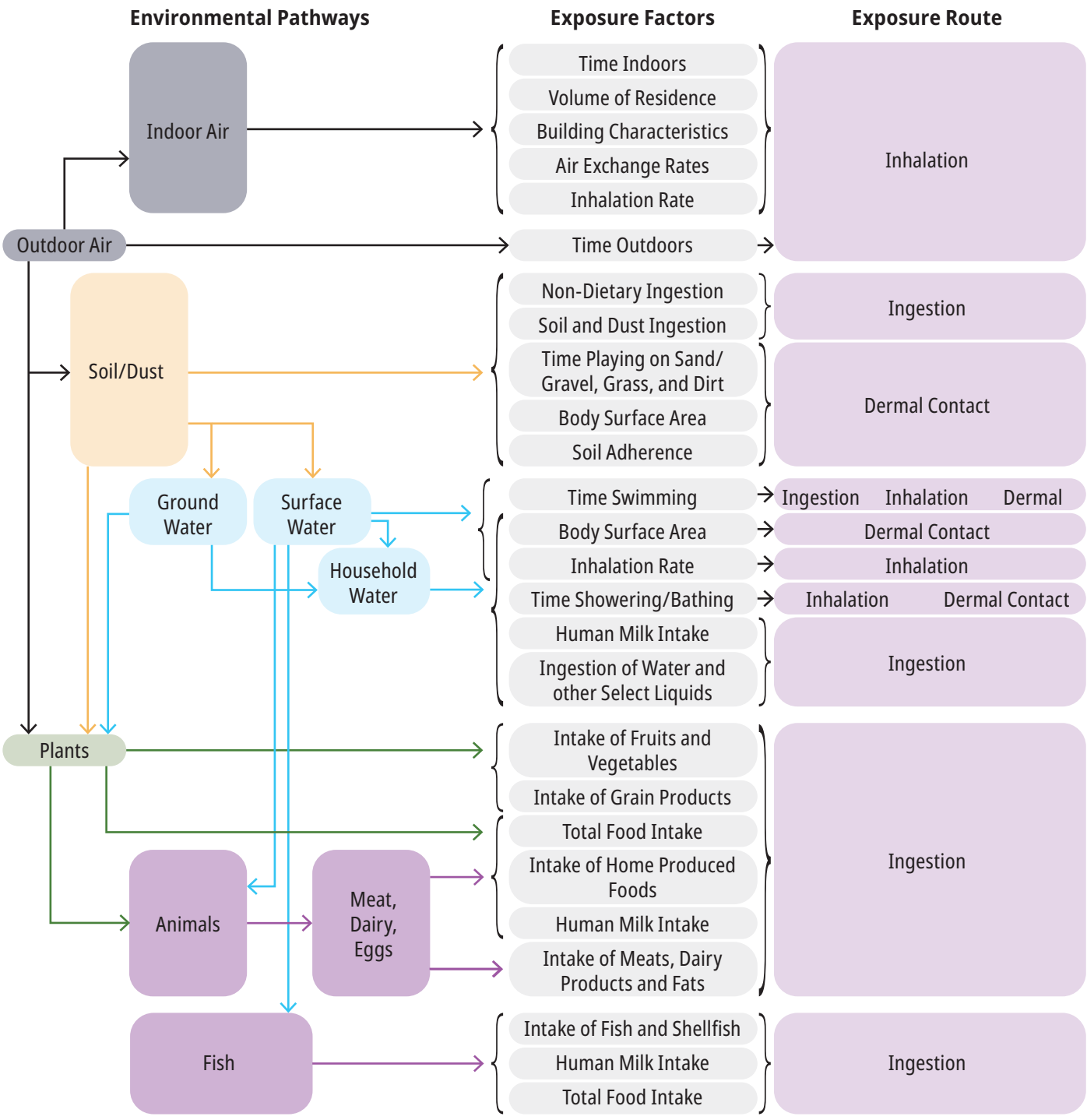
Table 16. International sources of guidance on exposure assessment

Document title	Reference
Human exposure assessment (EHC 214)	IPCS *(8)*
Human exposure assessment: an introduction	Berglund, Elinder and Järup *(114)*
Dietary exposure assessment of chemicals in food: report of a joint FAO/WHO consultation, Annapolis, MD, 2–6 May 2005	FAO/WHO *(115)*
Towards a harmonised total diet study approach: a guidance document	EFSA/FAO/WHO *(116)*
Occupational and consumer exposure assessments	OECD *(117)*
Principles of characterizing and applying human exposure models (Harmonization Project Document No. 3)	IPCS *(40)*
Dermal exposure (EHC 242)	IPCS *(15)*
Considerations when assessing children's exposure to chemicals from products	OECD *(118)*
Biomarkers and risk assessment: concepts and principles (EHC 155)	IPCS *(45)*
Biomarkers in risk assessment: validity and validation (EHC 222)	IPCS *(46)*
A state-of-the-science review of mercury biomarkers in human populations worldwide between 2000 and 2018	Basu et al. *(44)*
Human biomonitoring: facts and figures	WHO *(47)*
Review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment for food safety	Choi et al. *(119)*
Generic risk assessment model for insecticide-treated nets, second edition	WHO *(120)*
Generic risk assessment model for indoor and outdoor space spraying of insecticides, second edition	WHO *(121)*

4.8.2 Exposure factors

In order to characterize human exposure to chemicals, generic or default exposure factors are often incorporated. Exposure factors are 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. A schematic diagram of exposure pathways, exposure factors and exposure routes is presented in Figure 10.

Figure 10. Schematic diagram of exposure pathways, factors and routes



Note: The pathways presented are selected pathways. This diagram is not meant to be comprehensive. Products are not shown; humans can be exposed to products through all pathways and routes.
Source: United States EPA, ExpoBox *(122)*.

Default exposure factors for adults published by WHO are summarized in Table 17.

Table 17. Summary of selected exposure factors published by WHO

Exposure factor	Value	Reference
Drinking-water consumption	2 litres/day	WHO *(2)*
Body weight	60 kg	IPCS *(52)*
Food consumption	Diets for clusters of countries	WHO *(123)*

Other helpful resources for exposure factors are summarized in Table 18 and are discussed further below.

Table 18. Summary of additional resources on exposure factors

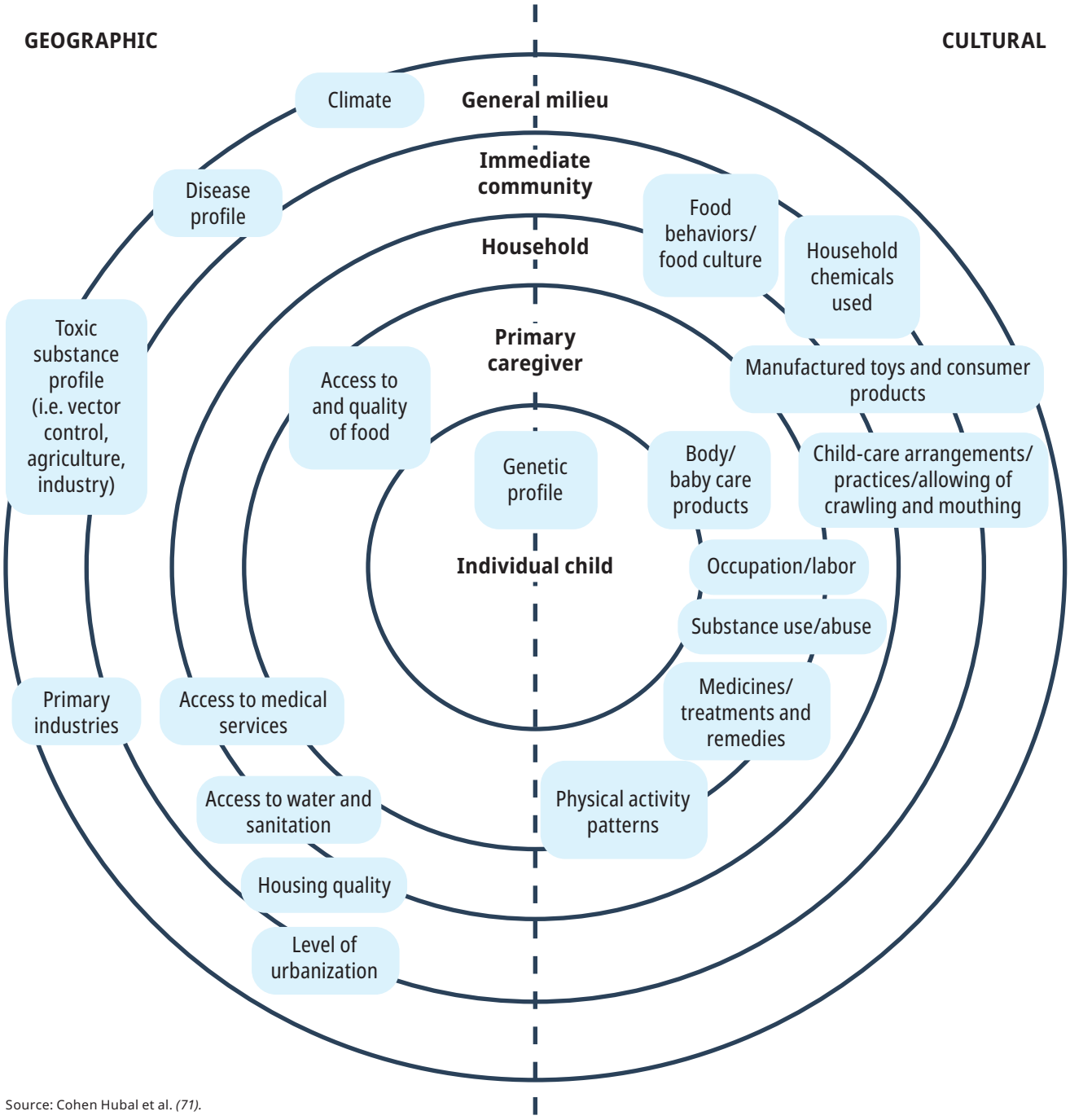
Document title	Reference
EPA ExpoBox: about the exposure factors handbook	United States EPA *(122)*
Neglected tropical diseases: guidelines and risk assessment models	WHO *(43)*
Generic risk assessment model for insecticide-treated nets, second edition	WHO *(120)*
Generic risk assessment model for indoor and outdoor space spraying of insecticides, second edition	WHO *(121)*
Exposure Factors Interactive Resource for Scenarios Tool (ExpoFIRST), Version 2.1	United States EPA *(124)*
Current fact sheets	RIVM *(125)*
Identifying important life stages for monitoring and assessing risks from exposures to environmental contaminants: results of a World Health Organization review	Cohen Hubal et al. *(71)*
Guidance on selecting age groups for monitoring and assessing childhood exposures to environmental contaminants	United States EPA *(126)*
Child-specific exposure factors handbook	United States EPA *(127)*
Highlights of the child-specific exposure factors handbook (final report)	United States EPA *(128)*
Child-specific exposure scenarios examples (final report)	United States EPA *(129)*

The United States EPA *(122)* has published an extensive *Exposure factors handbook* for assessing human exposure, including drinking-water consumption, soil ingestion, inhalation rates, dermal factors, consumption of various foodstuffs (including human breast milk), activity factors, product use and building characteristics. These exposure factors have been used by WHO in the development of guidelines and risk assessment models for neglected tropical diseases *(43).* Recommended values are presented for the general population and also for various segments of the population who may have characteristics different from the general population. Values for a particular segment of the United States population that is closer in terms of size parameters to the population of interest may be selected in preference to the values for the general population; for example, the 25th percentile values for females aged 30–40 years (with a bodyweight of 60 kg) have been used to represent the population of interest in areas where vector control is undertaken (for example, where malaria is endemic) in some WHO generic exposure models for use of insecticides *(120, 121).* To facilitate use of the *Exposure factors handbook* in conducting an exposure assessment, the United States EPA provides an interactive online tool, ExpoFIRST *(124)*, which allows users to draw on data found in the handbook to develop user-defined scenarios; the user can modify parameters to develop deterministic exposure estimates to suit the assessment situation.

The RIVM ConsExpo suite of models for estimating consumer exposures from products incorporate numerous default exposure factors, such as values for the room in which the exposure takes place (for example, room size), for the person that is exposed (such as body weight and the surface areas of different parts of the body), as well as information on ventilation in houses *(38, 39)*. Information is also provided on inhalation rates for adults and children while at rest and during exercise, along with data on activity patterns. These default factors are available in a series of fact sheets *(125)*.

However, chemical exposures can change throughout stages of life related to changes in anatomy, physiology, metabolism and behaviour. It may therefore be important to identify the ages or life stages most vulnerable to chemicals. To address this need, a group of experts convened by WHO developed a two-tier, fit-for-purpose approach for monitoring and assessing risks from exposures to chemicals for global use with a focus principally on early life stages, from preconception through adolescence *(71)*. The first tier involves the adoption of guidance similar to the childhood age groups recommended by the United States EPA *(126)*, while the second tier consolidates some of those age groups to reduce the burden of developing age-specific exposure factors for different regions. The harmonized age groups allow for greater consistency and better comparison across time, place and culture. The numerous factors that modify exposures to different age groups are also described (Figure 11).

Figure 11. Framework of modifying factors for exposure associated with geography and culture



Source: Cohen Hubal et al. *(71)*.

Also helpful in assessing exposure in young children is the *Child-specific exposure factors handbook* published by the United States EPA *(127, 128)*. Factors include drinking-water consumption, soil ingestion and non-dietary factors, inhalation rates, dermal factors including skin area and soil adherence factors, consumption of fruits and vegetables, fish, meats, dairy products, homegrown foods, human milk, activity patterns, body weight and products. A range of example scenarios specifically for children is available from the United States EPA *(129)*.

4.8.3 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 geographical 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.

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 more than 60 industry categories or use categories, including wood preservatives, plastic additives, leather processing, paper mills, flame retardants and many others *(130)*. ECHA *(14)* has also made available emission scenario documents that describe environmental releases for different industrial categories and biocidal products. These documents are useful for understanding processes that may contribute to emissions of contaminants and support the hazard identification process.

4.8.4 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 chemical 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 19). 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 19.

Table 19. Widely accepted resources on emissions

Source	Topic	Reference
European Monitoring and Evaluation Programme	Emission data for long-range transboundary air pollutants	EMEP *(131)*
European Environment Agency	Pollutant emission inventories for stationary and mobile sources	EEA *(132)*
National Atmospheric Emissions Inventory	Emission factors database	NAEI *(133)*
Intergovernmental Panel on Climate Change (IPCC) Emission Factors Database	Emission factors for greenhouse gases	IPCC *(134)*
Clearinghouse for Inventories and Emission Factors	Pollutant emission inventories for stationary and mobile sources	United States EPA *(135)*

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 *(8)*.

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 chemical 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*-dichlorodip henyltrichloroethane, or DDT), to volatilize 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.

4.8.5 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. An example of a dispersion model is AERMOD *(136)*.

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 *(137)*. 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 is 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 *(2)*.

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 chemical to predict its distribution among environmental media based on diffusive processes. As a result, the geographical 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. Environmental fate models continue to evolve; discussion of developments in this area can be found in the scientific literature.

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. The EUSES model, supporting documentation and training materials are available from the ECHA website *(138)*. EUSES is intended mainly for initial and refined risk assessments rather than for comprehensive assessments.

4.8.6 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 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 products that is 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. With respect 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 the annexes. Frequently used modelling approaches for estimating exposure concentrations are introduced in subsections 4.8.4 and 4.8.5. In reference to subsection 4.8.5, exposure assessment features in the EUSES model cover the entire life cycle of chemicals 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 *(8)*. 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. For example, the Joint Research Centre of the European Commission hosts the online Information Platform for Chemical Monitoring (IPCHEM), which collates data on chemical occurrences, mostly in Europe. IPCHEM is structured into four modules for environmental monitoring, human biomonitoring, food and feed, and products and indoor air *(139)*.

4.8.7 Exposure from products

In addition to exposure to chemicals in environmental media and food, the general population is also exposed on a daily basis to chemicals present in products, such as household cleaners, insecticide products, paints and personal care products. Awareness of products as an important source of exposure to chemicals has increased in recent years, and much attention has been focused on assessing exposures from products. Information on the presence of chemicals in products can be obtained from listings of product ingredients, the scientific literature and Safety Data Sheets (for products also used in the workplace), as well as from available databases such as the CompTox Chemicals Dashboard *(16)*.

Several models have been developed by agencies to estimate exposure to chemicals from products, such as the ConsExpo suite of models (see subsection 4.8.2) developed by the National Institute for Public Health and the Environment of the Netherlands (RIVM). ConsExpo is recommended for use as a higher-tier consumer exposure assessment model within the scope of the EU REACH *(38, 39)*. Numerous other models and tools are described in EHC 242 on dermal exposure *(15)*.

WHO has developed generic models for estimating exposure to insecticides used for space spraying (indoors and outdoors), as indoor residual sprays, for treatment of sleeping nets and for products used as larvicides and molluscicides *(43)*.

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 subsection 4.4.1.

5. EVOLVING APPROACHES AND METHODOLOGIES

Methodologies for chemical risk assessment continue to evolve over time as more knowledge and experience are gained, and with the increasing pace of technological advancements as a means of generating and analysing relevant data. International collaborative activities, such as those undertaken under the WHO Chemical Risk Assessment Network *(140)* and other initiatives, contribute significantly to the development of forward-looking and harmonized approaches to risk assessment. Some evolving developments in chemical risk assessment methodology, which may be incorporated into international evaluations that could be consulted by users of this toolkit, are described briefly below.

5.1 Evidence-based methodologies

The widespread adoption of evidence-based medicine has prompted scientists to apply the principles of evidence-based quality assessment and systematic review to toxicology and human health risk assessment. To assess the quality of a body of evidence and to develop and report recommendations when developing guidelines, WHO has adopted the widely used Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach *(141)*. This is a structured framework for assessing the quality of evidence using processes that are explicit and transparent *(58)*. The GRADE approach to rating quality of evidence is illustrated in Figure 12.

Figure 12. The GRADE approach to rating quality of evidence for each outcome

1 Establish initial level of quality or confidence		2 Consider lowering or raising level of quality or confidence		3 Final level of quality (confidence rating)
Study design	**Initial confidence in an estimate of effect**	**Reasons for considering lowering or raising confidence**		**Confidence in an estimate of effect across all considerations**
		↓ Lower if	**↑ Higher if#**	
Randomized controlled trials →	High confidence	**Risk of bias** **Inconsistency** **Indirectness** **Imprecision** **Publication bias**	**Large effect** **Dose response** **All plausible confounding and bias** — would reduce a demonstrated effect or — would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕○
Observational studies →	Low confidence			Low ⊕⊕○○
				Very low ⊕○○○

Note: Criteria for upgrading the quality are only applicable to observational studies without any reason for downgrading.
Source: WHO *(58)*.

As noted above in subsection 4.4.1, WHO is developing a high-level framework document on the use of systematic review in chemical risk assessment. Systematic review refers to a structured and documented process for consideration of relevant information with the goals of minimizing error and bias and the production of a transparent literature review. Other institutions, including the United States National Toxicology Program and EFSA, have developed detailed guidance for the use of systematic reviews and evidence integration in human health risk assessment *(142, 143)*.

5.2 Chemical grouping and read-across

To facilitate the assessment of multiple related chemicals simultaneously, including those for which limited information is available, OECD has published guidance on analogue and category approaches *(144)*. In the analogue approach, data gaps for a specific chemical are filled using data from one or more similar chemical(s) ("the analogue(s)") or "source" chemicals to predict the same end-point for the "target" chemical. In the category approach, chemicals whose physical-chemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group. This approach differs from the analogue approach, in which each chemical is assessed on an individual basis, in that the properties of the individual chemicals within a category are assessed on the basis of the evaluation of the category as a whole, rather than based on measured data for any one particular chemical alone. Data gaps can be filled in a number of ways, including by read-across (qualitatively or quantitatively) from one or more other chemicals in the category. Within a chemical category, the members are often related by a trend in an effect for a given end-point, and a trend analysis can be carried out through deriving a model based on the data for the members of the

category. Grouping and read-across approaches can reduce the need for experimental testing since every substance does not need to be tested if these approaches can be applied instead.

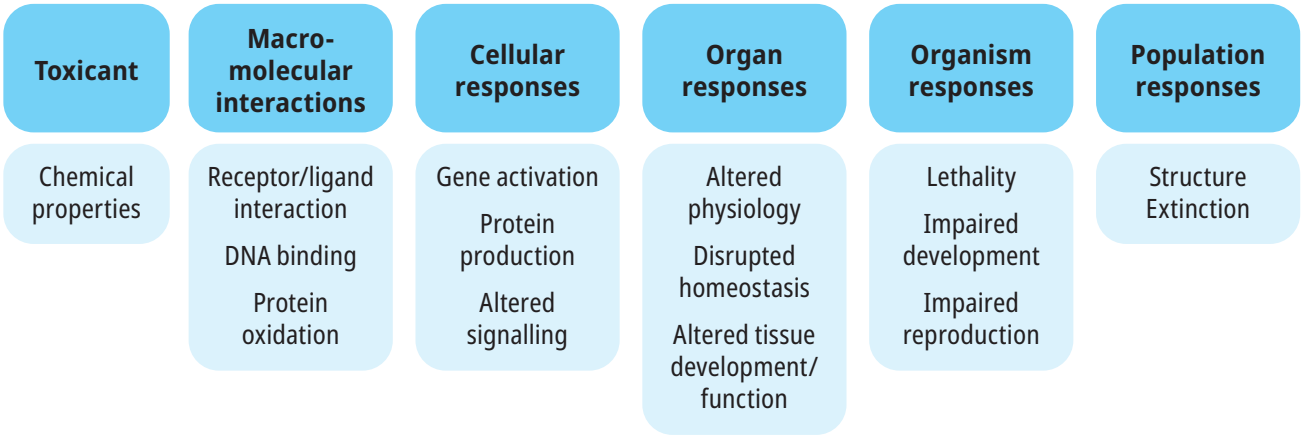
5.3 Threshold of toxicological concern

The threshold of toxicological concern (TTC) is a pragmatic risk assessment tool that may be used to assess potential human health concerns for a chemical based on its structural similarities to other chemicals and estimated exposure when chemical-specific toxicity data are scarce or absent. The TTC approach is a fit-for-purpose methodology that can be used as a screening tool, to assess low-dose chemical exposures and to identify those for which further data are necessary to assess the human health risk. It can be used where evaluation of a large number of compounds with low exposure is required, in prioritization of large numbers of compounds where resources are limited, or when a rapid safety assessment is needed. This approach has evolved over the years and was expanded by EFSA and WHO to develop a tiered approach and accompanying decision tree, recognizing that the TTC approach is not suitable for some types of chemicals, such as high-potency carcinogens, inorganics, metals and various others *(145)*. EFSA has published guidance on the use of the TTC approach in food safety assessment *(146)*.

5.4 Adverse Outcome Pathways

OECD, through engagement of its member countries, has been leading the ongoing development of Adverse Outcome Pathways (AOPs) to support development of testing strategies and hazard assessment based on mechanistic reasoning *(104)*. Based on the same principles as the WHO/IPCS Mode of Action framework *(11)*, an AOP describes a plausible sequence of causally linked key events (KEs) and key event relationships (KERs) at different levels of biological organization, from the molecular initiating event (MIE) resulting from exposure to a chemical stressor to an adverse outcome (health effect) in humans or wildlife. AOPs are available in the OECD AOP Wiki, an interactive and virtual encyclopaedia for AOP development. Following their development and review, endorsed AOPs are published in the OECD series on Adverse Outcome Pathways *(147)*. A guidance document for developing and assessing AOPs and a users' handbook are also available through OECD *(148)*. A schematic representation of the AOP is illustrated in Figure 13.

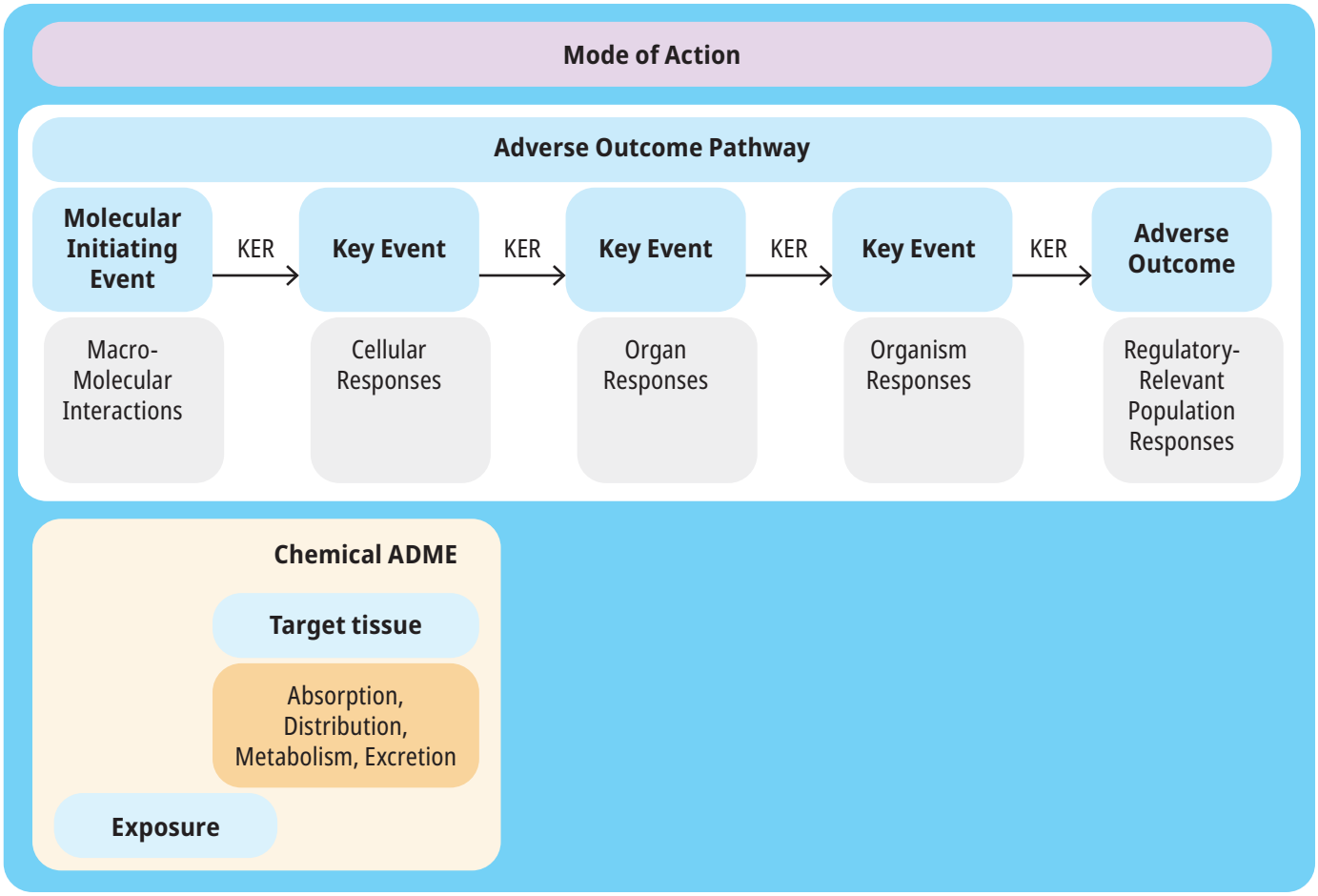
Figure 13. Schematic representation of the AOP illustrated with reference to a number of pathways



Source: Figure reproduced from OECD *(104)*

While AOPs and Mode of Action (MOA) analyses are conceptually identical in that they both describe a sequence of causally linked events leading to toxicity, AOPs do not apply to specific chemicals whereas MOA analyses are constructed for specific chemicals and therefore require incorporation of chemical-specific information, such as metabolism and toxicokinetics, in consideration of species concordance *(149)*. Therefore, a MOA could be considered an extension of an AOP (Figure 14).

Figure 14. Illustration of the relationship between MOA and AOP



Source: Edwards et al. *(149)*.

5.5 New approach methodologies

Extensive work continues to be undertaken by numerous national and international institutions (such as ECHA, OECD, and the Joint Research Centre of the European Community) to enhance the incorporation of new approach methodologies (often referred to as "NAMs") in human health risk assessment. New approach methodologies include a range of non-animal testing approaches including in silico tools, in chemico and in vitro assays, and high-throughput screening and high-content methods such as genomics, proteomics and metabolomics *(150)*. New approach methodologies are important in informing integrated approaches to testing and assessment *(151)*, providing guidance for targeted testing strategies. In addition to providing valuable information on the toxicity of chemicals, new approach methodologies are also being developed for application in exposure assessment, complementary to measurement data *(152)*.

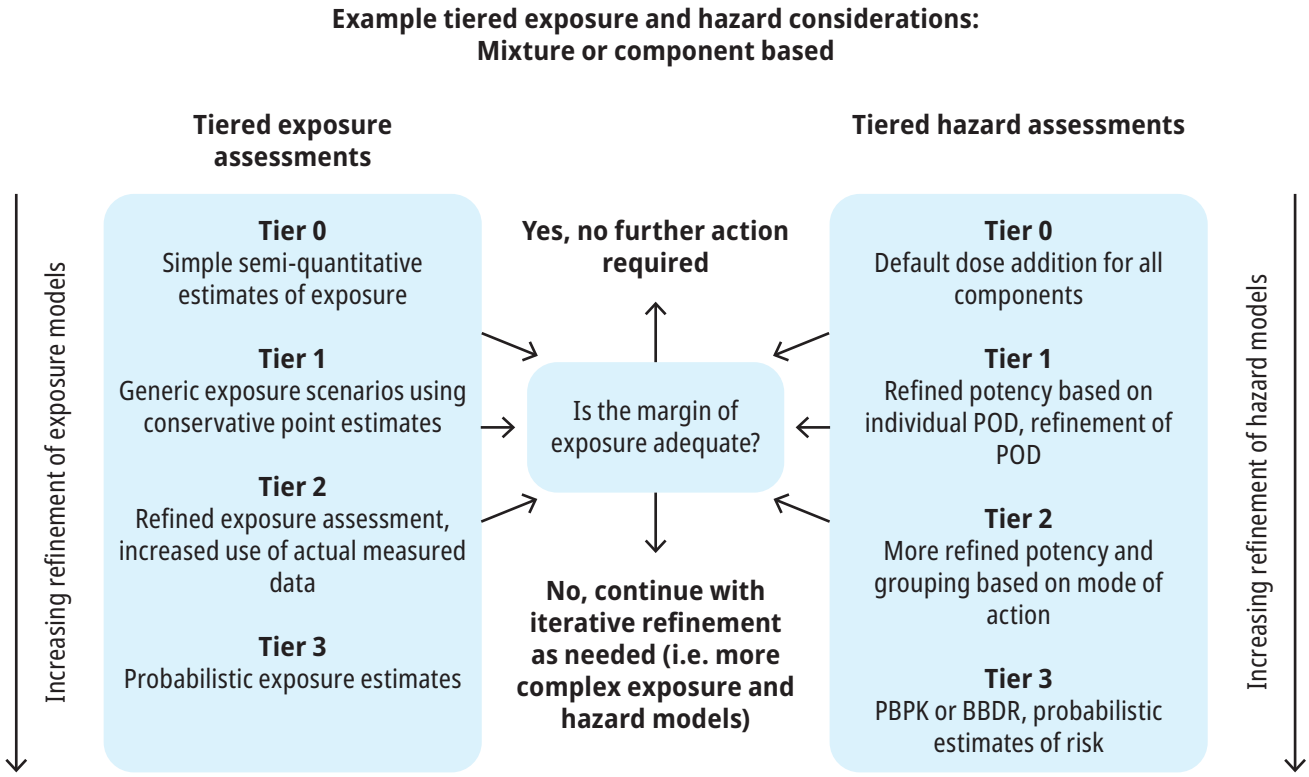
5.6 Use of in vitro data to characterize dose–response

In light of initiatives to reduce animal testing and to be more efficient and human relevant in toxicological assessment, dose–response data from in vitro studies are increasingly being considered in risk assessment. There are a number of challenges to be addressed in this area, including establishment of the qualitative and quantitative relationships between in vitro observations and adverse in vivo effects. An extensive ongoing area of research, referred to as quantitative in vitro to in vivo extrapolation (QIVIVE), addresses these challenges, facilitating greater quantitative use of in vitro data in human health risk assessment. For example, a workflow tool for conducting in vitro to in vivo extrapolation (IVIVE) analyses is available in the Integrated Chemical Environment (ICE) of the United States National Toxicology Program *(153)*.

5.7 Strategies for assessing and testing multiple chemical exposures

Since humans are usually exposed to several chemicals concurrently, WHO has also developed a framework to assess coexposures to multiple chemicals (Figure 15). The framework involves a tiered approach of increasing levels of refinement for integrated and iterative consideration of exposure and hazard at all phases *(61–63)*.

Figure 15. Conceptual representation of the IPCS framework for the risk assessment of combined exposure to multiple chemicals



Source: Meek et al. *(62)*.

OECD has published an overview of the technical aspects of the various approaches and methodologies available with respect to the assessment of risks from combined exposures to multiple chemicals that draws from approaches applied and experience gained in a regulatory context *(154)*. While the document does not provide guidance, it outlines key scientific considerations to be taken into account in assessing such exposure situations and the application of risk characterization through a tiered approach.

The EuroMix project *(155)* was initiated to support development of a harmonized tiered strategy for risk assessment of combined exposures to multiple chemicals from multiple sources as well as development of efficient strategies for testing to generate data for refining risk assessment of mixtures. Outputs of the EuroMix project include a Toolbox of models and data to support chemical mixture risk assessment *(156)* and the EuroMix handbook *(157)*.

The development of methodologies to assess risks from multiple chemicals is recognized as an important issue by all stakeholders, and this is a topic where methodologies are anticipated to continue to evolve over time.

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ANNEX 1. DRINKING-WATER CASE STUDY

A1.1 Objective

The objective of this fictional case study is to demonstrate how the principles and roadmaps 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 roadmaps for this scenario are shown in Figures A1.1, A1.2, A1.3 and A1.4.[1]

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 initial assessment of the potential scale of the problem and whether there is a need to take action.

A1.2 Statement of the problem

A metal finishing facility is located on the bank of the fictional Flowing River in the 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 hours per day, seven 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 has identified cadmium as a by-product of chrome plating operations. To address public health concerns, the Department of Environmental Health 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 in section 3.1 in the main toolkit document):

- 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?

1 Note: The case studies presented here were developed for illustrative purposes in the application of the toolkit to different scenarios and may not represent the most recent evaluations of the chemicals discussed.

- 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?

A1.3 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 (for example, 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 subsection 4.8.3 of the main toolkit document for information relevant to the current situation. The full-text search feature of the INCHEM database *(1)* 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 contain useful information about health hazards associated with the metal finishing operation. Also, initiating dialogue 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 *(1)*. Selecting the entry for cadmium brings the user to the International Chemical Safety Card (ICSC) for that chemical *(2)*. 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) classification scheme known as the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) *(3)*. The health hazards for cadmium according to the GHS classification scheme are shown in Table A1.1.

Table A1.1 GHS classification for cadmium

Hazard class and category[a]	Hazard statement
Acute toxicity (category 2)	H330: Fatal if inhaled
Germ cell mutagenicity category 2	H341: Suspected of causing genetic defects
Carcinogenicity category (1A)	H350: May cause cancer (route of exposure, if applicable)
Reproductive toxicity category 2	H361: Suspected of damaging fertility or the unborn child
Specific target organ toxicity (single exposure) Category 1	H372: Causes damage to organs (or affected organs) through prolonged or repeated exposure

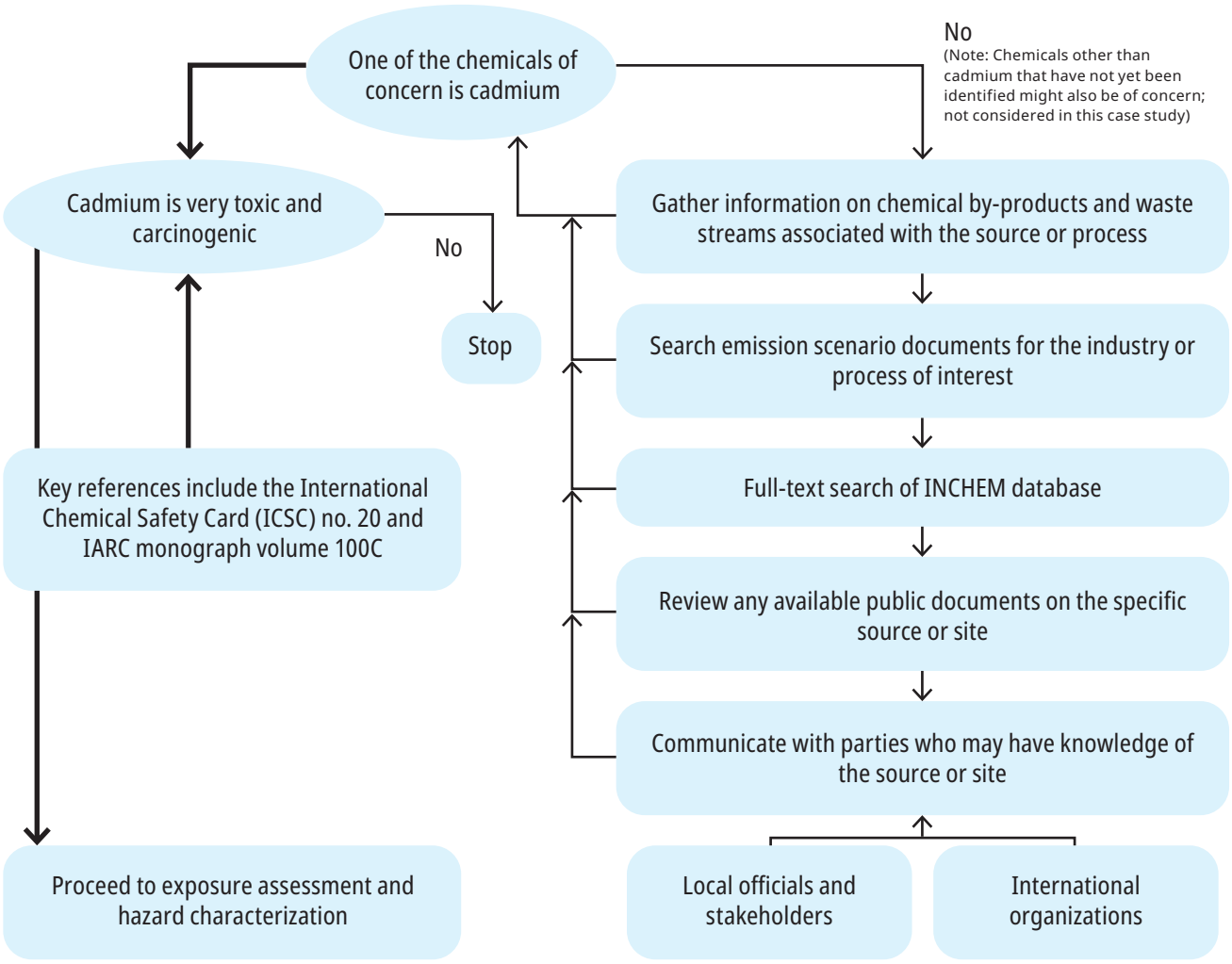
[a] Some older reference sources may also make reference to the former EU system for classification (with risk phrases such as R26 (very toxic by inhalation)). Guidance on the transition from that system to a system aligned with the GHS is available *(4)*.

Review of the IARC monographs *(5)* 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 roadmap for the hazard identification step of the drinking-water case study is shown in Figure A1.1.

Figure A1.1 Case-specific roadmap for hazard identification: drinking-water case study



Bold lines indicate the flow of information gathering and analysis described in the text.

A1.4 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) *(6)* and other documents, including an EHC monograph *(7)*, 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 recommended a provisional tolerable weekly intake (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 A1.2). WHO has not published a relevant health-based air quality guideline for cadmium (see also Tables 6 and 7 in the main toolkit document).

Table A1.2 International guidance and guideline values for cadmium

Type of value	Guidance or guideline value	Reference
Food guidance value	0.007 mg/kg body weight (PTWI)[a]	WHO *(8)*
Drinking-water guideline value	0.003 mg/L	WHO *(9)*

[a] The PTWI included for the purposes of this case study was published by JECFA in 2005. However, it should be noted that JECFA subsequently published, in 2010, a provisional tolerable monthly intake (PTMI) of 0.025 mg/kg body weight (8).

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 A1.5); therefore, the WHO drinking-water guideline for cadmium is of main interest. The WHO drinking-water guideline for cadmium is described in section 12.1 of the current edition of the WHO *Guidelines for drinking-water quality (9)*. According to the table of key items presented for cadmium 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 provisional tolerable weekly intake 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 acceptable daily intake (ADI), tolerable daily intake (TDI), PTWI, and similar values, 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 (such as food and air), it may be appropriate to allocate a greater proportion of

the ADI, TDI, PTWI, and other similar parameters to drinking-water to derive a guideline value more suited to the local conditions.

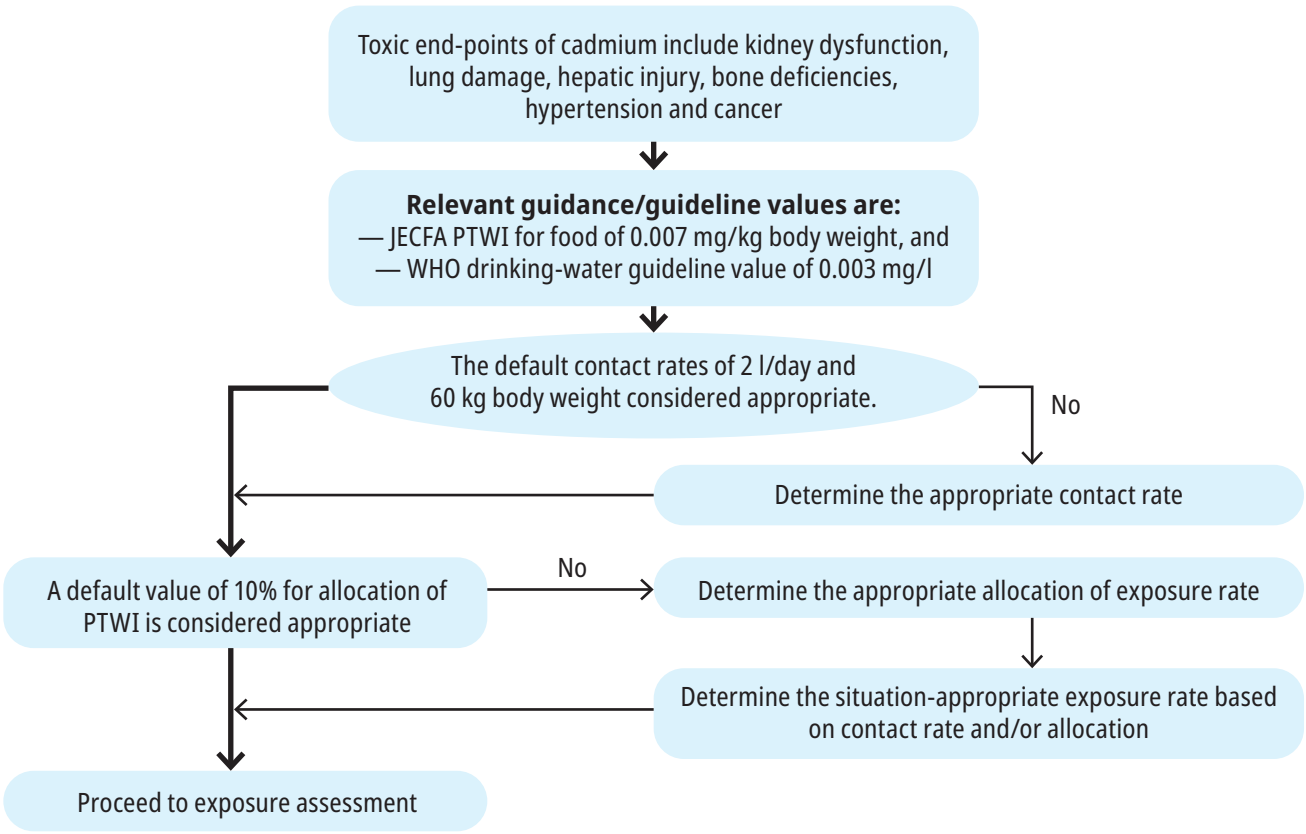
> *Output: The WHO drinking-water guideline value for cadmium is based on a default water consumption rate of 2 litres per day, a body weight of 60 kg and an allocation to water of 10% of the PTWI.*

Do those assumptions reflect conditions specific to the local situation?
In the case of Rivertown, the Rivertown Department of Environmental Health 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 Rivertown Department of Environmental Health 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 roadmap for the hazard characterization step of the drinking-water case study is shown in Figure A1.2.

Figure A1.2 Case-specific roadmap 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.

A1.5 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 of the main toolkit document, several combinations of guidance or guideline values and exposure metrics are possible, depending upon the medium (or media) and exposure routes 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.

> *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 *(10)*. 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 *(11)*.

Unable to obtain information needed to model the concentration of cadmium in water drawn from the river, the Rivertown Department of Environmental Health 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 *(7)* 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 United States EPA's *Method 1669: sampling ambient water for trace metals at EPA water quality criteria levels (12).*

The Rivertown Department of Environmental Health collects water samples from three locations on five 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 A1.3.

Table A1.3 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 hours per day, seven 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 the operations of the facility.*

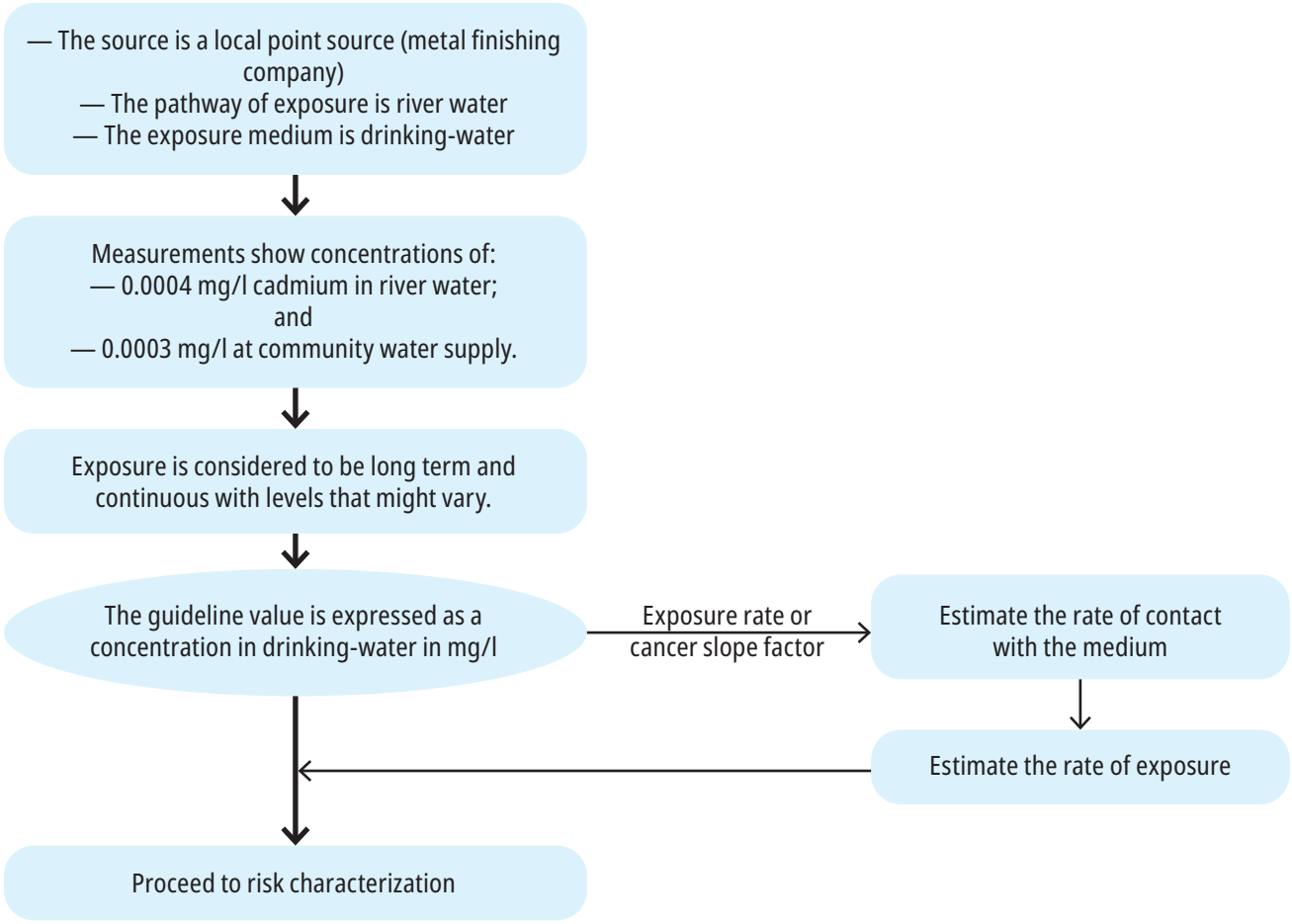
What metric of exposure is appropriate for characterizing health risks?
Having selected the environmental medium (water), exposure route (mainly ingestion) and exposure duration (long-term) of interest, the next step is to determine if an international guidance or guideline value exists that corresponds 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 roadmap for the exposure assessment step of the drinking-water case study is shown in Figure A1.3.

Figure A1.3 Case-specific roadmap for exposure assessment: drinking-water case study



Bold lines indicate the flow of information gathering and analysis described in the text.

A1.6 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 subsection 3.3.5 of the main toolkit document, 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 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 A1.4, the objective of the Rivertown Department of Environmental Health 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: (a) the average concentration of cadmium in drinking-water downstream of the metal finishing facility (0.0004 mg/L); and (b) 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.

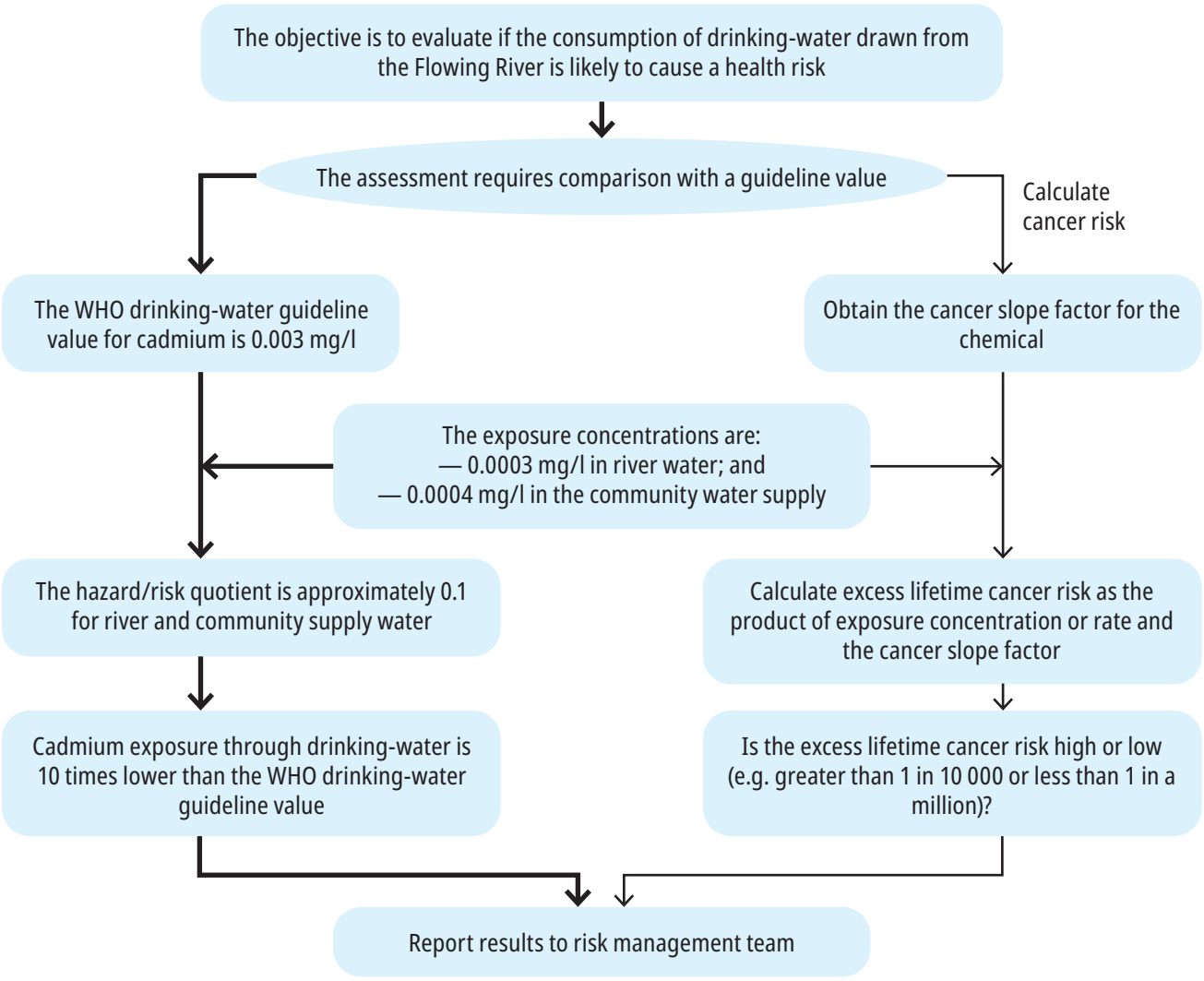
If the concentration in the river was below but close to the guideline value, it would still be appropriate to determine whether there was potential exposure from the plumbing system.

> *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 roadmap for the risk characterization step of the drinking-water case study is shown in Figure A1.4.

Figure A1.4 Case-specific roadmap for risk characterization: drinking-water case study



Bold lines indicate the flow of information gathering and analysis described in the text.

A1.7 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 exposure 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 five 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 exposure 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.

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ANNEX 2. RESPIRABLE PARTICULATE MATTER (PM_{10}) CASE STUDY

A2.1 Objective

The objective of this case study is to demonstrate how the principles and roadmaps 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 of the main toolkit document) *(1, 2)*. Specific roadmaps are shown in Figures A2.1, A2.2 and A2.3.[1]

The questions to be asked are as follows (see also Figure 2 in section 3.1 of the main toolkit document):

- 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.

1 Note: The case studies presented here were developed for illustrative purposes in the application of the toolkit to different scenarios and may not represent the most recent evaluations of the chemicals discussed.

A2.2 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,[2] 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, as well as policy-related factors, such as technological feasibility and economic considerations.

A2.3 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 A2.1. 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}.

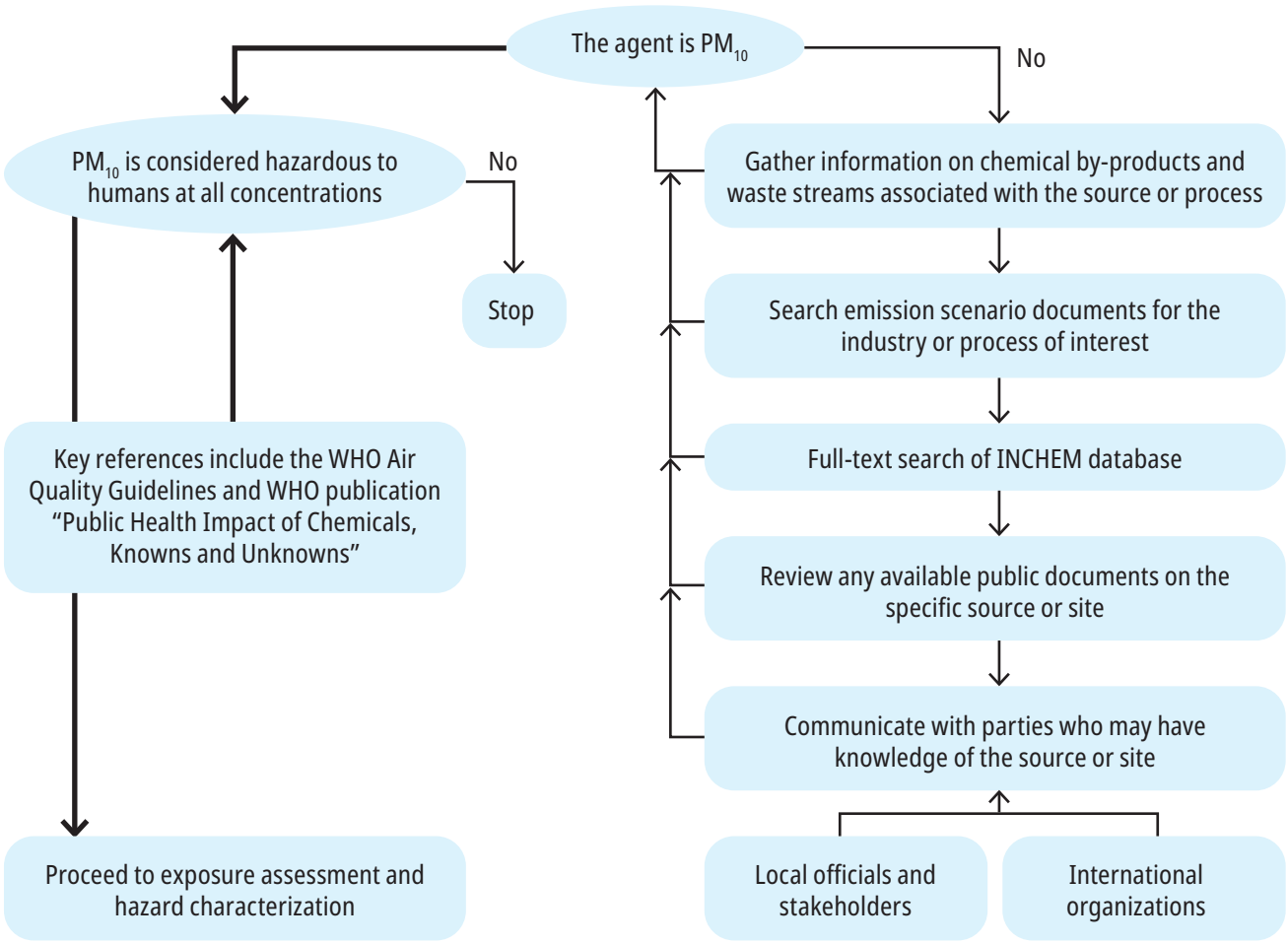
> *Output: Identification of PM_{10} as the pollutant of interest.*

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 *(1,2,3)*.

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

2 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.

Figure A2.1 Case-specific roadmap for hazard identification: particulate matter case study



Bold lines indicate the flow of information gathering and analysis described in the text.

A2.4 Hazard characterization/guidance or guideline value identification

What properties of PM_{10} have the potential to cause adverse health effects?
Air quality guidelines of the WHO Regional Office for Europe *(1, 2)* indicate 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, in the order of 1–4 hours. All populations are affected, but susceptibility to the pollutant may vary with health status or age. The risk for various outcomes has been shown to increase with exposure, and there is little evidence to suggest a threshold below which no adverse health effects would be anticipated.

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 hours (Table A2.1). 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 A2.1 WHO air quality guideline values for PM_{10}

Type of value	Guideline value	Reference
Annual mean	20 µg/m³	WHO Regional Office for Europe *(1, 2)*
24-hour mean	50 µg/m³	WHO Regional Office for Europe *(1, 2)*

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 exposure to PM, including PM_{10} (Table A2.2) *(1, 2).*

Table A2.2 WHO interim targets for PM_{10}: annual mean concentrations

Interim target	PM_{10} concentration	Basis for the selected level
1	70 µg/m³	This level is associated with about a 15% higher long-term mortality risk relative to the annual air quality guideline mentioned in Table A2.1.
2	50 µg/m³	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/m³	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/m³, with this issue to be revisited in subsequent years *(4)*. 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}.

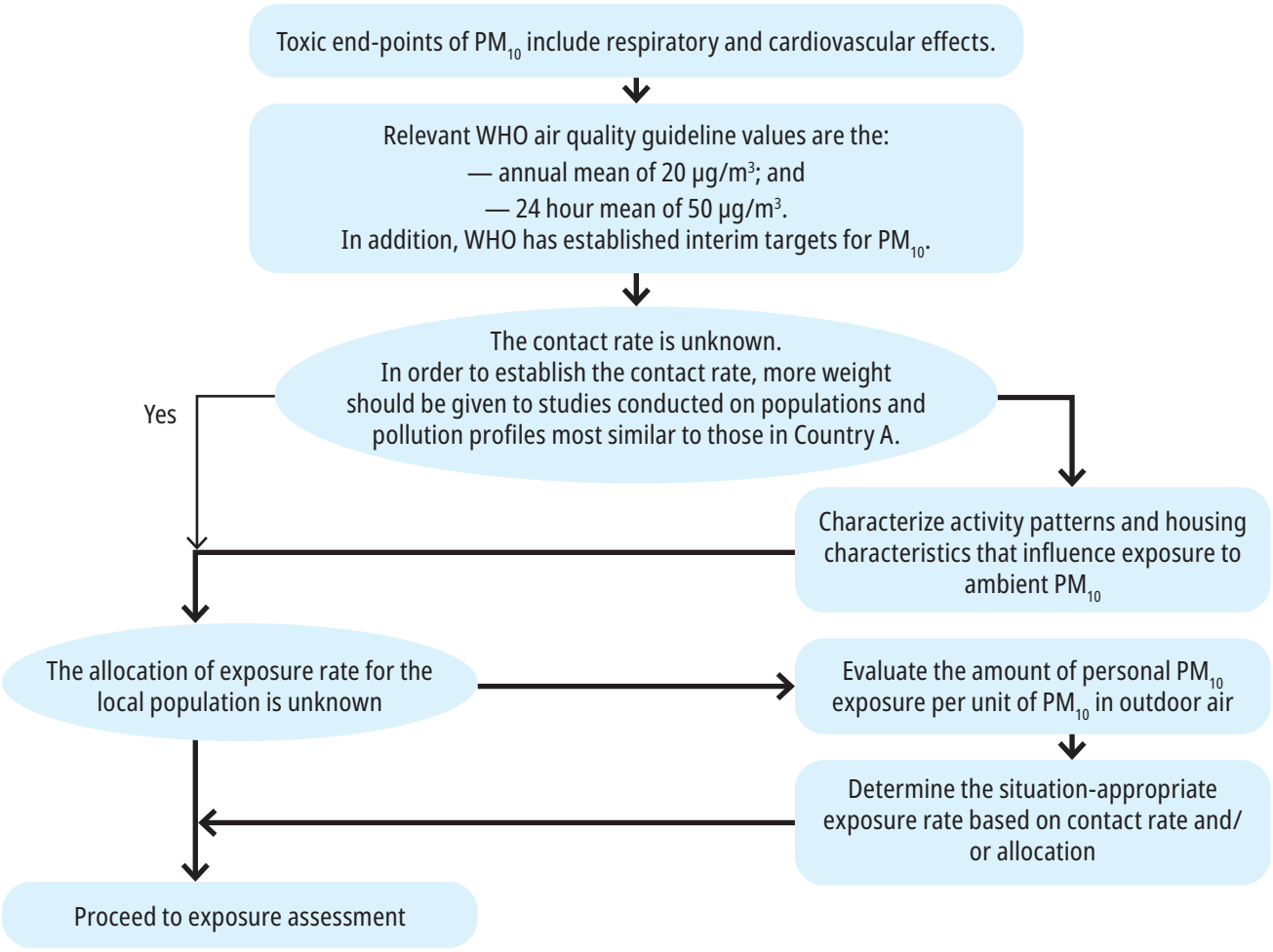
What assumptions about exposure and dose are incorporated into guideline values for PM_{10}?
As discussed in section A2.5, air quality standards for PM_{10} are expressed as concentrations in ambient air, given a specific averaging time, and often also specifying the location of compliance monitors. The WHO air quality guidelines and standards set by the EU, the United States of America and other countries reflect assumptions about the relative importance of observed health outcomes (for example, mortality being more important than asthma incidence), population characteristics and activity patterns of the population (for example, number of potentially susceptible individuals, time spent outside, indoor PM_{10} sources), and source characteristics and locations (for example, 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 to be 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 (a) a review of the scientific literature for PM_{10}, with specific emphasis on studies from Country A or surrounding countries; (b) PM_{10} standards for Country A or other countries; and (c) measurements or estimates of background PM_{10} concentrations, which can include PM_{10} that originates from anthropogenic sources outside Country A. A roadmap for the hazard characterization step is shown in Figure A2.2.

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

Figure A2.2 Case-specific roadmap 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.

A2.5 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.*

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 (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-hour 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 (a) PM_{10} monitoring data that show the relationship between annual and daily concentrations; and (b) 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.*

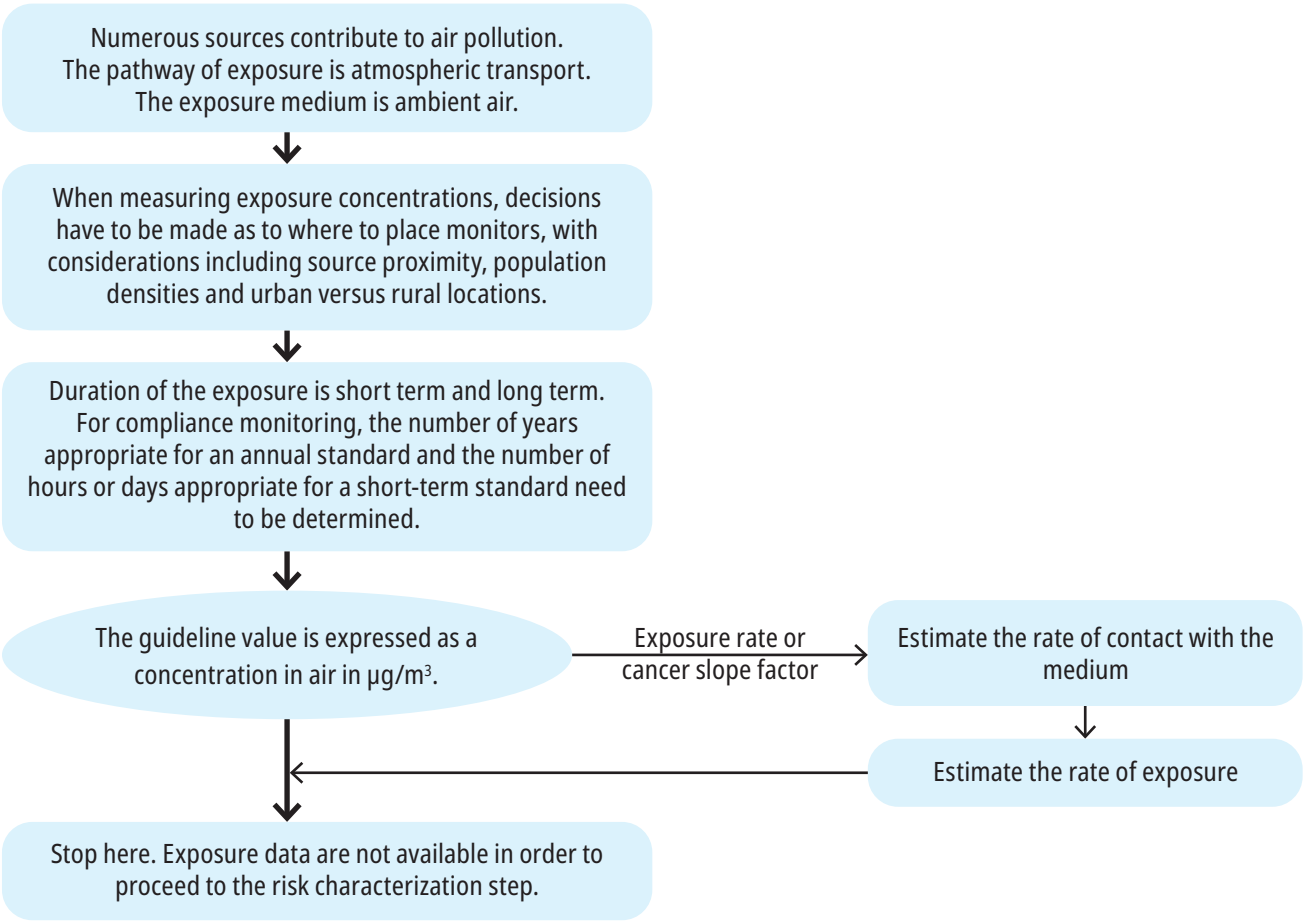
What metric of exposure is appropriate for characterizing health risks?
Once the appropriate averaging time is selected, the method used to calculate the exposure averaging time and the location of the compliance monitors must be determined. In terms of exposure averaging time, the WHO guidelines average data across one year for the annual concentration limit for PM_{10} and across one day for the 24-hour limit. In contrast, the annual PM_{10} standard in the United States is based on the three-year average of the weighted annual mean PM_{10} concentrations from single or multiple monitors representing population exposure. Similarly, the daily standard in the United States is based on the three-year average of the 98th percentile of 24-hour concentrations at each monitor representing population exposure. The calculations for the United States are intended to de-emphasize years or days with unusually high concentrations *(5)*.

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 (a) the calculation used to estimate PM_{10} concentrations for the specified exposure averaging times to allow comparisons with the PM_{10} standard; and (b) 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 roadmap for the exposure assessment step, as applied in this case study, is shown in Figure A2.3.

Figure A2.3 Case-specific roadmap for exposure assessment: particulate matter case study



Bold lines indicate the flow of information gathering and analysis described in the text.

A2.6 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.

A2.7 Summary

Principles and roadmaps 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 or 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, in the order of 1–4 hours. 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 µg/m^3 averaged over a year and 50 µg/m^3 averaged over 24 hours. 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.

REFERENCES: ANNEX 2

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ANNEX 3. PESTICIDE CASE STUDY

A3.1 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.[1]

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.

A3.2 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 in section 3.1 of the main toolkit document):

- 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?

1 Note: The case studies presented here were developed for illustrative purposes in the application of the toolkit to different scenarios and may not represent the most recent evaluations of the chemicals discussed.

A3.3 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 and 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 the country. The Hazardous Substances Data Bank (HSDB) *(1)* (see subsection 4.6.6 of the main toolkit document), 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 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 Department of Environmental Health 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. Class Ia (*extremely hazardous*) *(2).*
- IARC list of classifications. Group 3 (*not classifiable as to its carcinogenicity to humans*) *(3).*
- UN Globally Harmonized System of Classification and Labelling of Chemicals[2] (GHS) *(4)*
  - Acute toxicity 2: H300 Fatal if swallowed; H330 Fatal if inhaled
  - Acute toxicity 3: H311 Toxic in contact with skin
  - Specific target organ toxicity RE2: H373 May cause damage to organs (or affected organs) through prolonged or repeated exposure

> *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 *(5)*, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) monograph on the toxicological evaluation of methyl parathion (listed there as parathion-methyl) *(6)* and the HSDB *(1)*. As noted in these documents, exposure to methyl parathion at

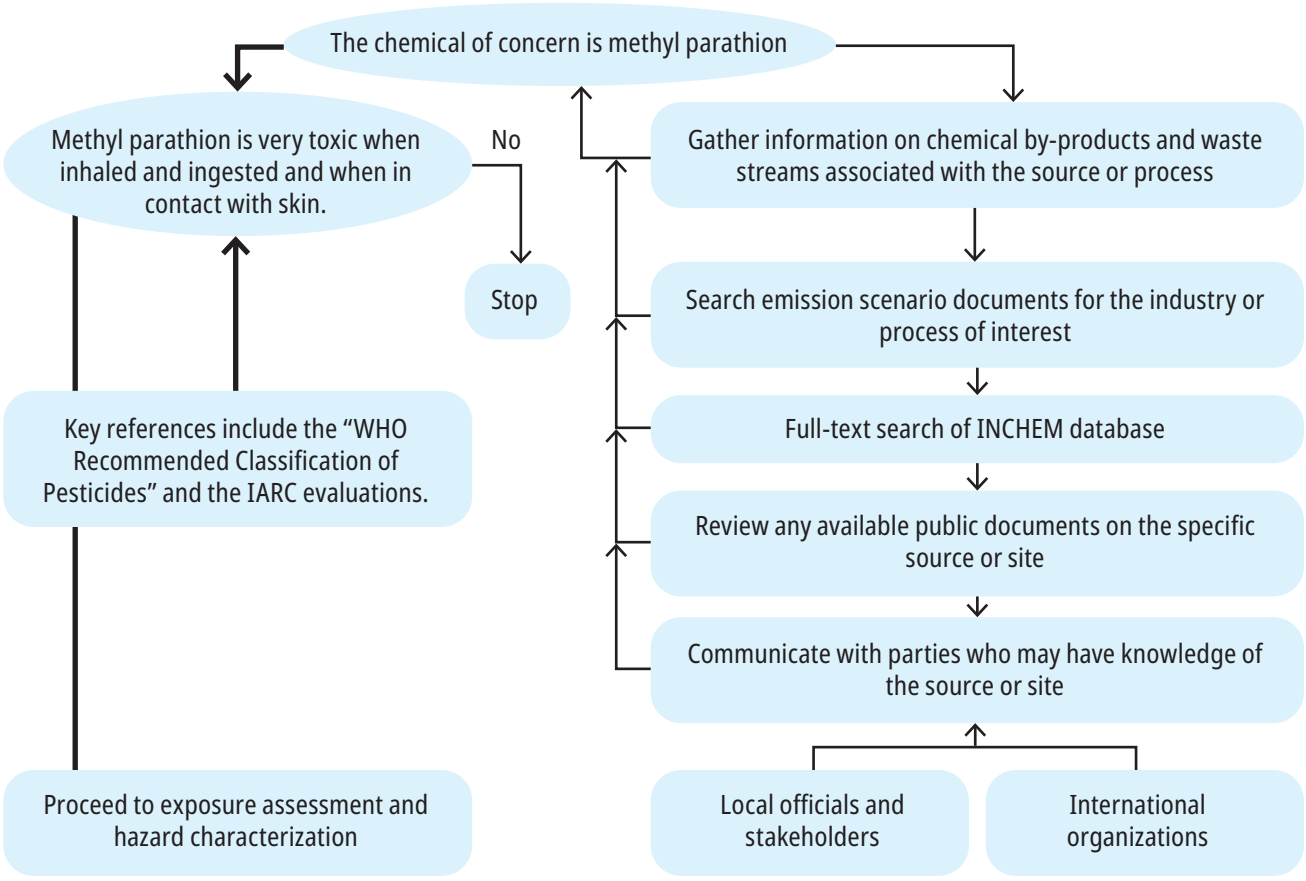
2 Some older reference sources may also make reference to the former EU system for classification (with risk phrases such as R26 (very toxic by inhalation)). Guidance on the transition from that system to a system aligned with the GHS is available (7).

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 (a few minutes) after exposure. When exposure occurs through skin contact, the severity of poisoning symptoms may increase over more than one day and may last several days. Exposure 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 (a few minutes) after exposure.*

A roadmap for the hazard identification step of the pesticide case study is shown in Figure A3.1.

Figure A3.1 Case-specific roadmap for hazard identification: pesticide case study



Bold lines indicate the flow of information gathering and analysis described in the text.

A3.4 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 acceptable daily intake (ADI) of 0–0.003 mg/kg body weight and an acute reference dose (ARfD) of 0.03 mg/kg body weight *(6).*

- The Codex Alimentarius Commission established maximum residue limits (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) *(8).*

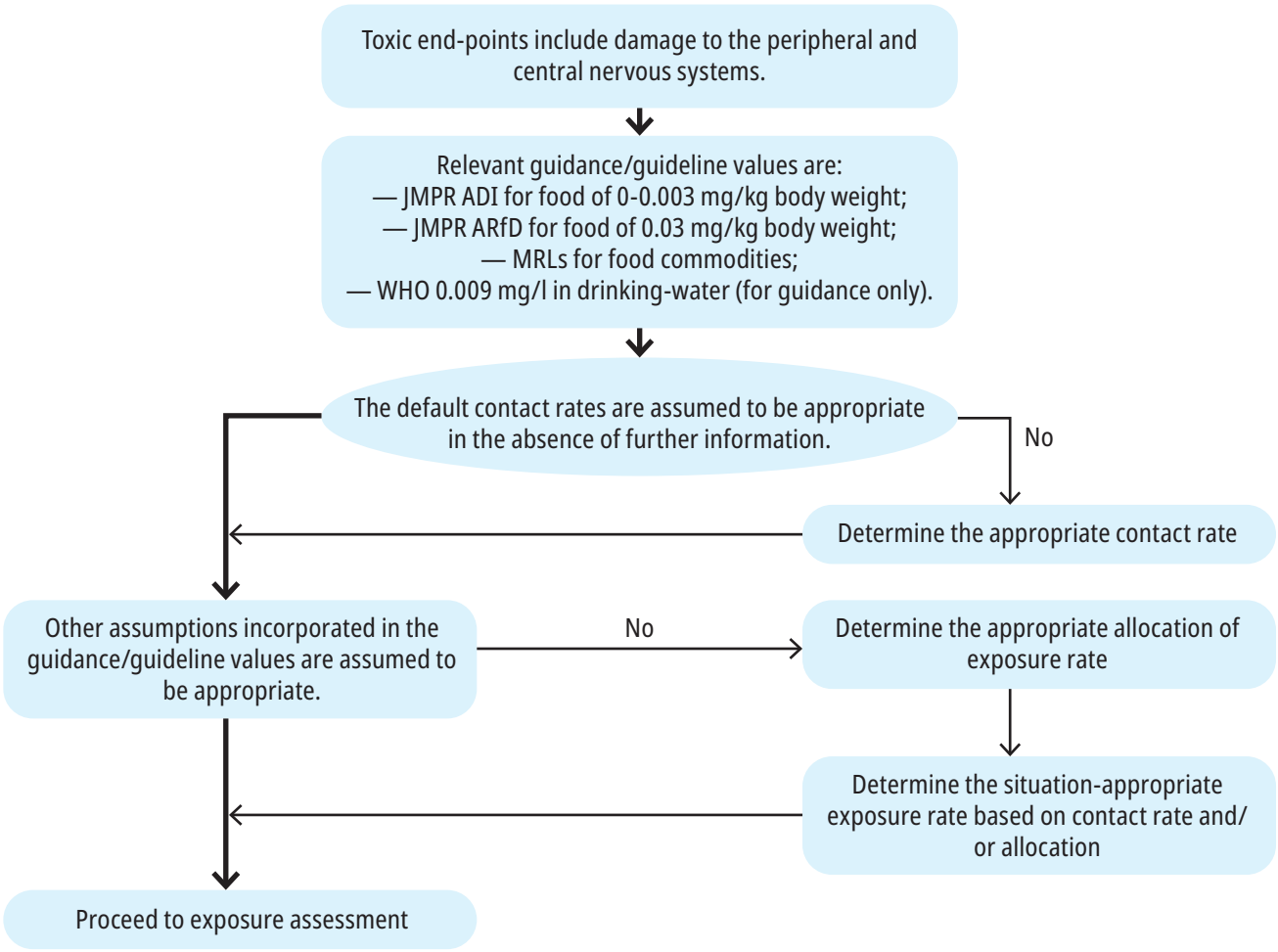
As a note, a formal WHO drinking-water guideline value for methyl parathion has not been established. In fact, a health-based value of 0.009 mg/L was derived (for guidance purposes), and as this value is much greater than concentrations likely to be found in water, no formal guideline value was deemed necessary *(9)*. WHO has not published an air quality guideline for methyl parathion.

> *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 maximum residue limits for a variety of food commodities. 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 A3.5, 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 Department of Environmental Health elects to rely upon the guidance/guideline values provided above in this section.

A roadmap for the hazard characterization step of the pesticide case study is shown in Figure A3.2.

Figure A3.2 Case-specific roadmap 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.

A3.5 Exposure assessment

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

The risk assessor gathers information from within the country that shows that the methyl parathion in the country is primarily applied to vegetable fields using rotary disc sprayers carried on the backs of workers. Through field visits and interviews with agricultural workers, the Department of Environmental Health finds that workers have not been 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 medical professionals at local health facilities reveal 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 *(5)* and the HSDB *(1)* – 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.

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 clean-up crews, bagging machine operators, basic manufacturing employees, laundry haulers, drum fillers, drum reconditioning personnel, dump personnel, field checkers, fieldworkers (who are 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. Based on information presented in the HSDB, 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 exposure is estimated to be 0.7 mg per hour. For formulators, median levels of methyl parathion on their non-washed body parts range between 510 and 9200 nanograms (ng), compared with a range of 74–345 ng for formulators who wash after work.

For the general population, exposure 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 exposure of the general population is 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 Department of Environmental Health conducts a literature search that reveals that a non-African country recently assessed the health risks of methyl parathion in order to support regulatory action. The Department of Environmental Health in the African country convenes 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 are organized along a template. The template and results are presented in Table A3.1.

Table A3.1 Relevance of study findings to an African country: template

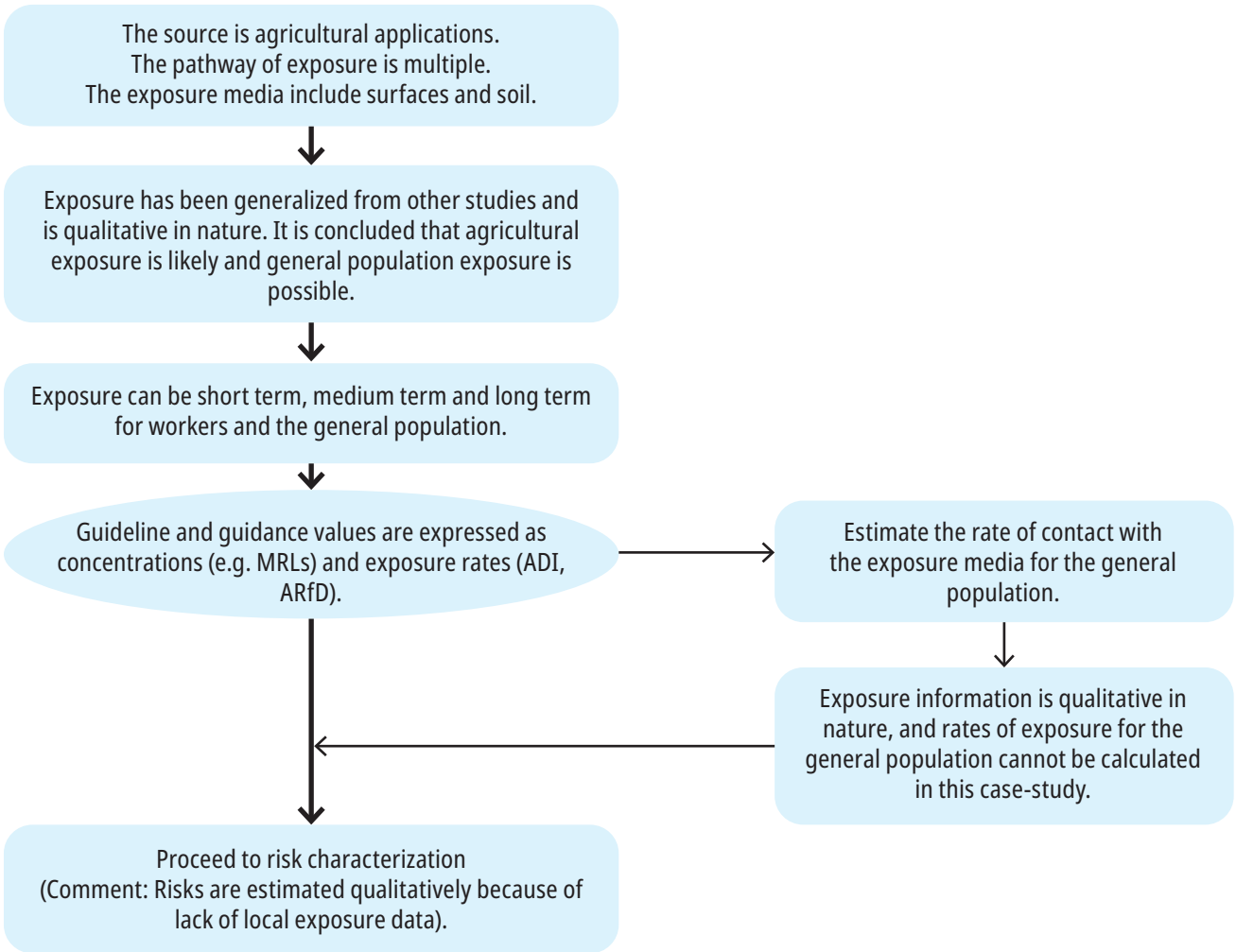
Study element	Local condition	Other country
1. Is the form in which the pesticide was used at the local level similar to those in the exposure assessment undertaken at the international level or in another country?		
(i) Has the same formulation been used (e.g. liquid, powder, granule; concentration 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 (e.g. agriculture, non-agriculture, public health, disinfectant)?	Agriculture, vegetables	Agriculture, vegetables
— Environment of use (e.g. greenhouse, field, indoor)?	Open field	Open field
— Environmental conditions (e.g. temperature, type of soil)?	Tropical climate	Moderate climate
— Rate, frequency and period of application?	Six times a year	Twice a year
— Application equipment (e.g. backpack sprayer, air blast sprayer)?	Rotary disc sprayer	Different back sprayers
— Transportation, dissemination and storage?	Uncontrolled	Very controlled (e.g. follow GHS, trained drivers, controlled dissemination)
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
4. 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
(iv) Are there signs of intoxication in the general population?	Unknown	No; surveillance system in place
5. Others		
Not applicable	Not applicable	Not applicable

The meeting concludes that the exposure conditions as described in the study of the other country are very different to those identified in the situation in Africa. Striking differences include the literacy of workers about the health risks of methyl parathion and the use of PPE, as well as the pesticide management system, which is 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 roadmap for the exposure assessment step of the pesticide case study is shown in Figure A3.3.

Figure A3.3 Case-specific roadmap for exposure assessment: pesticide case study



Bold lines indicate the flow of information gathering and analysis described in the text.

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 A3.4, guidance/guideline values are expressed in mg/kg body weight (ADI and ARfD), mg/kg of food item (maximum residue limits) and mg/L for drinking-water

> *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 or mg/L in drinking-water).*

A3.6 Risk characterization

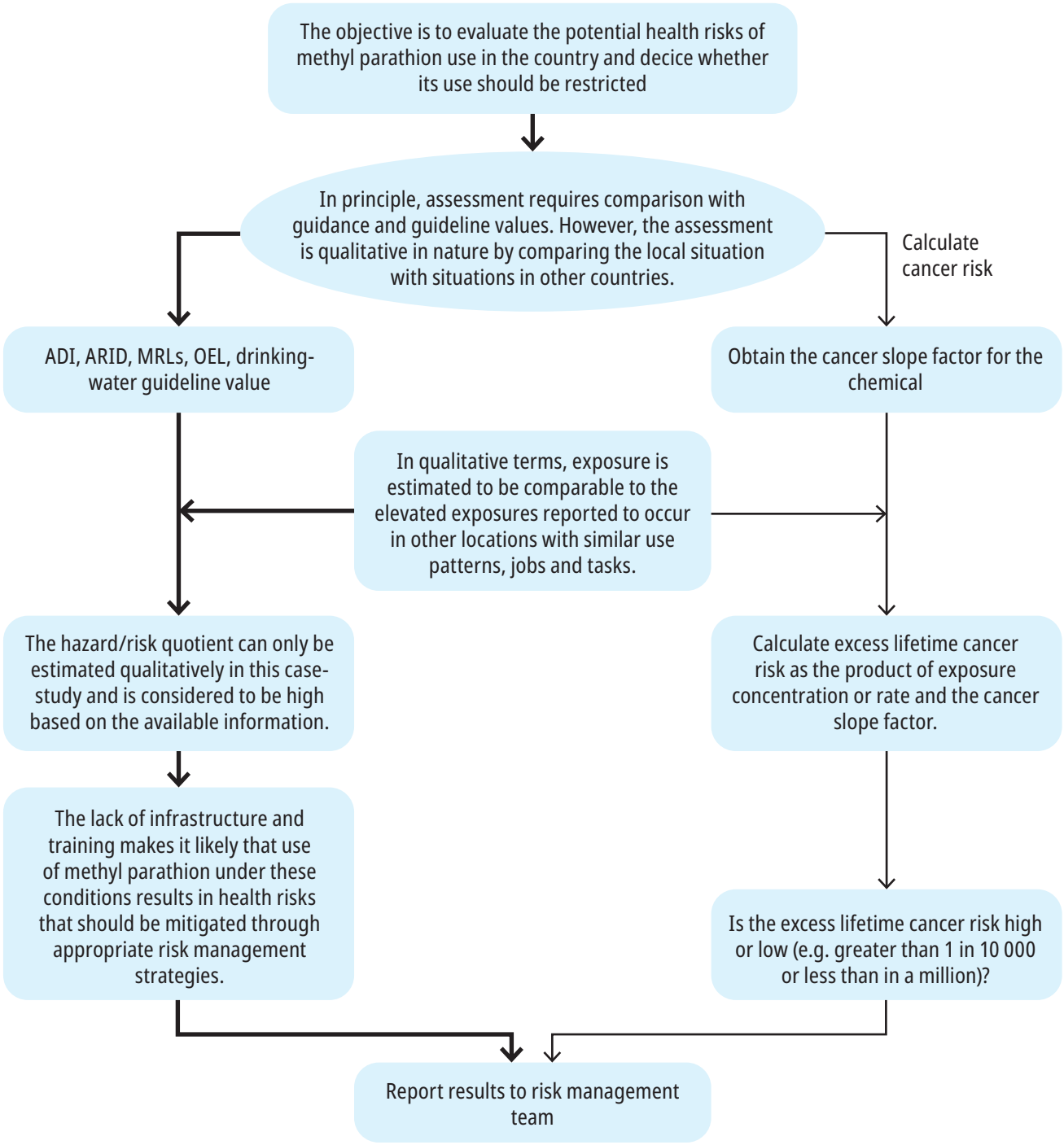
How does the estimated exposure compare with the health-based guidance or guideline values?
The above question cannot be answered, because the Department of Environmental Health has not come up with a measure of exposure, either exposure rate or exposure concentration. However, the Department of Environmental Health believes that the potential for exposure to workers is high, based on studies in other areas, as summarized in section A3.5. 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 signallers 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 exposure 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 Department of Environmental Health concludes that risks to human health are likely to be unacceptable under current conditions and considers restricting methyl parathion use.

A roadmap for the risk characterization step of the pesticide case study is shown in Figure A3.4.

Figure A3.4 Case-specific roadmap for risk characterization: pesticide case study



Bold lines indicate the flow of information gathering and analysis described in the text.

A3.7 Summary

A case study of methyl parathion was used to illustrate how principles, roadmaps 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.

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