

IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY



WHO



IPCS Harmonization Project

Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD



**World Health
Organization**

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

Harmonization Project Document No. 9

CHARACTERIZATION AND APPLICATION OF PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELS IN RISK ASSESSMENT

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

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

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

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

WHO Library Cataloguing-in-Publication Data

Characterization and application of physiologically based pharmacokinetic models in risk assessment.

(IPCS harmonization project document ; no. 9)

1.Risk assessment. 2.Pharmacokinetics. 3.Chemicals - pharmacokinetics. 4.Chemicals - toxicity. 5.Drug toxicity. I.International Programme on Chemical Safety. II.Inter-Organization Programme for the Sound Management of Chemicals. III.Series.

ISBN 978 92 4 150090 6

(NLM classification: QV 38)

© World Health Organization 2010

All rights reserved. Publications of the World Health Organization can be obtained from WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 3264; fax: +41 22 791 4857; e-mail: bookorders@who.int). Requests for permission to reproduce or translate WHO publications—whether for sale or for non-commercial distribution—should be addressed to WHO Press at the above address (fax: +41 22 791 4806; e-mail: permissions@who.int).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

Technically and linguistically edited by Marla Sheffer, Ottawa, Canada

TABLE OF CONTENTS

FOREWORD	1
LIST OF ACRONYMS AND ABBREVIATIONS	2
PREFACE	3
1. INTRODUCTION	8
1.1 Context	8
1.2 Objectives	9
1.3 Organization	9
2. TISSUE DOSIMETRY IN RISK ASSESSMENT	9
2.1 Concepts	9
2.2 Application and evaluation	13
2.2.1 Interspecies extrapolation	14
2.2.2 Interindividual variability	14
2.2.3 High dose to low dose extrapolation	15
2.2.4 Route-to-route extrapolation	15
2.2.5 Model evaluation	16
3. CHARACTERIZATION AND DOCUMENTATION OF PBPK MODELS	16
3.1 Introduction	16
3.2 Scope and purpose of the model	17
3.3 Model structure and biological characterization	18
3.4 Mathematical description of ADME	19
3.5 Computer implementation and verification	20
3.6 Parameter estimation and analysis	20
3.7 Model validation and evaluation	21
3.7.1 Characterizing the level of confidence in PBPK models	22
3.7.1.1 Biological basis	22
3.7.1.2 Comparison of model simulations with data	23
3.7.1.3 Reliability of dose metric predictions (model testing, uncertainty and sensitivity analyses)	24
3.7.2 Ability of PBPK models to address PK uncertainty relative to other approaches	30
3.7.2.1 Dose metric	30
3.7.2.2 Conceptual model	30
3.7.2.3 Input parameters	31
3.7.3 Purpose-specific model evaluation	31
3.7.3.1 Interspecies extrapolation	32
3.7.3.2 Interindividual variability	34
3.7.3.3 High dose to low dose extrapolation	35
3.7.3.4 Route-to-route extrapolation	36
3.8 Documentation	37

4. APPLICATION OF PBPK MODELS IN RISK ASSESSMENT	38
4.1 Choice of critical studies	38
4.2 Selection of PBPK models	39
4.3 Evaluation of dose metrics	42
4.4 Determination of human exposures	43
5. PROCESS CONSIDERATIONS	45
5.1 Expertise	45
5.2 Training	46
5.3 Communication	47
6. CONCLUDING REMARKS	49
REFERENCES	51
ANNEX 1: GLOSSARY OF TERMS	63
ANNEX 2: FREQUENTLY ASKED QUESTIONS	68
ANNEX 3: CASE-STUDY ON INTEGRATING PBPK MODELS IN A RISK ASSESSMENT OF A CHEMICAL	72

FOREWORD

Harmonization Project Documents are a family of publications by the World Health Organization (WHO) under the umbrella of the International Programme on Chemical Safety (IPCS) (WHO/ILO/UNEP). Harmonization Project Documents complement the Environmental Health Criteria (EHC) methodology (yellow cover) series of documents as authoritative documents on methods for the risk assessment of chemicals.

The main impetus for the current coordinated international, regional and national efforts on the assessment and management of hazardous chemicals arose from the 1992 United Nations Conference on Environment and Development (UNCED). UNCED Agenda 21, Chapter 19, provides the “blueprint” for the environmentally sound management of toxic chemicals. This commitment by governments was reconfirmed at the 2002 World Summit on Sustainable Development and in 2006 in the Strategic Approach to International Chemicals Management (SAICM). The IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals (Harmonization Project) is conducted under Agenda 21, Chapter 19, and contributes to the implementation of SAICM. In particular, the project addresses the SAICM objective on Risk Reduction and the SAICM Global Plan of Action activity to “Develop and use new and harmonized methods for risk assessment”.

The IPCS Harmonization Project goal is *to improve chemical risk assessment globally, through the pursuit of common principles and approaches, and, hence, strengthen national and international management practices that deliver better protection of human health and the environment within the framework of sustainability*. The Harmonization Project aims to harmonize global approaches to chemical risk assessment, including by developing international guidance documents on specific issues. The guidance is intended for adoption and use in countries and by international bodies in the performance of chemical risk assessments. The guidance is developed by engaging experts worldwide. The project has been implemented using a stepwise approach, first sharing information and increasing understanding of methods and practices used by various countries, identifying areas where convergence of different approaches would be beneficial and then developing guidance that enables implementation of harmonized approaches. The project uses a building block approach, focusing at any one time on the aspects of risk assessment that are particularly important for harmonization.

The project enables risk assessments (or components thereof) to be performed using internationally accepted methods, and these assessments can then be shared to avoid duplication and optimize use of valuable resources for risk management. It also promotes sound science as a basis for risk management decisions, promotes transparency in risk assessment and reduces unnecessary testing of chemicals. Advances in scientific knowledge can be translated into new harmonized methods.

This ongoing project is overseen by a geographically representative Harmonization Project Steering Committee and a number of ad hoc Working Groups that manage the detailed work. Finalization of documents includes a rigorous process of international peer review and public comment.

LIST OF ACRONYMS AND ABBREVIATIONS

AD _{AF}	chemical-specific adjustment factor for interspecies differences in toxicodynamics
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism and excretion
AD _{UF}	default uncertainty factor for interspecies differences in toxicodynamics
AK _{AF}	chemical-specific adjustment factor for interspecies differences in toxicokinetics
AK _{UF}	default uncertainty factor for interspecies differences in toxicokinetics
AUC	area under the concentration versus time curve
BMC	benchmark concentration
BMCL	lower confidence limit of the exposure concentration associated with a predetermined response level (e.g. 5%)
BMD	benchmark dose
BMDL	lower confidence limit of the dose associated with a predetermined response level (e.g. 5%)
BW	body weight
CSAF	chemical-specific adjustment factor
CV	coefficient of variation
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
GSH	glutathione
HD _{AF}	chemical-specific adjustment factor for human variability in toxicodynamics
HD _{UF}	default uncertainty factor for human variability in toxicodynamics
HK _{AF}	chemical-specific adjustment factor for human variability in toxicokinetics
HK _{UF}	default uncertainty factor for human variability in toxicokinetics
IPCS	International Programme on Chemical Safety
K _m	Michaelis-Menten constant
LOAEC	lowest-observed-adverse-effect concentration
LOAEL	lowest-observed-adverse-effect level
MOA	mode of action
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
PBPK	physiologically based pharmacokinetic
PBTK	physiologically based toxicokinetic
QSAR	quantitative structure–activity relationship
PD	pharmacodynamic
PK	pharmacokinetic
POD	point of departure
RfC	reference concentration
RfD	reference dose
TD	toxicodynamic
TDI	tolerable daily intake
TK	toxicokinetic
VC	hypothetical volatile chemical
V _{max}	maximal rate of metabolism

PREFACE

This document was prepared through a project on physiologically based pharmacokinetic (PBPK) modelling under the auspices of the World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) Project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals.

The document content was planned at a meeting of the WHO/IPCS PBPK Planning Group, hosted by the United Kingdom's Health and Safety Laboratory on 5–6 November 2007 in Buxton, England.

The first draft was prepared by Kannan Krishnan, Université de Montréal, Canada, with input from the WHO/IPCS PBPK Planning Group. Woody Setzer and John Wambaugh of the National Center for Computational Toxicology, United States Environmental Protection Agency, Research Triangle Park, NC, United States of America (USA), provided additional input to the first draft.

The draft document was released for public and peer review in September 2008. A second draft was prepared, taking into account comments received, by Kannan Krishnan, with input from the WHO/IPCS PBPK Planning Group.

The second draft document was reviewed and discussed at a WHO/IPCS International Workshop on Principles of Characterizing and Applying PBPK Models in Chemical Risk Assessment, held on 6–8 July 2009, hosted by the German Medical Association (Bundesärztekammer) in Berlin, Germany. Recommendations of the workshop for further development of guidance were considered by the WHO/IPCS PBPK Planning Group in order to prepare the final document. Andy Nong, Health Canada, contributed to the revision of the draft under the guidance of the WHO/IPCS PBPK Planning Group, and the final draft text was reviewed by Kannan Krishnan.

All contributions to the development of the guidance document are gratefully acknowledged.

WHO/IPCS PBPK Planning Group members

M.E. (Bette) Meek (*Chair*)

McLaughlin Centre for Population Health Risk Assessment | University of Ottawa | Ottawa

预览已结束，完整报告链接和二维码如下：

https://www.yunbaogao.cn/report/index/report?reportId=5_29093

