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

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.

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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