Harmonization Project Document No. 2

CHEMICAL-SPECIFIC ADJUSTMENT FACTORS FOR INTERSPECIES DIFFERENCES AND HUMAN VARIABILITY: GUIDANCE DOCUMENT FOR USE OF DATA IN DOSE/CONCENTRATION–RESPONSE 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.

World Health Organization
Geneva, 2005

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

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

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TABLE OF CONTENTS

FOREWORD

Harmonization Project Documents are a new family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP). Harmonization Project Documents join 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 United Nations Conference on Environment and Development (UNCED) held in 1992 and was reconfirmed at the 2002 World Summit on Sustainable Development. UNCED Agenda 21, Chapter 19, the "blueprint" for the environmentally sound management of toxic chemicals under the principles of sustainable development, has guided most international and national chemical-related activities. Chapter 19 is the agreed upon, endorsed international programme of action of governments for developing and implementing national programmes for management of chemicals within the principles of sustainable development.

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. The Intergovernmental Forum on Chemical Safety (IFCS) Forum III, held in Salvador da Bahia in October 2000, agreed on Priorities for Action Beyond 2000, which further define the actions recommended to be taken. Forum III declared that by 2004, IPCS and the Inter-Organization Programme for the Sound Management of Chemicals (IOMC, which comprises seven intergovernmental organizations) should have ensured that recommendations for harmonized assessment approaches were available for terminology, cancer and reproductive and developmental toxicology and that common principles for the assessment approach to other specific toxicological end-points, such as immunotoxicology, endocrine disruptors and ecotoxicology, should be adopted wherever possible.

The IPCS Harmonization Project, which is ongoing, states that "harmonization," in the context of chemical risk assessment, should not simply be equated with standardization. It is not a goal of the project to standardize risk assessments globally, as that is considered to be neither appropriate nor feasible. Instead, harmonization is thought of as an effort to strive for consistency among approaches and to enhance understanding of the various approaches to chemical risk worldwide. Thus, harmonization is defined, in a step-wise fashion, as an understanding of the methods and practices used by various countries and organizations so as to develop confidence in, and acceptance of, assessments that use different approaches. It further involves a willingness to work towards convergence of these approaches or methods as a longer-term goal.

Achieving harmonization of approaches is considered to provide a framework for comparing information on risk assessment; understanding of the basis for exposure standards for specific chemicals in different countries; savings of time and expense by sharing information and avoiding duplication of work; and credible science through better communication among

organizations and peer review of assessments and assessment procedures. The stated project mission is to ensure better chemical risk assessment and hence management practices that promote the protection of human health and the environment within the framework of sustainable development.

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.

PREFACE

This guidance document was prepared under the auspices of the IPCS project on the Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals. The Working Group that planned and initiated the work comprised the following members:

Erik Dybing, National Institute of Public Health, Norway (Chair)
Robin Fielder, Department of Health, United Kingdom
Donald Grant, Consultant to IPCS, Canada
Ursula Gundert-Remy, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), Germany
Bette Meek, Health Canada, Canada
Sharon Munn, European Chemicals Bureau, Italy
Edward Ohanian, Environmental Protection Agency, USA
Andrew Renwick, University of Southampton, United Kingdom
Jun Sekizawa, National Institute of Health Sciences, Japan
Cindy Sonich-Mullin, IPCS Harmonization Project and Environmental Protection Agency, USA
Theo Vermeire, National Institute of Public Health and Environmental Protection (RIVM), The Netherlands
Vanessa Vu, Environmental Protection Agency, USA
Drew Wagner, Department of Human Services and Health, Australia
Maged Younes, Secretariat, IPCS

The draft guidance document was further developed with input from an IPCS Workshop on Incorporating Uncertainty and Variability into Risk Assessment, held in May 2000 in Berlin, Germany, and through a follow-up meeting convened in August 2000 in Ottawa, Ontario, Canada, by the following Drafting Group, consisting of several of the Working Group members and participants in the Berlin Workshop:

Alan Boobis, Imperial College School of Medicine and Technology, United Kingdom
Michael Dourson, Toxicology Excellence for Risk Assessment, USA
Donald Grant, Consultant to IPCS, Canada
Ursula Gundert-Remy, Federal Institute for Health Protection of Consumers and Veterinary Medicine (BGVV), Germany
Bette Meek, Health Canada, Canada
Sharon Munn, European Chemicals Bureau, Italy
Edward Ohanian, Environmental Protection Agency, USA
Andrew Renwick, University of Southampton, United Kingdom

The draft guidance document was circulated for review by all participants in the Berlin Workshop, review comments were incorporated and the guidance document was finalized for peer review in 2001.

The document was placed on the IPCS Internet site for open public comment/peer review in late 2001. However, no comments were received. In late 2003, it was decided to call for

another round of review, and the document was distributed to relevant WHO Collaborating Centres, IPCS Participating Institutions and selected experts involved in IPCS activities. Twelve submissions containing comments were received. Dr Andrew Renwick prepared a revised document, taking into account the comments received, for consideration by a newly constituted expert group comprising some members of the Drafting Group listed above and selected reviewers from the peer review round. The group members were:

Alan Boobis, Imperial College School of Medicine and Technology, United Kingdom
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