RISK ASSESSMENT OF CHEMICALS

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An Introduction

2nd edition

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PREFACE

Chemicals are used to make virtually every man-made product and play an important role in the everyday life of people around the world. The chemical industry is the third largest industrial sector in the world and employs millions of people. Since 1930, global production of chemicals has risen from 1 million tonnes to over 400 million tonnes annually. In 2004 the global sales were estimated at € 1776 billion. The EU accounts for approximately 33% of global sales. This gradual increase in the production and widespread use of chemicals was not without "cost". While chemicals play an important role in products for health and well-being, they may also pose risks to human health and the environment.

In 1992, at the United Nations Conference on Environment and Development (UNCED) in Rio de Janeiro, agreement was reached on an action plan for sustainable development in a number of policy areas. "Agenda 21" was born. The management of chemicals features prominently in Agenda 21, including the need to expand and accelerate the international assessment of chemical risks and strengthen national capacities for the management of chemicals. In the light of all of this, it is no coincidence that chemicals were again high on the agenda of the World Summit on Sustainable Development in Johannesburg in 2002. In South Africa our heads of state and governments undertook to minimize all adverse effects of chemicals within one generation, by the year 2020.

With the new legislative framework for industrial chemicals, i.e. REACH, Europe has moved from words to deeds in meeting the Johannesburg goal. REACH stands for Registration, Evaluation, Authorization and Restriction of CHemicals. The Regulation creates one system for the evaluation of all industrial chemicals with regard to their production, formulation, use and disposal. It will provide a high level of protection of human health and the environment and, at the same time, enhance the competitiveness of the EU chemicals industry.

Successful implementation of REACH will be a challenge. It will involve 30,000 chemicals, 30,000 companies, a newly created European Chemicals Agency and many other stakeholders. REACH will also be a scientific challenge. It will boost further scientific research into sustainable chemistry. It will also make us aware of the scarce human resources currently available to meet these challenges. Therefore I hope that the scientific community will shoulder its responsibility for training students in chemistry, technology, biology, toxicology and other sciences related to the development, assessment and management of chemicals.

The present volume is the 2nd edition of a book published in 1995. It is an introduction to the risk assessment of chemicals and contains basic background information on sources, emissions, distribution and fate processes for the estimation of exposure of plant and animal species in the environment and humans exposed via the environment, consumer products and in the workplace. It includes chapters on environmental chemistry, toxicology and ecotoxicology, as well as information on estimation methods and intelligent testing strategies. It describes the basic principles and methods of risk assessment in their legislative frameworks (EU, USA, Japan and Canada). The book is intended to be used by students in technology, health and environmental sciences. It also provides background material for those who are currently involved in the risk assessment of chemicals. I hope that this book will contribute to meeting the challenges we are currently facing throughout the world.

Janez Potočnik
Commissioner for Science and Research
European Commission

EDITORS

Cornelis Johannes (Kees) Van Leeuwen (1955) studied biology at the University of Utrecht (UU), where he received his masters' degree in 1980 *(cum laude)* and obtained his PhD further to a thesis about the ecotoxicological effects of pesticides in 1986. He began his career in 1980 as a plant ecologist at the University of Groningen and, shortly thereafter, became head of the Laboratory of Ecotoxicology at the Ministry of Transport and Public Works. He served in a research and advisory role in the implementation of the Netherlands' Pollution of Surface Waters Act. In 1987 he joined the Chemicals Division of the Ministry of Housing, Spatial Planning and Environment (VROM). In 1991 he became head of the Risk Assessment and Environmental Quality Division. He held a part-time professorship in biological toxicology at the Institute for Risk Assessment Sciences (IRAS) at the University of Utrecht. From 1997-2002 he was deputy director of the Centre for Substances and Risk assessment (CSR) at the National Institute for Public Health and the Environment (RIVM). He has been member of various policy and expert groups in the European Union, the International Rhine Committee, the Organization for Economic Co-operation and Development, the European and Mediterranean Plant Protection Organization and the Council of Europe. He was chairman of the OECD Hazard Assessment Advisory Body, vice-chairman of the OECD Joint Committee on Chemicals and member of the Scientific Committee on Toxicology, Ecotoxicology and the Environment (CSTEE) of the European Commission and external advisor to the Long-range Research Initiative (LRI) of CEFIC. In 2002 he became director of the Institute for Health and Consumer Protection of the Joint Research Centre of the European Commission. In this role he was responsible for the European Chemicals Bureau (ECB), the European Centre for the Validation of Alternative Methods (ECVAM), the Biotechnology and GMO unit, the Physical and Chemical Exposure unit and Biomedical Materials and Systems. In 2007 he retired from the European Commission and was appointed as principal scientist at TNO Quality of Life in the Netherlands.

Theodorus Gabriël (Theo) Vermeire (1953) studied chemistry and toxicology at the University of Utrecht. He received his MSc and teaching qualifications in 1978. After a 3-year teaching period as a volunteer in Zambia, he joined the Dutch Directorate-General of Environmental Protection in 1982 and started his career in risk assessment as a toxicologist contributing to projects of the WHO International Programme on Chemical Safety (IPCS) and UNEP International Register of Potentially Toxic Chemicals (currently: UNEP Chemicals). In 1987, he joined the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Netherlands and has served in several scientific and managerial functions up to this day. As a project leader, he was involved in many projects in the area of toxicological standard setting, human and environmental exposure assessment, human toxicological dose-response assessment and the development of risk assessment methodologies and tools. Major projects include the development of the Netherlands' Uniform System for the Evaluation of Substances (industrial chemicals, plant protection products and biocides) and the European Union System for the Evaluation of Substances (industrial chemicals and biocides). His present position at RIVM is deputy head of the RIVM Expertise Centre for Substances. As an expert with a wide knowledge of toxicology and risk assessment, he has been involved in many expert groups developing risk assessment guidance for IPCS, the European Union and the Organization for Economic Co-operation and Development. Further to his interest in capacity building and teaching he has been involved in the organization of international risk assessment courses and EU twinning projects and taken part in them. He is a member of the Scientific Committee of the European Environment Agency and editor of the journal Human and Ecological Risk Assessment.

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EXPLANATORY NOTES

Prefixes to the names of units

M	mega (10^6)
k	kilo (10^3)
d	deci (10^1)
c	centi (10^{-2})
m	milli (10^{-3})
µ	micro (10^{-6})
n	nano (10^{-9})
p	pico (10^{-12})
f	femto (10^{-15})

Chemical prefixes

o	ortho
m	meta
p	para
n	normal
sec	secondary
tert	tertiary

Units

Å	Ångstrom (0.1 nm)
atm	atmosphere
°C	degree Celsius or centigrade
cal	calorie
d	day
g	gram
h	hour
ha	hectare
J	Joule
K	degree absolute (Kelvin)
kg	kilogram
L	litre
m	metre
M	molar (mol/litre)
min	minute
Pa	Pascal (unit of pressure; 100kPa = 1 bar)
s	second
V	Volt
W	Watt
y	year

Abbreviations

ACD	Allergic Contact Dermatitis
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism and Excretion
AEC	Anion Exchange Capacity
AF	Assessment Factor or Application Factor
a.i.	Active ingredient
AIM	Analog Identification Methodology, USEPA
AIST	National Institute of Advanced Industrial Science and Technology, Japan
ALARA	As Low As Reasonably Achievable
ANN	Artificial Neural Network
ANOVA	ANalysis Of VAriance
APHA	American Public Health Association
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under the blood/plasma concentration vs. time Curve, representing the total amount of substance reaching the plasma
AVS	acid volatile sulphide
B	Bioaccumulation
BAF	Bioaccumulation Factor
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BfR	German federal Institute for Risk Assessment
BIAC	Business and Industry Advisory Committee
BLM	Biotic Ligand Model
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biological Oxygen Demand
b.p.	Boiling point
bw	body weight
CA	Competent Authority
CAS	Chemical Abstract Services
CBA	Cost-Benefit Analysis
CBB	Critical Body Burden
CBI	Confidential Business Information
CBR	Critical Body Residue
CCPs	Capacity Controlling Properties
CDC	Centre for Disease Control (and prevention)
CEC	Cation Exchange Capacity
CED	Critical Effect Dose
CEN	European Standardization Organization
CES	Critical Effect Size
CEPA	Canadian Environmental Protection Act

CFCs	Chlorofluorocarbons
ChemRTK	Chemical Right-to-Know initiative, USEPA
CICAD	Concise International Chemical Assessment Document, IPCS
C&L	Classification and Labelling
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
ComET	Complex Exposure Tool, Canada
ComHaz	Complex Hazard tool, Canada
CSA	Chemical Safety Assessment
CSCL	Chemical Substances Control Law, Japan
CSR	Chemical Safety Report
CTV	Critical Toxicity Value
CT50	Clearance Time, elimination or depuration expressed as half-life
C.V.	coefficient of variation
Cyt	cytochrome
DfE	Design for the Environment program, OPPT
dfi	daily food intake
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DNEL	Derived No Effect Level
DOC	Dissolved Organic Carbon
DOM	Dissolved Organic Matter
DSL	Domestic Substances List, Canada
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DU	Downstream User
EASE	Estimation and Assessment of Substance Exposure [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECA	(1) Environmental Contaminants Act, Canada; (2) Enforceable Consent Agreement, USEPA
ECB	European Chemicals Bureau
ECHA	European CHemicals Agency
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
ED50	median Effective Dose
EEB	European Environment Bureau
EEC	European Economic Community
EEM	Emission Estimation Model
EEV	Estimated Exposure Value
Eh	Electrode potential
EHPV	Extended HPV chemicals programme, USEPA
EINECS	European Inventory of Existing Commercial Chemical Substances
ELS	Early Life Stage
EN	European Norm
ENEV	Estimated No Effects Value
EP	(1) European Parliament; (2) Equilibrium Partitioning
EPA	Environmental Protection Agency
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
EQO	Environmental Quality Objective
EQS	Environmental Quality Standard
ERA	Environmental Risk Assessment
ES	Exposure Scenario
ESD	Emission Scenario Document
ESIS	European chemical Substances Information System
EST	Embryonic Stem cell Test
EU	European Union
EUSES	EU System for the Evaluation of Substances [software tool in support of the TGD]
F	Variance ratio
FACA	Federal Advisory Committee Act, USA
FAO	Food and Agriculture Organization, UN
FCV	Final Chronic Value
FDA	Food and Drug Administration
FELS	Fish Early Life Stage
FFRP	Furniture Flame Retardancy Partnership, USEPA
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act, USA
FYI	For Your Information submissions under TSCA
GAP	Good Agricultural Practice
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
GHS	Globally Harmonised System of classification and labelling, UN
GLC	Gas-Liquid chromatography
GLP	Good Laboratory Practice, OECD
GPE	Greatest Potential for Exposure (of the general population), Canada
H	Henry coefficient
HC5	Hazardous Concentration for 5% of the

	species
H2E	Hospitals for a Healthy Environment program, USEPA
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission - Baltic Marine Environment Protection Commission
HOMO	Highest Occupied Molecular Orbital
HPLC	High Pressure Liquid Chromatography
HPV	High Production Volume
HPVC	High Production Volume Chemical (> 1000 t/y)
HPVIS	HPV Information System, USEPA
HRA	Health Risk Assessment
IBT	Inherent Biodegradability Test
IC	Industrial Category
ICAPO	International Council on Animal Protection in OECD Programmes
IC50	median Immobilization Concentration or median Inhibitory Concentration
ICCA	International Council of Chemical Associations
ICHC	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILSI	International Life Science Institute
IOMC	Inter-Organization Programme for the Sound Management of Chemicals,
IPCS	International Programme on Chemical Safety
IPE	Intermediate Potential for Exposure (of the general population), Canada
ISO	International Organization for Standardization
ISO/DIS	International Organization for Standardization/Draft International Standard
ITC	Interagency Testing Committee, USEPA
ITS	Intelligent Testing Strategies
IUCLID	International Uniform Chemical Information Database
IUR	Inventory Update Rule under TSCA
i.v.	intravenous
JMPR	Joint Meeting of Experts on Pesticide Residues, WHO/FAO
k	Rate constant
K	Partition coefficient or equilibrium constant or distribution ratio or carrying capacity
K_{oa}	n-octanol-air partition coefficient
K_{oc}	organic carbon normalised solids-water partition coefficient
K_{ow}	n-octanol-water partition coefficient
K_p	solids-water partition coefficient
log	Logarithm (common, base 10)
ln	Logarithm (natural, base e)
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LFER	Linear Free Energy Relationship
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOQ	Limit Of Quantitation
LPE	Lowest Potential for Exposure (of the general population), Canada
LUMO	Lowest Unoccupied Molecular Orbital
m	Mean of population
MAC	Maximum Allowable Concentration
MAD	Mutual Acceptance of Data
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MDS	Minimum Data Set
MFO	Mixed Function Oxidase
MIC	Minimum Inhibitory Concentration
M/I	Manufacturer / Importer
MITI	Ministry of International Trade and Industry, Japan
MM	Micromass (test)
MOA	Mode Of Action
MOE	Margin Of Exposure
MOS	Margin Of Safety
m.p.	Melting point
MRL	Maximum Residue Limit
MS	Mass spectrometry
MS-test	Multi-species test
MSDS	Material Safety Data Sheet
MW	Molecular Weight
NAEL	No Adverse Effect Level
n or N	Total number of individuals or variates
N-DSL	Non-Domestic Substances List, Canada
NF	Norme Française
NGO	Non-Governmental Organization
NIMBY	Not In My BackYard
NITE	National Institute for Technology Evaluation, Japan

No.	Number (in tables and parentheses)
NOAEL	No Observed Adverse Effect Level
NOEC(L)	No Observed Effect Concentration (Level)
NPPTAC	National Pollution Prevention and Toxics Advisory Committee, USEPA
NSN	New Substances Notification, Canada
NTP	National Toxicology Program, US
OCT	OECD Confirmatory Test (biodegradation)
OECD	Organization for Economic Cooperation and Development
OM	Organic Matter
OPPT	Office of Pollution Prevention and Toxics, USEPA
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
p	Level of significance (probability of wrongfully rejecting the null hypothesis)
P	Persistent
P2	Pollution Prevention framework, USEPA
PAH	Polycyclic Aromatic Hydrocarbon
PBDE	PolyBrominated Diphenyl Ether
PBPK	Physiologically-Based PharmacoKinetic modelling
PBT	Persistent, Bioaccumulative and Toxic
PBTK	Physiologically-Based ToxicoKinetic modelling
PCBs	PolyChlorinated Biphenyls
PCDD	PolyChlorinated Dibenzo Dioxin
PCDF	PolyChlorinated Dibenzo Furan
PCRM	Physicians Committee for Responsible Medicine, USA
PEC	Predicted Environmental Concentration
PETA	People for the Ethical Treatment of Animals, USA
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctyl sulfonate
PLS	Partial Least Square
PMN	Premanufacture Notification under TSCA
PNC	Pre-Notification Consultation, OECD
PNEC	Predicted No Effect Concentration
p.o.	per os
POC	Particulate Organic Carbon
PoD	Point of Departure
POM	Particulate Organic Matter
POP	Persistent Organic Pollutant
PPA	Pollution Prevention Act, USA
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
PPORD	Product and Process Oriented Research and Development
PRTR	Pollutant Release and Transfer Register
PSI	Predetermined Set of Information, OECD
PSL	Priority Substances List, Canada
QA	Quality Assurance
QAAR	Quantitative Activity-Activity Relationship
QC	Quality Control
QSAAR	Quantitative Structure-Activity-Activity Relationship
QSAR	Quantitative Structure-Activity Relationship
r^2	Squared correlation coefficient or Coefficient of (multiple) determination
R (phrases)	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RBC	Red Blood Cell
RBT	Ready Biodegradability Test
RCF	Root Concentration Factor
REACH	Registration, Evaluation, Authorization and restriction of CHemicals
RIVM	National Institute for Public Health and the Environment, the Netherlands
RMM	Risk Management Measure
RNA	RiboNucleic Acid
RP	Reference Point
RRM	Risk Reduction Measure
RWC	Reasonable Worst Case
S (phrases)	Safety phrases according to Annex III of Directive 67/548/EEC
s^2	sample variance
σ	standard deviation of population
SAB	USEPA's Science Advisory Board
SAICM	Strategic Approach to International Chemicals Management
SAM	Standardized Aquatic Microcosm
SAR	Structure-Activity Relationships
SARA	Superfund Amendment and Reauthorization Act, USA
SCE	Sister Chromatic Exchange
SD	Standard deviation of series
SDS	Safety Data Sheet
SE	Standard error of mean
SETAC	Society of Environmental Toxicology And Chemistry
SF	Sustainable Futures initiative, OPPT
SIDS	Screening Information Data Set, OECD
SIEF	Substance Information Exchange Forum
SimHaz	Simple Hazard tool, Canada

SME	Small and Medium Enterprise
SimET	Simple Exposure Tool, Canada
SNac	Significant New Activity, Canada
SNAN	Significant New Activity Notice, Canada
SNIF	Summary Notification Interchange Format (new substances)
SNUR	Significant New Use Rule under TSCA
sp.	Species (when part of a bionomial)
SQO	Sediment Quality Objective
SSD	Species Sensitivity Distribution
SS-test	Single Species test
STP	Sewage Treatment Plant
$t_{1/2}$	Half-life
TCDD	2,3,7,8-tetrachloro-dibenzo-*p*-dioxin
TDI	Tolerable Daily Intake
TEER	Trans-Epithelial Electrical Resistance
TEF	Toxicity Equivalency Factor
TGD	Technical Guidance Document on risk assessment, EU
TIE	Toxicity Identification Evaluation
TLC	Thin Layer Chromatography
TLV	Threshold Limit Value
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organization for Applied Scientific Research
TSCA	Toxic Substances Control Act, USA
TSCF	Transpiration Stream Concentration Factor
TTC	Threshold of Toxicological Concern
TUAC	Trade Union Advisory Committee
TWA	Time-Weighted Average
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNCED	UN Conference on Environment and Development
UNEP	United Nations Environment Programme
USEPA	Environmental Protection Agency, USA
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
VSD	Virtually Safe Dose
WEC	Whole Embryo Culture
WHO	World Health Organization
UV	Ultraviolet
v/v	volume/volume (concentration)
WoE	Weight of Evidence
w/v	weight/volume (concentration)
ww	wet weight
WWTP	Waste Water Treatment Plant

CONTENTS

PART IV. DATA