

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

	species	K_{oa}	<i>n</i> -octanol-air partition coefficient
H2E	Hospitals for a Healthy Environment program, USEPA	K_{oc}	organic carbon normalised solids-water partition coefficient
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)	K_{ow}	<i>n</i> -octanol-water partition coefficient
		K_p	solids-water partition coefficient
HELCOM	Helsinki Commission - Baltic Marine Environment Protection Commission	log	Logarithm (common, base 10)
		ln	Logarithm (natural, base e)
HOMO	Highest Occupied Molecular Orbital	L(E)C50	median Lethal (Effect) Concentration
HPLC	High Pressure Liquid Chromatography	LAEL	Lowest Adverse Effect Level
HPV	High Production Volume	LC50	median Lethal Concentration
HPVC	High Production Volume Chemical (> 1000 t/y)	LD50	median Lethal Dose
		LEV	Local Exhaust Ventilation
HPVIS	HPV Information System, USEPA	LFER	Linear Free Energy Relationship
HRA	Health Risk Assessment	LLNA	Local Lymph Node Assay
IBT	Inherent Biodegradability Test	LOAEL	Lowest Observed Adverse Effect Level
IC	Industrial Category	LOEC	Lowest Observed Effect Concentration
ICAPO	International Council on Animal Protection in OECD Programmes	LOED	Lowest Observed Effect Dose
		LOQ	Limit Of Quantitation
IC50	median Immobilization Concentration or median Inhibitory Concentration	LPE	Lowest Potential for Exposure (of the general population), Canada
ICCA	International Council of Chemical Associations	LUMO	Lowest Unoccupied Molecular Orbital
ICHC	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use	m	Mean of population
		MAC	Maximum Allowable Concentration
ILSI	International Life Science Institute	MAD	Mutual Acceptance of Data
IOMC	Inter-Organization Programme for the Sound Management of Chemicals,	MATC	Maximum Acceptable Toxic Concentration
IPCS	International Programme on Chemical Safety	MC	Main Category
		MDS	Minimum Data Set
IPE	Intermediate Potential for Exposure (of the general population), Canada	MFO	Mixed Function Oxidase
ISO	International Organization for Standardization	MIC	Minimum Inhibitory Concentration
		M/I	Manufacturer / Importer
ISO/DIS	International Organization for Standardization/Draft International Standard	MITI	Ministry of International Trade and Industry, Japan
		MM	Micromass (test)
ITC	Interagency Testing Committee, USEPA	MOA	Mode Of Action
ITS	Intelligent Testing Strategies	MOE	Margin Of Exposure
IUCLID	International Uniform Chemical Information Database	MOS	Margin Of Safety
		m.p.	Melting point
IUR	Inventory Update Rule under TSCA	MRL	Maximum Residue Limit
i.v.	intravenous	MS	Mass spectrometry
JMPR	Joint Meeting of Experts on Pesticide Residues, WHO/FAO	MS-test	Multi-species test
		MSDS	Material Safety Data Sheet
<i>k</i>	Rate constant	MW	Molecular Weight
<i>K</i>	Partition coefficient or equilibrium constant or distribution ratio or carrying capacity	NAEL	No Adverse Effect Level
		<i>n</i> or <i>N</i>	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)	PPORD	Product and Process Oriented Research and Development
NOAEL	No Observed Adverse Effect Level		
NOEC(L)	No Observed Effect Concentration (Level)	PRTR	Pollutant Release and Transfer Register
NPPTAC	National Pollution Prevention and Toxics Advisory Committee, USEPA	PSI	Predetermined Set of Information, OECD
NSN	New Substances Notification, Canada	PSL	Priority Substances List, Canada
NTP	National Toxicology Program, US	QA	Quality Assurance
OCT	OECD Confirmatory Test (biodegradation)	QAAR	Quantitative Activity-Activity Relationship
OECD	Organization for Economic Cooperation and Development	QC	Quality Control
OM	Organic Matter	QSAAR	Quantitative Structure-Activity-Activity Relationship
OPPT	Office of Pollution Prevention and Toxics, USEPA	QSAR	Quantitative Structure-Activity Relationship
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic	r^2	Squared correlation coefficient or Coefficient of (multiple) determination
p	Level of significance (probability of wrongfully rejecting the null hypothesis)	R (phrases)	Risk phrases according to Annex III of Directive 67/548/EEC
P	Persistent	RAR	Risk Assessment Report
P2	Pollution Prevention framework, USEPA	RBC	Red Blood Cell
PAH	Polycyclic Aromatic Hydrocarbon	RBT	Ready Biodegradability Test
PBDE	PolyBrominated Diphenyl Ether	RCF	Root Concentration Factor
PBPK	Physiologically-Based Pharmacokinetic modelling	REACH	Registration, Evaluation, Authorization and restriction of Chemicals
PBT	Persistent, Bioaccumulative and Toxic	RIVM	National Institute for Public Health and the Environment, the Netherlands
PBTK	Physiologically-Based Toxicokinetic modelling	RMM	Risk Management Measure
PCBs	PolyChlorinated Biphenyls	RNA	RiboNucleic Acid
PCDD	PolyChlorinated Dibenzo Dioxin	RP	Reference Point
PCDF	PolyChlorinated Dibenzo Furan	RRM	Risk Reduction Measure
PCRM	Physicians Committee for Responsible Medicine, USA	RWC	Reasonable Worst Case
PEC	Predicted Environmental Concentration	S (phrases)	Safety phrases according to Annex III of Directive 67/548/EEC
PETA	People for the Ethical Treatment of Animals, USA	s^2	sample variance
PFOA	Perfluorooctanoic acid	σ	standard deviation of population
PFOS	Perfluorooctyl sulfonate	SAB	USEPA's Science Advisory Board
PLS	Partial Least Square	SAICM	Strategic Approach to International Chemicals Management
PMN	Premanufacture Notification under TSCA	SAM	Standardized Aquatic Microcosm
PNC	Pre-Notification Consultation, OECD	SAR	Structure-Activity Relationships
PNEC	Predicted No Effect Concentration	SARA	Superfund Amendment and Reauthorization Act, USA
p.o.	per os	SCE	Sister Chromatic Exchange
POC	Particulate Organic Carbon	SD	Standard deviation of series
PoD	Point of Departure	SDS	Safety Data Sheet
POM	Particulate Organic Matter	SE	Standard error of mean
POP	Persistent Organic Pollutant	SETAC	Society of Environmental Toxicology And Chemistry
PPA	Pollution Prevention Act, USA	SF	Sustainable Futures initiative, OPPT
ppb	Parts per billion	SIDS	Screening Information Data Set, OECD
PPE	Personal Protective Equipment	SIEF	Substance Information Exchange Forum
ppm	Parts per million	SimHaz	Simple Hazard tool, Canada

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

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