
Klaus Kümmerer

(Editor)

Pharmaceuticals in the Environment

Sources, Fate, Effects and Risks

Klaus Kümmerer
(Editor)

Pharmaceuticals in the Environment

Sources, Fate, Effects and Risks

Third edition
With 108 Figures and 62 Tables

 Springer

Editor

Prof. Dr. Klaus Kümmerer

Department of Environmental Health Sciences
University Medical Center Freiburg
Breisacher Straße 115 B
79106 Freiburg, Germany
E-mail: klaus.kuemmerer@uniklinik-freiburg.de

ISBN: 978-3-540-74663-8

e-ISBN: 978-3-540-74664-5

Library of Congress Control Number: 2008926949

© 2008, 2004, 2001 Springer-Verlag Berlin Heidelberg

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitations, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer. Violations are liable to prosecution under the German Copyright Law.

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Cover design: WMX Design GmbH, Heidelberg
Typesetting: Uwe Imbrock, Stasch · Verlagsservice, Bayreuth (stasch@stasch.com)
Production: Christine Adolph

Printed on acid-free paper 30/2133/CA – 5 4 3 2 1 0

springer.com

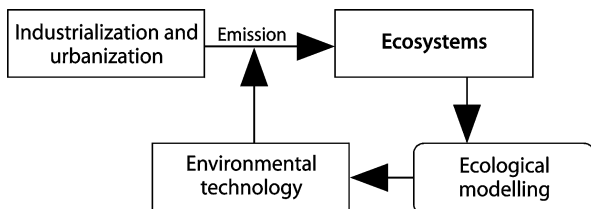
Foreword

When the first green wave appeared in the mid and late 1960s, it was considered a feasible task to solve pollution problems. The visible problems were mostly limited to point sources, and a comprehensive “end of the pipe technology” (= environmental technology) was available. It was even seriously discussed in the US that what was called “zero discharge” could be attained by 1985.

It became clear in the early 1970s that zero discharge would be too expensive, and that we should also rely on the self purification ability of ecosystems. That called for the development of environmental and ecological models to assess the self purification capacity of ecosystems and to set up emission standards, considering the relationship between impacts and effects in the ecosystems. This idea is illustrated in Fig. 0.1. A model is used to relate an emission to its effect on the ecosystem and its components. The relationship is applied to select a good solution to environmental problems by application of environmental technology.

Meanwhile, it has been disclosed that what we could call the environmental crisis is much more complex than we initially thought. We could, for instance, remove heavy metals from wastewater, but where should we dispose the sludge containing the heavy metals? Resource management pointed towards recycling to replace removal. Non-point sources of toxic substances and nutrients, chiefly originating from agriculture, emerged as new threatening environmental problems in the late 1970s. The focus on global environmental problems such as the greenhouse effect and the decomposition of the ozone layer added to the complexity. It was revealed that we use as much as about 100 000 chemicals, which may threaten the environment due to their more or less toxic effects on plants, animals, humans and entire ecosystems. In most industrialised countries comprehensive environmental legislation was introduced to regulate the wide spectrum of different pollution sources. Trillions of dollars have been invested in pollution abatement on a global scale, but it seems that two or more new problems emerge

Fig. 0.1. The strategy applied in environmental management in the early 1970s is illustrated. An ecological model is used to relate an emission to its effect on the ecosystem and its components. The relationship is applied to select a good solution to environmental problems by application of environmental technology



for each problem that we solve. Our society does not seem geared toward solving environmental problems, or is there perhaps another explanation?

Recently, standards for environmental management in industries and green accounting have been introduced. The most widely applied standards today for industrial environmental management are the ISO 14000-series. These initiatives attempt to analyse our production systems to find new ways and methods to make our production more environmentally friendly. More than 100 countries have backed up the international standards for effective management of environmental impacts.

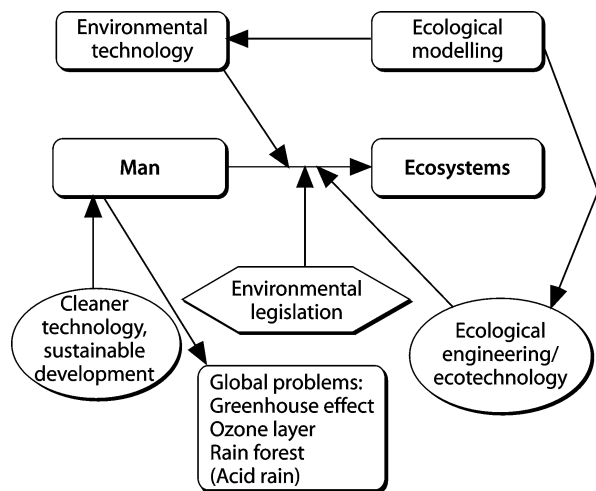
Figure 0.2 illustrates how complex environmental management is today. The first figure shows that a simultaneous application of environmental technology, ecotechnology, cleaner technology and environmental legislation is needed in environmental management.

Environmental technology offers a wide spectrum of methods that are able to remove pollutants from water, air and soil. These methods are particularly applicable to coping with point sources.

Cleaner technology explores the possibilities of recycling by-products or the final waste products or attempting to change the entire production technology to obtain reduced emissions. It attempts to answer the pertinent question: couldn't we produce our product using a more environmentally friendly method? It will to a great extent be based on environmental risk assessment, LCA and environmental auditing. The ISO 14000-series and risk reduction techniques are among the most important tools in the application of cleaner technology. The environmental risk assessment of chemicals is in this context a very important tool, as it results in a quantification of the environmental risk.

Ecotechnology covers the use of ecosystems to solve pollution problems, including the erection of artificial ecosystems. It also encompasses the technology that is applicable to the restoration of more or less deteriorated ecosystems. The mentioned classes of technologies cover a wide spectrum of methods. We have, for instance, many environmental technological methods to cope with different wastewater problems, and to

Fig. 0.2. The use of environmental models in environmental management, which, today, is very complex and must apply environmental technology, cleaner technology and ecotechnology. Models are used to select the right environmental management strategy. In addition, the global environmental problems, which also require the use of models as a synthesizing tool, play an increasing role



select the right method or most often the right combination of methods, a profound knowledge of the applicability of the methods and of the processes and characteristics of the ecosystem receiving the emission is necessary.

Environmental legislation and green taxes may be used in addition to these classes of technology. They may in principle be used as regulating instruments in every step of the flow from raw materials and energy to final waste disposal of the used product.

The 20th century has introduced more than 100 000 chemicals that are used in our every day life, either in households, industries or agriculture. We have “blindly” introduced these chemicals without realising the consequences for the environment and directly and indirectly for human health. EU started to list these chemicals in the late 1970s, and since the mid 1980s it has been compulsory to set up an environmental risk assessment for all new chemicals. It was the idea, meanwhile, to make environmental risk assessments for the chemicals already in use, but it is going very slowly, and at the present rate, we shall not be able finish ERAs for all the applied chemicals in this century. Probably, it is necessary to speed up the evaluation of the chemicals in use, for instance by forging a closer cooperation between the environmental agencies and the chemical industry, in order to obtain a realistic picture of the environmental risk associated with the many chemicals we apply today.

It is strange that drugs were not included when a compulsory environmental risk assessment was introduced for new chemicals, because drugs have properties that cause suspicion about environmental effects. Drugs are

- biologically active.
- often mobile as the water solubility is high relative to the molecular weight. This is particularly true for metabolites of the drugs that can be found in urine and therefore also in the wastewater.
- not readily biodegradable.

Drugs have, in other words, properties that make them environmentally interesting.

Today, an environmental risk assessment is required for all new medical compounds used in veterinary drugs, but it is expected that this will also be required for human drugs in the near future.

This volume focuses on what we know but also what we don't know about drugs, or rather what we ought to know to understand the occurrence, the fate and the effect of the about 4 000 medical compounds that we are using in the drugs applied today. What basic knowledge do we have today about drugs to be able to set up ERAs for the medical compounds?

Recently (February 2000) Chemosphere published a special issue on “drugs in the environment.” This issue contained several interesting papers on these topics. This volume is, however, the first book to review “drugs in the environment.” A book can, of course, give more detailed information than scientific papers, and also make links to what is known more generally about chemical compounds in our environment. The publication of this book is therefore an important step forward in our effort to

1. understand the environmental occurrence and processes of drugs,
2. quantify their effects and risks and

3. properly abate the associated pollution problem by trying to give an answer to the following two pertinent questions:
 - Which medical compounds should be phased out and substituted by other compounds?
 - Could we solve some of the problems with environmental or cleaner technology? How?

At least a decade will pass before we have a proper overview of the many environmental problems that are associated with medical compounds discharged into the environment. At that time – ten or fifteen years from now? – we may have substituted the most environmentally harmful chemicals with other compounds as a concluding result of the performed ERAs. The focal point is, however, that we have a realistic knowledge about the risk involved in the use of medical compounds and can phase out the most risky compounds. This process has already started – slowly but surely – because the medical industry is very concerned today about the fate and effect of antibiotics and recommendations on which antibiotics to use from an environmental point of view can already to a certain extent be given today.

Sven Erik Jørgensen¹

¹ *Current address:* Prof. Sven Erik Jørgensen, The Royal Danish School of Pharmacy, Department of Analytical and Pharmaceutical Chemistry, Universitetsparken 2, 2100 Copenhagen, Denmark, E-mail: SEJ@dfh.dk.

Preface to the Third Edition

Pharmaceuticals in the environment are still a “hot bed” of interest. Since the publication of the first edition in 2001 and the second edition in 2004 the focus of research has changed again. In the meantime, we have learned quite a lot about the fate, effects, and risks associated with the presence of pharmaceuticals in the aquatic and terrestrial environment. Anyway, there is still an increasing need for knowledge of pharmaceuticals in the environment.

The input and fate of parent compounds and the relative importance of different sources including compounds that up to now have only been scarcely investigated are still of interest. However, metabolites of human and animal metabolism are coming into focus. The same holds for products of transformation of parent compounds and metabolites in the environment, such as dead-end transformation products of biodegradation, oxidation or photolysis.

As it has been extensively demonstrated that the active compounds are present in the environment some of the interest in this field of research has moved from analysis of the compounds, which is still undertaken to effect studies to more extensive fate studies in the lab and in field trials. It has been found that environmental concentrations can cause effects in wildlife if proper tools are applied for effect assessment. The question of mixture toxicity has gained more and more attention. It has been learned that classical tests may underestimate effects and risks. The significance of antibiotic resistance in the environment is still not clear.

The long-awaited guideline for environmental risk assessment for human pharmaceuticals in the European Union has been in force since December 2006. Accordingly, more work has been done in the field of risk assessment and risk management. For compounds already on the market that constitute by far the biggest share this guideline is only applicable in case of the need for a renewal of the license. As for risk management strategies to eliminate pharmaceuticals from waste water or from the effluent of sewage treatment plants have been proposed and investigated. A tremendous amount of literature can now be found describing technical management measures such as oxidative or photolytic effluent treatment, filtering techniques, and application of charcoal. It has been learned however, that each of these approaches has its specific shortcomings. Therefore, additional approaches such as including people handling and using the compounds, and focussing on the properties of the compounds (“green pharmacy”) have come into focus.

Accordingly, the 3rd edition has been largely changed again in comparison with the previous ones to address these new issues and the new lines of discussions and new findings. As in the previous editions, it gives an overview of the present state of knowledge presenting typical results and lines of discussion. Like the previous editions, this

one doesn't claim to give a complete overview including the fully detailed body of knowledge of pharmaceuticals in the environment. Rather, it addresses important and typical topics. In contrast, it highlights the most important questions and issues related to the presence of pharmaceuticals in the environment. It also provides many new findings that raise new questions and confirm earlier results.

This edition contains four major parts. In the first part, specifics of pharmaceuticals that distinguish them from "classical" micro-pollutants are addressed. In the second part, new findings on sources, occurrence and fate of pharmaceuticals in the environment are presented. In the third part, an overview of the current state of knowledge of effects of pharmaceuticals in aquatic and terrestrial environment is given. New, promising approaches to the study of the effects of pharmaceuticals in the environment are described. The fourth part addresses risk assessment issues starting with the EU guideline and practical experiences of its application. Shortcomings of the EU guidelines are discussed in several contributions. A brief description of the state of regulation of chemicals in Japan is also included. The final part is dedicated to risk management. As advanced STP effluent treatment as a management approach has already been addressed in the second edition and no generally new findings have been published since this time, only little space has been devoted to it. Instead mainly non technical approaches are presented here that are also of importance and are often overseen.

Accordingly, most of the contributions have replaced the ones of the second edition. They are addressing these new foci of research. The remaining ones have been updated. As a result, the 3rd edition is not only a revised and updated one but an additional new volume in a "series" of pharmaceuticals in the environment. The 1st and 2nd edition are still valuable sources of information and should be used together with this 3rd edition. Research needs are addressed within each chapter. Therefore, a separate chapter on research needs was omitted in this edition.

Again the edition of the book would have not been possible without the support of my co-workers in the research group of the Applied Environmental Research Section at the Department of Environmental Health Sciences at the Medical Center at Freiburg University. Special thanks to Radka Alexy, Petra Heiberger and Andreas Längin for their support of my daily routine, which gave me the necessary time to edit a book in such a dynamic field. Numerous discussions with colleagues, with contributors to the book and other people have been stimulating. Thank you to all those people who created the opportunity for discussion, the exchange of ideas and the sharing of results on the role of pharmaceuticals in the environment. This, as well as the encouraging comments and overwhelmingly positive feedback received for the second edition from many experts in the field encouraged the publisher and myself to publish a third edition. Thank you to Christian Witschel and his team from Springer Verlag Heidelberg who strongly supported the idea and helped to make the third edition possible. Thank you also to all the authors who gave up their precious time to contribute to this book.

A big thank you again to my wife Isolde, and my children Sarah and Yannik, with whom I was able to spend precious family time and without whose patience and encouragement neither this nor the preceding editions of the book would ever have been completed.

Klaus Kümmerer
Freiburg, January 2008

Preface to the Second Edition

The first edition of “Pharmaceuticals in the Environment” was sold out within two years. This is quite surprising for a book on such a specialised topic. Obviously, pharmaceuticals in the environment, their fate, effects, and the risks associated with their presence there are a “hot bed” of interest.

Since publication of the first edition, so much literature on the topic has been published in journals and proceedings that it is hard to keep an overview. Most of these papers have been of an analytical nature. The majority deal with the detection of pharmaceuticals in the aquatic environment, while others describe methods used to analyse pharmaceuticals in soil and the results of these analyses. The proportion of publications describing the occurrence and fate of pharmaceuticals in soils has increased since publication of the first edition. A minority of papers describe and assess the effects of pharmaceuticals on organisms in the aquatic environment and in the soil. The initiation of resistance and the selection of resistant bacteria in the environment has been addressed and intensively discussed. However, the significance of this topic is not yet clear. Furthermore, strategies to eliminate pharmaceuticals from waste water or from the effluent of STPs have been proposed and investigated. Introduction of restrictions relating to environmental aspects of pharmaceuticals are being discussed within the scope of EU regulatory procedure.

I have taken the opportunity provided by a second edition to revise and extend the book according to the enlarged body of knowledge on as yet unresolved, as well as newly emerging issues related to the input, occurrence and fate of pharmaceuticals in the environment, as well as the risks which they pose. The new edition gives an overview of the present state of knowledge with respect to typical results and lines of discussion. Like the first edition, this one makes no claim to give a complete overview of the state of the art of pharmaceuticals in the environment. Rather, it addresses important and typical topics and highlights the most important questions and issues related to the presence of pharmaceuticals in the environment. It also provides many new findings which raise new questions and confirm earlier results. The increased number of contributions and authors gathered in the second edition reflects with greater number of papers published, and of issues addressed, as well as the growing number of people from academia, official bodies and companies involved in the topic. It also reflects the intensified and ongoing discussions and the increased public awareness. Thus, in character, the second edition is more that of a general summary than was the case with the first edition.

The second edition of the book would have not been possible without the support of my co-workers in the research group of the Applied Environmental Research Sec-

tion of the Freiburg University Hospital Institute of Environmental Medicine and Hospital Epidemiology. Special thanks to Radka Alexy for her support in my daily routine, which gave me the necessary time to edit a book in such a dynamic field. I greatly acknowledge the support of Franz Daschner, Director of the Institute of Environmental Medicine and Hospital Epidemiology. Numerous discussions with colleagues, with contributors to the book and other people have been stimulating. Thank you to all those people who created the opportunity for discussion, the exchange of ideas and the sharing of results on the role of pharmaceuticals in the environment. This, as well as the encouraging comments and positive feedback received to the first edition from many experts in the field encouraged the publisher and myself to publish a second edition so soon after the first edition. Thank you to Christian Witschel and his colleagues from Springer-Verlag Heidelberg, who strongly supported the idea and helped make the second edition possible. Thank you also to all the authors who gave up their precious time to contribute to this book.

A big thank you also to my wife Isolde, and my children Sarah and Yannik, with whom I was able to spend precious family time and without whose patience and encouragement neither this nor the first edition of the book would ever have been completed.

Klaus Kümmerer
Freiburg, November 2003

Preface to the First Edition

All of us use pharmaceuticals for ourselves or for our pets, in husbandry, in agriculture or in aquaculture. But who knows what will happen to the compounds after their administration or use? Are they distributed in the environment or are they eliminated beforehand? What are the possible effects and risks for humans and the environment in connection with the emission of pharmaceuticals into the environment? Pharmaceuticals, diagnostic aids as well as disinfectants used in medicine enter municipal sewage and the aquatic environment. Drugs and growth promoters used in veterinary medicine and husbandry are excreted by animals and emitted into soil via manure or can be part of the runoff from soils after heavy rain fall, which then passes into surface water. Drugs used in aquaculture are passed directly into surface water. Some, such as X-ray contrast media, are excreted completely unchanged, while others are metabolised either into metabolites, which are still active or inactive metabolites. Outdated medications or their remnants are sometimes disposed of down household drains or as (household) waste. The fate, occurrence and effects of pharmaceuticals in the aquatic and terrestrial environment is still mainly unknown.

The disposal of pharmaceuticals in the environment means that a huge number of different substances in different amounts, products and modes of action have to be considered. Therefore, it is difficult to obtain an appropriate overview on the ongoing research. It is even more difficult to identify the most important questions for a systematic approach. The information available is still scarce and not sufficient for sound assessment and decision-making. For this reason, the European Science Foundation (ESF), located in Strasbourg (France), commissioned the workshop "Pharmaceuticals in the Environment." It was held in July 1999 in Freiburg (Germany). The core of the book consists of issues discussed and explored in depth during this workshop. Some other authors, not present at the workshop, have been added.

The book does not claim to give a complete review of the state of the art related to pharmaceuticals in the environment. There is a lot of literature, symposia, international networking and research organising on EDSs. This is still lacking for pharmaceuticals other than hormones. This book gives a short review of the fate, occurrence and effects of pharmaceuticals using examples of some typical compounds to highlight the most important questions and issues related to pharmaceuticals in the environment. Input, occurrence, fate and effects as well as the possible risks and their assessment are addressed. The book also gives an introduction to this new field of environmental chemistry, ecotoxicology and environmental hygiene.

This book would not have been realised without the workshop "Pharmaceuticals in the Environment" commissioned by the European Science Foundation (ESF). Dr. A. Moth-

Wiklund and her team from the Life and Environment Standing Committee (LESC) at the ESF always gave good support whenever necessary. All the participants of the workshop contributed to the lively discussions and the identification of the important questions of research in the future. The contributors to this volume were very patient with the editor. The workshop and the book would have not been realised without the support of the director of the Institute of Environmental Medicine and Hospital Epidemiology at the Freiburg University Hospital, Prof. Dr. med. Franz Daschner, and of all my co-workers in the field of pharmaceuticals in the environment. Tina Kümpel and Birgit Stadel helped with the manuscripts. Dr. Witschel from Springer Verlag (Heidelberg) created the opportunity to publish this book. Special thanks to my wife and my children for their encouragement and their support.

Thank you!

Klaus Kümmerer
Freiburg, January 2001

Contents

Part I General Aspects	1
1 Pharmaceuticals in the Environment – A Brief Summary	3
1.1 Parent Compounds, Metabolites and Transformation Products	3
1.1.1 Parent Compounds	3
1.1.2 Metabolites and Transformation Products	4
1.1.3 Consumption and Use Patterns	7
1.1.4 Manufacturers	8
1.1.5 Hospitals	8
1.1.6 Private Households	8
1.1.7 Landfills	9
1.1.8 Animal Husbandry and Veterinary Medicine	9
1.2 Occurrence and Fate in the Environment	9
1.2.1 Elimination by Adsorption and Complexation	12
1.2.2 Biodegradation	13
1.3 Effects	14
1.3.1 Single Compounds	14
1.3.2 Mixtures	15
1.3.3 Indirect Effects	15
1.4 Risk Assessment	16
1.5 Risk Management	17
1.6 Conclusion	17
References	17
2 Special Characteristics of Pharmaceuticals Related to Environmental Fate	23
2.1 Introduction	23
2.2 Solid State Chemistry of Pharmaceuticals	23
2.3 Metabolism	24
2.4 Molecular Structure	26
2.5 Ionization	28
2.5.1 Dissociation Constant	28
2.5.2 Octanol/Water Distribution Coefficient	29
2.5.3 Sludge Sorption/Desorption (K_{biomass} or K_p)	30
References	33

Part II Sources, Occurrence and Fate	35
3 Drug Production Facilities – An Overlooked Discharge Source for Pharmaceuticals to the Environment	37
3.1 Introduction	37
3.2 Regional Perspectives	38
3.3 Major Release of Drugs from Indian Manufacturers	38
3.4 The Value of APIs Going Down the Drain	39
3.5 More Evidence of Release of APIs from Production Units	40
3.6 Some Management Issues	41
Acknowledgements	41
References	42
4 Substance Flows Associated with Medical Care – Significance of Different Sources	43
4.1 General Considerations	43
4.1.1 Substance Flows	43
4.1.2 Use Patterns	44
4.2 The Most Important Sources	44
4.2.1 Economical Data	44
4.2.2 Accounting of Pharmaceuticals	46
4.2.3 Disinfectants, Diagnostics and AOX	51
4.2.4 Gadoliniums	54
4.2.5 Mercury and Other Heavy Metals	55
References	56
5 Pharmaceutical Residues in Northern European Environments: Consequences and Perspectives	61
5.1 Background Information	61
5.1.1 Daylight Conditions	62
5.1.2 Temperature Conditions	62
5.1.3 Demographics	62
5.2 Quantification of Pharmaceutical Substances in Swedish, Norwegian and Finnish Aqueous Samples	62
5.3 Environmental Levels of Pharmaceuticals in Northern European Environments	63
5.4 Variable Degradation Rates	68
5.5 Transformation Under Cold Environmental Conditions	70
5.6 Antimicrobial Residues Under Cold Environmental Conditions	71
5.7 Perspectives and Consequences	72
Acknowledgements	72
References	73
6 Antibiotics in the Environment	75
6.1 Introduction	75
6.2 Sources	78
6.2.1 Natural Background	78

6.2.2	Production	78
6.2.3	Human Medicine	79
6.2.4	Veterinary Medicine and Animal Husbandry	81
6.2.5	Plant Agriculture	83
6.2.6	Aquaculture	83
6.3	Occurrence	83
6.3.1	Wastewater, Surface Water, Groundwater, Drinking Water, and Seawater	84
6.3.2	Sewage Sludge and Sediments	85
6.3.3	Manure and Soil	85
6.4	Elimination	85
6.4.1	Sorption	85
6.4.2	Photolysis, Hydrolysis, and Thermolysis	86
6.4.3	Biodegradation	87
	References	88
7	Veterinary Antibiotics in Dust: Sources, Environmental Concentrations, and Possible Health Hazards	95
7.1	Introduction	95
7.2	Sources and Environmental Concentrations of Antibiotics in Dust	95
7.3	Possible Health Effects of Antibiotics in Dust	97
7.4	Summary and Outlook	99
	Acknowledgement	100
	References	100
8	Fate of Veterinary Medicines Applied to Soils	103
8.1	Introduction	103
8.2	Releases to the Environment	103
8.2.1	Persistence in Manure and Slurry	104
8.3	Fate in Soil	105
8.3.1	Sorption in Soil	106
8.3.2	Persistence in Soil	107
8.3.3	Dissipation in Field	109
8.4	Transport from Soils to Water Bodies	110
8.4.1	Overland Flow	110
8.4.2	Drainflow	111
8.4.3	Leaching	112
8.5	Uptake into Biota	112
8.6	Fate in Surface Waters	113
8.7	Summary and Recommendations	115
	References	116
9	Pharmaceuticals as Environmental Contaminants: Modeling Distribution and Fate	121
9.1	Introduction	121
9.2	Data Evaluation	121
9.3	Generic Model	123

9.4	Regional Model	127
9.5	Site Specific Models	131
9.6	Discussion and Conclusions	131
	References	132
10	Environmental Exposure Modeling: Application of PhATE™ and GREAT-ER to Human Pharmaceuticals in the Environment	133
10.1	Introduction	133
10.2	Pathway Analysis	134
10.3	Environmental Exposure Modeling of Pharmaceutical Compounds	134
10.3.1	General Averaging Method for PECs	134
10.4	Watershed/Catchment-Based Environmental Models	137
10.4.1	PhATE™	138
10.4.2	GREAT-ER	140
10.5	Parameterization, Sensitivity Analysis and Uncertainty	143
10.6	Comparisons of PECs and MECs	143
10.7	Integration of Modeling and Monitoring	144
	References	146
11	Exposure Assessment Methods for Veterinary and Human-Use Medicines in the Environment: PEC vs. MEC Comparisons	147
11.1	Introduction	147
11.2	Veterinary Medicines Released into the Environment	147
11.2.1	PEC Calculations	148
11.2.2	PEC vs. MEC Comparisons in Soil and Water	149
11.3	Human-Use Medicines Released into the Environment	155
11.3.1	PEC Calculations	155
11.3.2	Comparisons of Predicted and Measured Concentrations	157
11.3.3	Batch Test Systems for Predicting Degradation and Sorption	164
11.4	Assessing the Risks of Human-Use Pharmaceuticals in Biosolids	166
11.5	Conclusions	167
	References	169
Part III	Effects	173
12	Effects of Pharmaceuticals on Aquatic Organisms	175
12.1	Introduction	175
12.2	Modes of Action in Humans and Mammals and Targets in Lower Vertebrates and Invertebrates	178
12.3	Ecotoxicological Effects	182
12.3.1	Acute Effects	182
12.3.2	In Vitro Studies	186
12.3.3	Chronic Effects	187
12.3.4	Toxicity of Pharmaceutical Mixtures and Community Effects	190
12.4	Comparison of Effect Concentrations with Environmental Concentrations	192
12.5	Conclusions and Future Directions	193

12.5.1	Future Strategy	194
12.5.2	Unexpected Effects	196
12.5.3	Mixtures and Comparisons of Environmental and Effect Levels	196
	Acknowledgements	197
	References	197
13	Another Example of Effects of Pharmaceuticals on Aquatic Invertebrates: Fluoxetine and Ciprofloxacin	205
13.1	Introduction	205
13.2	Materials and Methods	207
13.3	Results and Discussion	209
13.3.1	Chemical Analysis	209
13.3.2	Acute Toxicity	211
13.3.3	Life-Cycle Test and Reproduction Test	211
13.4	Outlook	219
	References	220
14	Effects of Antibiotics and Virustatics in the Environment	223
14.1	Introduction	223
14.2	Wastewater and Sewage System	223
14.3	Surface Water	224
14.4	Soil and Sediments	226
14.5	Resistance	227
14.5.1	Antibiotics and Resistance in Test Systems	228
14.5.2	Resistance in the Environment	231
14.5.3	Role of Hospitals	232
14.5.4	Wastewater, Municipal Sewage and Sewage Treatment Plants	234
14.5.5	Surface Water	236
14.5.6	Groundwater	237
14.5.7	Drinking Water	237
14.5.8	Sediments	237
14.5.9	Soil	238
14.5.10	Plant Agriculture	239
14.5.11	Antiviral Resistance	239
14.6	Conclusion	240
	References	240
15	Realizing the Potential Benefits of Small Animal Models for the Aquatic Hazard Assessment of Human Pharmaceuticals: A Conceptual Approach	245
15.1	Introduction	245
15.2	Proteins as Therapeutic Targets for Pharmaceuticals	245
15.3	Genes and Proteins are Often Conserved During Evolution	246
15.4	Crustaceans and Insects (Ecdysozoans) as Test Species	247
15.5	Annelids and Mollusks (Lophotrochozoans) as Test Species	249
15.6	Echinoderms as Test Species	250
15.7	Ascidians as Test Species	250

15.8	A Rough Guide to Protein Targets and ADME Complexity	251
15.9	Opportunities and Limitations	251
	Acknowledgements	253
	References	253
16	On the Ecotoxicology of Pharmaceutical Mixtures	257
16.1	Introduction	257
16.1.1	Mixture Effects are of Special Concern	257
16.2	Approaches for Studying Mixture Toxicities	260
16.2.1	Whole-mixture Tests of Pharmaceutical Mixtures	260
16.2.2	Component-Based Approaches	262
16.2.3	Concentration Addition	264
16.2.4	Independent Action	265
16.2.5	Input Requirements	265
16.2.6	Synergism and Antagonism	266
16.3	Empirical Evidence on the Predictive Power of CA and IA	267
16.3.1	Should Mixture Effects be Generally Expected from Low-Effect Concentrations of Individual Pharmaceuticals?	269
16.4	CA and IA in the Context of Risk Assessment of Pharmaceutical Mixtures	270
16.5	Regulation and Management	271
16.6	Open Questions, Challenges, Recommendations	272
	References	273
17	Chronic Mixture Toxicity of Pharmaceuticals to <i>Daphnia</i> – the Example of Nonsteroidal Anti-Inflammatory Drugs	277
17.1	Introduction	277
17.1.1	Background	277
17.1.2	Mixture Toxicity	278
17.2	Materials and Methods	279
17.2.1	Test Compounds	279
17.2.2	<i>Daphnia</i> Reproduction Test	279
17.3	Results	280
17.4	Discussion	280
	References	282
18	The Ecotoxicological Effects of Pharmaceuticals (Antibiotics and Antiparasiticides) in the Terrestrial Environment – A Review	285
18.1	Introduction	285
18.2	Methods	286
18.3	Results and Discussion	286
18.3.1	Parasiticides	286
18.3.2	Antibiotics	291
18.3.3	Other Drugs	296
18.3.4	Terrestrial Effects in the Current Guidance Documents	297
18.4	Conclusion	298
	References	300

19 Odorants – Potent Substances at Minor Concentrations: The Ecological Role of Infochemicals	305
19.1 Introduction: Ecosystems are Controlled by Odors	305
19.1.1 Odor Worlds	305
19.1.2 Emission of Chemicals versus Perception of Odors	307
19.1.3 Terminology	307
19.1.4 Properties of Odor Signals	308
19.1.5 Potent Substances	308
19.2 Sender – Infochemicals – Receiver	308
19.2.1 Sender: Who and What Emits Infochemicals and When?	308
19.2.2 Infochemicals: What is Known About Their Chemical Identities?	309
19.2.3 Receiver: When and How Does a Receiver React?	312
19.2.4 Applications	313
19.2.5 What Test Designs Were Used in Basic Research?	316
19.2.6 The Infochemical Effect: Anthropogenic Substances Can Act as Infochemicals	317
19.3 Summary and Outlook: Will the Infochemical Effect Change Ecotoxicology?	318
References	318
Part IV Risk Assessment	321
20 European Developments in the Environmental Risk Assessment of Pharmaceuticals	323
20.1 Legal Background	323
20.2 The EU Guidance Document on the Environmental Risk Assessment of Medicinal Products for Human Use	324
20.2.1 General Principles	325
20.2.2 Phase I Risk Assessment	326
20.2.3 Phase II Risk Assessment	327
20.2.4 Outcome	329
20.3 One Year after Adoption of the Guideline – Experiences	329
20.4 Outlook	332
References	333
21 The State and the Future Development/Perspective of Environmental Risk Assessment of Medicinal Products for Human Use: Aspects of Its Regulations in Japan	335
21.1 Historical Background for the Regulation of Chemicals	335
21.2 Regulation of Chemicals in Japan	336
21.3 Regulation on General Chemicals	336
21.3.1 The Number of New Chemicals Submitted	336
21.3.2 Outlines of Chemical Substance Control Law	336
21.3.3 Test Guidelines and Procedures	337
21.3.4 Regulatory Classification of Chemicals	337
21.4 Regulation of New Agricultural Chemicals	339

21.5	Regulation on Veterinary Medical Products	340
21.6	Regulation on Human Health Products	340
21.6.1	The Status of Drug Pollution and Regulation in Japan	340
21.6.2	Framework for Pharmaceutical Regulation	340
21.6.3	Regulation of Pharmaceuticals in Japan	341
	References	341
22	Deterministic and Probabilistic Environmental Risk Assessment for Diazepam	343
22.1	Introduction	343
22.2	Diazepam Basic Data and Methods	343
22.3	Results	346
22.3.1	Environmental Exposure and Fate Assessment	347
22.3.2	Environmental Effects Assessment	351
22.3.3	Risk Assessment	354
22.3.4	Sediment Risk	357
22.4	Discussion and Refinement of the ERA	359
22.4.1	PECs and MECs	359
22.4.2	The Hydra Chronic Data Crucial for PNEC and HC ₅	361
22.4.3	Persistence, Bioaccumulation and Toxicity Considerations	362
22.4.4	Going Probabilistic With Fewer Chronic Tests	363
22.4.5	Including Metabolites, Going Semi-Deterministic Again	363
22.5	Conclusion	364
	Acknowledgements	365
	References	366
	Appendix: Diazepam Data Tables	371
23	Comparison of Prospective and Retrospective Environmental Risk Assessments of Human Pharmaceuticals	385
23.1	Introduction	385
23.2	Conceptual Approaches for the Pro- and Re-ERA of Human Pharmaceuticals	385
23.3	Examples for Pro- and Retrospective Environmental Risk Assessments	387
23.4	Summary and Outlook	390
	Acknowledgments	390
	References	391
24	Methodological Aspects Concerning the Environmental Risk Assessment for Medicinal Products; Research Challenges	393
24.1	Introduction	393
24.2	Risk Management	395
24.3	Risk Assessment: The Risk Model	396
24.4	Risk Assessment at Registration of Human Medicines	398
24.4.1	Metabolites versus Drug Substance	399
24.4.2	Medicines in Environmental Quality Policy and Legislation	401
24.5	Discussion	402
	References	404

Part V Risk Management	409
25 Strategies for Reducing the Input of Pharmaceuticals into the Environment	411
25.1 Introduction	411
25.1.1 Advanced Effluent Treatment	411
25.1.2 Training, Education and Information	415
25.1.3 Green and Sustainable Pharmacy	416
25.2 Conclusion	416
References	417
26 COST ACTION 636 Xenobiotics in the Urban Water Cycle – A Network for Collaboration within Europe	419
26.1 Introduction	419
26.1.1 COST	419
26.1.2 COST Action 636 Xenobiotics in the Urban Water Cycle	420
26.2 Objectives and Expected Benefit for Europe	421
26.3 Organization and Activities	422
26.3.1 Working Group 1: Identification, Sources and Fluxes	424
26.3.2 Working Group 2: Methods for Treatment	424
26.3.3 Working Group 3: Impact Assessment	425
26.3.4 Working Group 4: Analytical Issues	425
26.4 Summary	426
References	426
27 Removal of Pharmaceutical Residues from Contaminated Raw Water Sources by Membrane Filtration	427
27.1 Introduction	427
27.2 Application of Membrane Bioreactors (MBR) using Micro- or Ultrafiltration Units	427
27.3 Application of Nanofiltration (NF) and Reverse Osmosis (RO)	429
27.4 Mobile Drinking Water Purification Units (MDWPU)	434
27.5 Experimental Details	435
27.5.1 Specifications of the Tested MDWPU	435
27.5.2 Description of the First Field Site at the Teltowkanal	440
27.5.3 Description of the Second Field Site and Experimental Design	440
27.5.4 Sample Storage and Analysis	441
27.6 Results and Discussion	441
27.6.1 Results from the First Field-Trial at the Teltowkanal in Berlin, Germany	441
27.6.2 Results from the Second Field Trial at the Sewage Treatment Plant in Ruhleben (Berlin, Germany)	442
27.7 Conclusions and Future Applications of MDWPU	448
27.8 Summary and Outlook	448
Acknowledgements	450
References	450

28 Photooxidation as Advanced Oxidation Treatment of Hospital Effluents	455
28.1 Introduction	455
28.2 Pharmaceutical Photooxidation	455
28.2.1 Photodegradation of Pharmaceuticals during Photochemical AOPs	461
28.2.2 Costs Related to the Use of Photoprocesses	463
28.3 Conclusions	463
References	464
29 Pharmaceuticals and Environment: Role of Community Pharmacies	467
29.1 Introduction	467
29.2 Unwanted Medicines	467
29.3 Collection of Unwanted Medicines in Community Pharmacies	469
29.4 Patient Information and Drug Donation Issue	471
29.5 Prevention of the Waste of Medicines	472
29.6 Conclusion	472
References	473
30 Mitigation of the Pharmaceutical Outlet into the Environment – Experiences from Sweden	475
30.1 Background	475
30.2 EU and national Authorities	475
30.2.1 The New EU Directives for Pharmaceuticals	475
30.2.2 Initiatives by the Swedish Government	477
30.3 Assessment of Environmental Hazard and Risk of Pharmaceuticals	477
30.3.1 Environmental Classification of Drugs	477
30.3.2 Hazard Assessment of Drugs	478
30.3.3 Risk Assessment of Drugs	478
30.3.4 Risk or Hazard Assessment as a Basis for Environmental Classification?	479
30.3.5 “The Stockholm Model”	480
30.3.6 “The Swedish Model”	481
30.3.7 Comments on the Classification Systems	483
30.4 Return of Unused Drugs	483
30.5 Personal Care Products	484
30.6 Communication	484
30.7 Levels of Pharmaceuticals in Drinking Water and Surface Water in Stockholm	486
References	487
31 Pharmaceutical Waste	489
31.1 Introduction	489

31.2	Planning Waste Management	489
31.2.1	Legislation	490
31.2.2	Waste Sources	492
31.2.3	Waste Streams	492
31.2.4	Collection and Segregation	495
31.2.5	Treatment and Disposal	497
31.3	Minimizing Pharmaceutical Waste	498
31.4	Conclusion	498
	References	499
Subject Index		501

Contributors

Alder, Alfredo C., Dr.

Swiss Federal Institute of Aquatic
Science and Technology (Eawag)
Überlandstr. 133
8600 Dübendorf, Switzerland
alder@eawag.ch

Backhaus, Thomas, Dr.

Department of Plant and Environmental
Sciences
University of Gothenburg
Carl Skottbergs Gata 22B
40530 Göteborg, Sweden
thomas.backhaus@dpes.gu.se

Benfenati, Emilio, Dr.

Department of Environmental Health
Sciences, Mario Negri Institute for
Pharmacological Research
Via Eritrea 62
20157 Milan, Italy
benfenati@marionegri.it

Blanck, Hans, Prof.

Dep. of Plant and Env. Sciences
Göteborg University
Carls Skottsbergs Gata 22 b
Box 461
40530 Göteborg, Sweden

Boxall, Alistair B.A., Prof.

Central Sciences Laboratory
Sand Hutton
York Yo41 1LZ, United Kingdom
a.boxall@csl.gov.uk

Bugnon, Olivier, Adjunct Prof.

Community Pharmacy Research Unit
Section of Pharmaceutical Sciences
University of Geneva and University of
Lausanne
Pharmacie PMU, Rue du Bognon 44
1011 Lausanne, Switzerland
olivier.bugnon@hospvvd.ch

Calamari, Davide, Prof. Dr.

University of Insubria, Department of
Structural and Functional Biology
Environmental Research Group
Via J. H. Dunant 3
21100 Varese VA, Italy
davide.calamari@uninsurbia.it

Castensson, Staffan, Ph.D., Assoc. Prof.

R&D Department
Apoteket AB
118 81 Stockholm, Sweden
staffan.castensson@apoteket.se

Cleuvers, Michael, Dr.

Head of Business Unit Industrial
Chemicals – REACH
Dr. Knoell Consult GmbH
Marie-Curie-Straße 8
51377 Leverkusen, Germany
mcleuvers@dr-knoell-consult.com

Cunningham, Virginia L., Dr.

ClaxoSmithKline
200 North 16th St.
Philadelphia, PA 19102, USA
Cunningham_v@msn.com

Di Guardo, Antonio, Dr.
University of Insubria
Department of Structural and
Functional Biology
Via J. H. Dunant 3
21100 Varese VA, Italy
antonio.diguardo@uninsurbia.it

Fanelli, Roberto, Dr.
Department of Environmental Health
Sciences
Mario Negri Institute for
Pharmacological Research
Via Eritrea 62
20157 Milan, Italy
fanelli@marionegri.it

Feldmann, Dirk F., Dr.
Bausch & Lomb/Dr. Mann Pharma
Brunsbüttler Damm 165-173
13581 Berlin, Germany
dirk.feldmann@bausch.com

Fenner, Kathrin, Dr.
Swiss Federal Institute of Aquatic Sci-
ence and Technology (Eawag)
Überlandstr. 133
8600 Dübendorf, Switzerland
kathrin.fenner@eawag.ch

Fent, Karl, Prof. Dr.
University of Applied Sciences
Northwestern Switzerland
School of Life Sciences and Swiss
Federal Institute of Technology Zürich
(ETHZ)
Gruendenstraße 40
4132 Muttenz, Switzerland
karl.fent@bluewin.ch

Fick, Jerker
Umeå University
Environmental Chemistry
901 87 Umeå, Sweden
jerker.fick@chem.umu.se

Gunnarsson, Bo, Dr.
Apoteket AB
Söndermalmsallén 36
118 81 Stockholm, Sweden
bo.gunnarsson@apoteket.se

Halling-Sørensen, Bent, Prof.
Faculty of Pharmaceutical Sciences
Copenhagen University
Universitetsparken 2
2100 Copenhagen, Denmark
bhs@farma.ku.dk

Hamscher, Gerd, Prof. Dr.
University of Veterinary Medicine,
Foundation
Institute for Food Toxicology
Bischofsholer Damm 15
30173 Hannover, Germany
gerd.hamscher@tiho-hannover.de

Hartung, Jörg, Prof. Dr.
University of Veterinary Medicine,
Foundation
Insitute for Animal Hygiene, Animal
Welfare and Behaviour
of Farm Animals
Bünteweg 17p
30559 Hannover, Germany
itt@tiho-hannover.de

Heberer, Thomas, PD Dr.
Director of the Food Institute
Oldenburg (LI-OL)
Lower Saxony Federal State Office of
Consumer Protection and Food Safety
(LAVES)
Martin-Niemöller-Straße 2
26133 Oldenburg, Germany
Thomas.Heberer@laves.niedersachsen.de

Henriques, Danielle Marranquiel, M.Sc.
Universidade Federal de Santa Maria
Departamento de Química da UFSM,
Prédio 18 Campus Camobi
97105-900 Santa Maria, RS, Brasil
danielle@mail.ufsm.br

Hickmann, Silke
Umweltbundesamt
Wörlitzer Platz 1
06844 Dessau-Roßlau, Germany
silke.hickmann@uba.de

Hutchinson, Thom, Prof.
Associate Director Environmental Safety
Assessment
AstraZeneca Global Safety, Health & Environment
Brixham Environmental Laboratory
Brixham, Devon TQ5 8BA
United Kingdom
tom.hutchinson@astrazeneca.com

Kallenborn, Roland, Prof. Dr.
University Centre in Svalbard (UNIS)
Street 230 house 1, P.O. Box 156
9171 Longyearbyen, Norway
roland.kallenborn@unis.no

Klaschka, Ursula, Prof. Dr.
University of Applied Sciences Ulm
Prittwitzstr. 10
89075 Ulm, Germany
Klaschka@hs-ulm.de

Knacker, Thomas, Dr.
ECT Oekotoxikologie GmbH
Böttgerstraße 2-14
65439 Flörsheim a. M., Germany
th-knacker@ect.de

Koschorreck, Jan
Umweltbundesamt
Corrensplatz 1
14195 Berlin, Germany
jan.koschorreck@uba.de

Krogh, Kristine, Prof.
Faculty of Pharmaceutical Sciences
Copenhagen University
Universitetsparken 2
2100 Copenhagen, Denmark
kak@farma.ku.dk

Lapen, David R., Dr.
Agriculture and Agri-Food Canada
Central Experimental Farm
Ottawa, Ontario K1A 0C6, Canada
lapend@agr.gc.ca

Larsbo, Mats, Dr.
Department of Soil Sciences,
Swedish University of Agricultural Sciences
Box 7014
750 07 Uppsala, Sweden
mats.larsbo@mv.slu.se

Larsson, D. G. Joakim, PhD, Assoc. Prof.
Institute of Neurosciences and Physiology,
the Sahlgrenska Academy at the University of Gothenburg
Box 434
405 30, Gothenburg, Sweden
joakim.larsson@fysiologi.gu.se

Ledin, Anna Birgitta, Prof. PhD
Technical University of Denmark
Department of Environmental Engineering
Street Bygningstorvet, Building 115
2800 City Kgs. Lyngby, Denmark
anl@env.dtu.dk

Liebig, Markus, Dr.
ECT Oekotoxikologie GmbH
Böttgerstraße 2-14
65439 Flörsheim a. M., Germany
m-liebig@ect.de

Lindberg, Richard
Umeå University
Environmental Chemistry
901 87 Umeå, Sweden
richard.lindberg@chem.umu.se

Martins, Ayrton Figueiredo, Prof. Dr.
Universidade Federal de Santa Maria
Departamento de Química da UFSM,
Prédio 18, Campus Camobi
97105-900 Santa Maria, RS, Brasil
martins@quimica.ufsm.br

Metcalfe, Chris, Prof.
Environmental and Resource Studies
Trent University
1600 West Bank Drive
Peterborough, Ontario, K9J 7B8, Canada
cmetcalfe@trentu.ca

Moe, Morten K.
Norwegian Institute for Air Research
(NILU)
Polar Environmental Centre
9296 Tromsø, Norway
mkm@nilu.no

Moltmann, Johann F., Dr.
ECT Oekotoxikologie GmbH
Böttgerstraße 2-14
65439 Flörsheim a. M., Germany
j-moltmann@ect.de

Montforts, Mark, Dr.
National Institute for Public Health and
the Environment
Expertise Centre for Substances
P.O. Box 1
3720 BA Bilthoven, The Netherlands
mark.montforts@rivm.nl

Nentwig, Gerrit, Dr.
Insitute for Ecology, Evolution and Di-
versity
Department Aquatic Ecotoxicology
Siesmayerstraße 70
60054 Frankfurt, Germany
nentwig@em.uni-frankfurt.de

Nielsen, Kåre M.
Tromsø University
Department of Pharmacy
9037 Tromsø, Norway
kaare.nielsen@farmasi.uit.no

Niquille, Anne, Pharmacist PhD Candidate
Community Pharmacy Research Unit,
Section of Pharmaceutical Sciences
University of Geneva and University of
Lausanne
Pharmacie PMU, Rue du Bugnon 44
1011 Lausanne, Switzerland
anne.niquille@hospsvd.ch

Patureau, Dominique, Dr.
Chargée de Recherche INRA
INRA, URO50, Laboratoire de
Biotechnologie de l'Environnement
Avenue des Etangs
11100 Narbonne, France
patureau@supagro.inra.fr

Römbke, Jörg, Dr.
ECT Oekotoxikologie GmbH
Böttgerstraße 2-14
65439 Flörsheim a. M., Germany
j-roembke@ect.de

Schmitt, Heike, PhD
IRAS, Utrecht University
Yalelaan 2
3584 CM Utrecht, The Netherlands
h.schmitt@uu.nl

Silveira Frank, Carla da, M.Sc.
Universidade Federal de Santa Maria
Departamento de Química da UFSM,
Prédio 18 Campus Camobi
97105-900 Santa Maria, RS, Brasil
dasilveirafrank@gmail.com

Straub, Jürgen Oliver, Dr. EuroProBiol.
CBiol. MIBiol.
F. Hoffmann-La Roche Ltd.
Corporate Safety, Health & Environmen-
tal Protection
CSE, 49/2.033
4070 Basel, Switzerland
juerg.straub@roche.com

Sumpter, John, Prof.
Inst. for the Environment
Brunel University
Uxbridge,
Middlesex UB8 3PH, United Kingdom

Ternes, Thomas A., Dr.
Bundesanstalt für Gewässerkunde (BfG)
Am Mainzer Tor 1
56068 Koblenz, Germany
ternes@bafg.de

Topp, Edward, Dr.
Agriculture and Agri-Food Canada
1391 Sandford Street
London, Ontario N5V 4T3, Canada
toppe@agr.gc.ca

Tysklind, Mats
Umeå University
Environmental Chemistry
901 87 Umeå, Sweden
Mats.Tysklind@chem.umu.se

Vasconcelos, Tibiriçá Gonçalves, Dr.
Universidade Federal de Santa Maria
LAMIC, Predio 44, 3 andar, Campus Camobi
97105-900 Santa Maria, RS, Brasil
tgvasconcelos@yahoo.com.br

Vasskog, Terje
Tromsø University
Department of Pharmacy
9037 Tromsø, Norway
terje.vasskog@farmasi.uit.no

Wennmalm, Åke, Prof.
Chief Executive Board
P.O. Box 22550
104 22 Stockholm, Sweden
ake.wennmalm@sll.se

Yoshioka, Yoshitada, Prof. Dr.
Faculty of Education and Welfare
Oita University
700 Dannoharu
870-1192 Oita, Japan
yoshioka@cc.oita-u.ac.jp

Zuccato, Ettore, Dr.
Department of Environmental Health
Sciences, Mario Negri Institute for
Pharmacological Research
Via Eritrea 62
20157 Milan, Italy
zuccato@marionegri.it