Fate and Effects of Anticancer Drugs in the Environment

Ester Heath • Marina Isidori • Tina Kosjek
Metka Filipič
Editors

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Editors
Ester Heath
Department of Environmental Sciences
Jožef Stefan Institute
Ljubljana, Slovenia

Jožef Stefan International Postgraduate School
Ljubljana, Slovenia

Tina Kosjek
Department of Environmental Sciences
Jožef Stefan Institute
Ljubljana, Slovenia

Jožef Stefan International Postgraduate School
Ljubljana, Slovenia

Marina Isidori
Department of Environmental, Biological and Pharmaceutical Sciences and Technologies
University of Campania "L.Vanvitelli"
Caserta, Italy

Metka Filipič
Department of Genetic Toxicology and Cancer Biology
National Institute of Biology
Ljubljana, Slovenia

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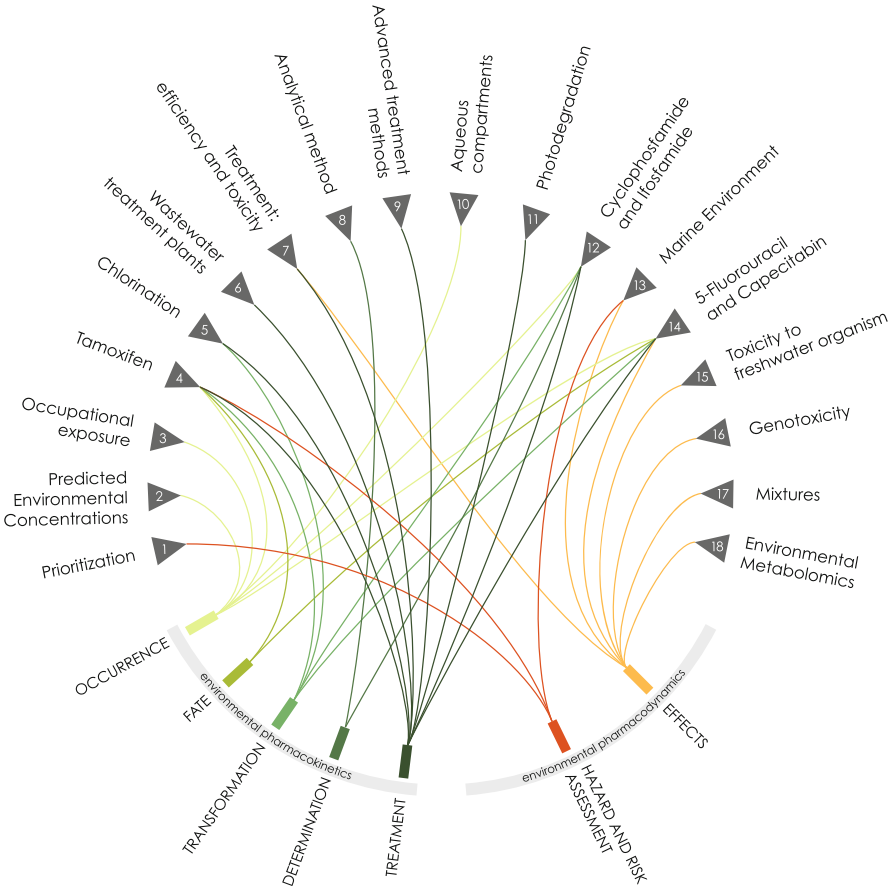
Preface

Cytostatic drugs (also known as anticancer drugs or antineoplastics) have been at the forefront of treating cancer since the 1940s. However, many of these drugs are themselves carcinogenic, mutagenic and teratogenic, triggering widespread concerns about the risks they pose to the environment. The scientific community is now turning its attention toward investigating the occurrence, effects, and fate of cytostatic pharmaceutical residues in the environment. A watershed moment was in 2011 with the funding of two major FP7 EU projects CytoThreat and Pharmas, which led to an increase in the number of scientific publications, including a special issue in *Environmental Science and Pollution Research* (Fate and effects of the residues of anticancer drugs in the environment, 2016, vol. 23, no. 15, pp. 14687–14691). The motivation for this book was the desire to bring together current knowledge and research on the presence and effects of cytostatic drug residues in the aqueous environment. This book contains 18 chapters and represents the combined work of leading scientists from different research institutions from across the globe. It covers all relevant aspects of the presence of cytostatic drug residues in wastewaters and natural aquatic systems, where numerous analogies are made between their pharmacokinetics and pharmacodynamics in humans and their effects on the environment. For example, in the case of pharmacokinetics, their levels in humans or animals can be analogous with their *occurrence* in waste and natural waters, distribution in the body with environmental cycling (*fate)*, human metabolism with their *transformation*, and their elimination from humans or animals with their removal. All these parameters are based on the *determination* (analytical method development) of cytostatic drug residues in different, often complex matrices. In terms of pharmacodynamics, their effects on target tissues along with unwanted adverse reactions are also analogous with their *effects* (toxicity) on non-target organisms, which must be known in order to perform *hazard and risk assessment*.

Scheme 1 provides the reader with an overview of how the various chapters relate to environmental pharmacokinetics and pharmacodynamics.



With regards to environmental pharmacokinetic**s,** Chaps. 3, 4, 10, 12 and 14 discuss the *occurrence* of these compounds in the workplace (hospitals, pharmacies), wastewaters, surface waters and drinking water using data obtained experimentally, while Chap. 2 calculates the predicted environmental concentrations (PEC) based on consumption data, excretion, elimination in the WWTP and dilution in receiving waters. Chapter 10 reviews studies performed in 18 countries reporting the levels of compounds in different water compartments and highlights the importance of planning efficient sampling strategies to obtain representative water samples. Chapter 3 discusses occupational exposure to drugs containing 5-fluorouracil (FU), cyclophosphamide (CP), and platinum in 21 hospitals in the Czech Republic. Unwanted releases have been documented during all steps in the preparation and administration of these drugs to patients leading to contamination of both the work place and the environment. In many cases, monitoring and discussions with

responsible managers resulted in the implementation of proper handling procedures and decreased contamination. Chapter 12 covers the occurrence of CP and ifosfamide (IF) residues in hospital wastewaters, municipal wastewaters and surface waters. The occurrence of tamoxifen and its metabolites in water bodies and the risk posed to aquatic organisms due to its known toxicity and its potential for bioaccumulation are subject of Chap. 4, while Chap. 14 examines the available literature on the cycling and effects of 5-FU and capecitabine (CAP) residues. Chapters 4, 5, 12 and 14 address *transformation* during various treatment processes, and Chaps. 4 and 14 cover their environmental *fate*. Method development and analysis (*determination)* is the focus of Chaps. 8 and 12. Chapter 8 provides a comprehensive overview of the different methodologies used, including extraction and clean-up techniques (solid-phase extraction for liquid samples and pressurized liquid extraction and ultrasound extraction for sludge samples) and detection methods (mostly liquid chromatography with mass spectrometry detection). Chapter 12 describes the analytical method development for determining CP and IF transformation products formed during water treatment.

Whereas the previously mentioned chapters measure the levels of cytostatic residues, Chap. 2 introduces the concept of predicted environmental concentrations (PECs), an approach first suggested by the European Medicines Agency (EMA). It describes how to calculate PECs, provides raw data for their calculation and discusses the applicability of PECs for assessing cytostatics in wastewater and river water.

Different *treatment* technologies are also extensively discussed in the book. *Biological treatment* is discussed in several of the book chapters. For instance, conventional activated sludge treatment is discussed in Chaps. 6, 12 and 14. Membrane bioreactors (MBR) are described in Chaps. 6, 9 and 12 and sequential batch reactors (SBR) in Chap. 12. Bioreactors with attached biomass are covered in Chap. 12 and biological treatment using fungi in Chaps. 4, 7 and 12. *Abiotic treatment* involves UV irradiation, chlorination, ozonation and advanced oxidation processes (AOPs). UV irradiation and direct photolysis are discussed in Chaps. 6, 7, 11, 12 and 14. Ozonation is covered in Chaps. 6, 7, 12 and 14 and chlorination in Chaps. 4, 5, 6, 7, 9. Different AOPs, including ozonation and/or UV in combination with different oxidants (H_2O_2) or catalysts (Fe^{2+}, TiO_2) and other non-conventional oxidation processes like electrochemical oxidation, are discussed in Chaps. 4, 7, 9, 11, 12 and 14. *Physical treatments* are also discussed at length, including adsorption (Chaps. 9, 12 and 14), nanofiltration (Chaps. 9 and 12) and reverse osmosis (Chaps. 9 and 12).

With regards to *environmental pharmacodynamics*, single compound *effects* are the subject of Chaps. 14, 15 and 16. Chapter 15 investigates the acute and chronic effects of cytostatic drugs in freshwater organisms, while Chap. 14 describes the effects of 5-FU and CAP residues in the aqueous environment and Chap. 16 discusses how residues of specific drugs are genotoxic for aquatic organisms. Their main conclusions are that more work into the toxicological effects of environmental mixtures of cytotoxic compounds still needs to be performed, further actions

are needed to ensure more reliable environmental risk assessments, and that stricter measures are necessary to prevent contamination of the environment by cytostatic drug residues. Mixture effects are addressed in Chaps. 13 and 17. The acute and chronic effects on non-target organisms at levels typically found in the marine environment are reviewed in Chap. 13, together with their ecotoxicological potential, synergistic, additive and antagonist effects. Similarly, Chap. 17 focuses on the toxicity of mixtures of 5-FU, cisplatin, etoposide, imatinib mesylate, and CP and their transformation products on various biological models (bacteria, algae, animals, plants and human cells). Chapter 7 uses the toxicity of mixtures of cytostatic drugs, their metabolites and/or transformation products in addition to the removal of the parent compound in order to evaluate removal efficiency during wastewater treatment. In Chap. 18, environmental metabolomics is used to enrich our understanding of the response of an organism to environmental stressors, while Chaps. 1, 4 and 13 focus on *hazard and risk assessment.* Chapter 1 introduces different approaches for screening, ranking and prioritizing specific cytostatic compounds that pose the most significant risk. For example, environmental risk posed by tamoxifen is evaluated in Chap. 4, while Chap. 13 focuses on the risks posed by cytotoxic drug residues in the marine environment. It also makes recommendations about suitable biological models to assess the ecotoxicological effects on marine organisms.

We are aware that this book tackles only a small part of what is a far more extensive and complex issue, but we hope that information provided within this book will enable readers to learn about the fate and effects of cytostatic pharmaceuticals in the aqueous environment and be cognizant of the many challenges that remain. We are thankful to the authors for their contribution and their patience during the publication of the book. We thank the Springer team, namely Alexandrine Cheronet and Judith Terpos, for their continued support during the project.

Ljubljana, Slovenia — Ester Heath
Caserta, Italy — Marina Isidori
Ljubljana, Slovenia — Metka Filipič
Ljubljana, Slovenia — Tina Kosjek
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Contents

Contributors

Mustafa Al Aukidy Department of Engineering, University of Ferrara, Ferrara, Italy

Arminda Alves LEPABE – Laboratory for Process, Environmental, Biotechnology and Energy Engineering, Faculty of Engineering, University of Porto, Porto, Portugal

Maria João Bebianno CIMA, University of Algarve, Faro, Portugal

Ludek Blaha Faculty of Science, RECETOX, Masaryk University, Brno, Czech Republic

Lucie Blahova Faculty of Science, RECETOX, Masaryk University, Brno, Czech Republic

Aina Campos Garrigós Department of Engineering, University of Ferrara, Ferrara, Italy
Faculty of Earth Science, University of Barcelona, Barcelona, Spain

Marjeta Česen Department of Environmental Sciences, Jožef Stefan Institute, Ljubljana, Slovenia
Jožef Stefan International Postgraduate School, Ljubljana, Slovenia

Chiara Russo Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "L.Vanvitelli", Caserta, Italy

Concetta Piscitelli Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "L.Vanvitelli", Caserta, Italy

Tainá Garcia da Fonseca CIMA, University of Algarve, Faro, Portugal

Miren López de Alda Water, Environmental and Food Chemistry Unit, Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Barcelona, Spain

Lenka Dolezalova Masaryk Memorial Cancer Institute, Brno, Czech Republic

Carlos Escudero-Oñate Norwegian Institute for Water Research (NIVA), Oslo, Norway

Despo Fatta-Kassinos Nireas-International Water Research Center, University of Cyprus, Nicosia, Cyprus
Department of Civil and Environmental Engineering, University of Cyprus, Nicosia, Cyprus

Laura Ferrando-Climent Tracer Technology Department, Fluid Flow and Environmental Technology Section, Institute for Energy Technology (IFE), Kjeller, Norway

Metka Filipič Department of Genetic Toxicology and Cancer Biology, National Institute of Biology, Ljubljana, Slovenia

Antonio Fiorentino Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "L.Vanvitelli", Caserta, Italy

Helena Franquet-Griell Department of Environmental Chemistry, IDAEA-CSIC, Barcelona, Catalonia, Spain

Goran Gajski Mutagenesis Unit, Institute for Medical Research and Occupational Health, Zagreb, Croatia

Marko Gerić Mutagenesis Unit, Institute for Medical Research and Occupational Health, Zagreb, Croatia

Cristian Gómez-Canela Department of Environmental Chemistry, IDAEA-CSIC, Barcelona, Catalonia, Spain

Juan Carlos Guillen Water, Environmental and Food Chemistry Unit, Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Barcelona, Spain

Ester Heath Department of Environmental Sciences, Jožef Stefan Institute, Ljubljana, Slovenia
Jožef Stefan International Postgraduate School, Ljubljana, Slovenia

Lida Ioannou-Ttofa Nireas-International Water Research Center, University of Cyprus, Nicosia, Cyprus

Marina Isidori Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "L. Vanvitelli", Caserta, Italy

Tina Kosjek Department of Environmental Sciences, Jožef Stefan Institute, Ljubljana, Slovenia
Jožef Stefan International Postgraduate School, Ljubljana, Slovenia

Sarka Kozakova Masaryk Memorial Cancer Institute, Brno, Czech Republic

Klaus Kümmerer Sustainable Chemistry and Material Resources, Institute of Sustainable and Environmental Chemistry, Faculty of Sustainability, Leuphana University of Lüneburg, Lüneburg, Germany

Jan Kuta Faculty of Science, RECETOX, Masaryk University, Brno, Czech Republic

Silvia Lacorte Department of Environmental Chemistry, IDAEA-CSIC, Barcelona, Catalonia, Spain

Margherita Lavorgna Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "L. Vanvitelli", Caserta, Italy

Teik-Thye Lim School of Civil and Environmental Engineering, Nanyang Technological University, Singapore, Singapore

Milka Ljoncheva Department of Environmental Sciences, Jožef Stefan Institute, Ljubljana, Slovenia

Carlos Alexandre Lutterbeck Graduate Program in Environmental Technology, Universidade de Santa Cruz do Sul, Santa Cruz do Sul, Rio Grande do Sul, Brazil

Ênio Leandro Machado Graduate Program in Environmental Technology, Universidade de Santa Cruz do Sul, Santa Cruz do Sul, Rio Grande do Sul, Brazil

Giovanni Mastroianni Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "L.Vanvitelli", Caserta, Italy

Sarah Montesdeoca-Esponda Instituto Universitario de Estudios Ambientales y Recursos Naturales (i-UNAT), Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

Matjaž Novak Department of Genetic Toxicology and Cancer Biology, National Institute of Biology, Ljubljana, Slovenia

Adrián Olalla Research Group in Environmental Toxicology and Risk Assessment (TAyER), Rey Juan Carlos University, Alcorcón, Madrid, Spain

Jose Luis Rodriguez-Gil Department of Biology, University of Ottawa, Ottawa, ON, Canada

Sara Rodríguez-Mozaz Catalan Institute for Water Research (ICRA), H2O Building, Scientific and Technological Park of the University of Girona, Girona, Spain

José Juan Santana-Rodríguez Instituto Universitario de Estudios Ambientales y Recursos Naturales (i-UNAT), Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

Sergio Santana-Viera Instituto Universitario de Estudios Ambientales y Recursos Naturales (i-UNAT), Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

Mónica S. F. Santos LEPABE – Laboratory for Process, Environmental, Biotechnology and Energy Engineering, Faculty of Engineering, University of Porto, Porto, Portugal

Monica Scognamiglio Department of Environmental, Biological and Pharmaceutical Sciences and Technologies, University of Campania "L.Vanvitelli", Caserta, Italy

Ewa Maria Siedlecka Department of Chemistry, University of Gdansk, Gdansk, Poland

Zoraida Sosa-Ferrera Instituto Universitario de Estudios Ambientales y Recursos Naturales (i-UNAT), Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

Yolanda Valcárcel Research Group in Environmental Toxicology and Risk Assessment (TAyER), Rey Juan Carlos University, Alcorcón, Madrid, Spain
Department of Medicine and Surgery, Psychology, Preventive Medicine and Public Health, Immunology and Medical Microbiology, Faculty of Health Sciences, Rey Juan Carlos University, Alcorcón, Madrid, Spain

Francesc Ventura Department of Environmental Chemistry, IDAEA-CSIC, Barcelona, Catalonia, Spain

Paola Verlicchi Department of Engineering, University of Ferrara, Ferrara, Italy
Terra&Acqua Tech, Technopole of the University of Ferrara, Ferrara, Italy

Verica Garaj Vrhovac Mutagenesis Unit, Institute for Medical Research and Occupational Health, Zagreb, Croatia

Bojana Žegura Department of Genetic Toxicology and Cancer Biology, National Institute of Biology, Ljubljana, Slovenia

Yiqing Zhang School of Civil and Environmental Engineering, Nanyang Technological University, Singapore, Singapore

Božo Žonja Water, Environmental and Food Chemistry Unit, Department of Environmental Chemistry, Institute of Environmental Assessment and Water Research (IDAEA-CSIC), Barcelona, Spain