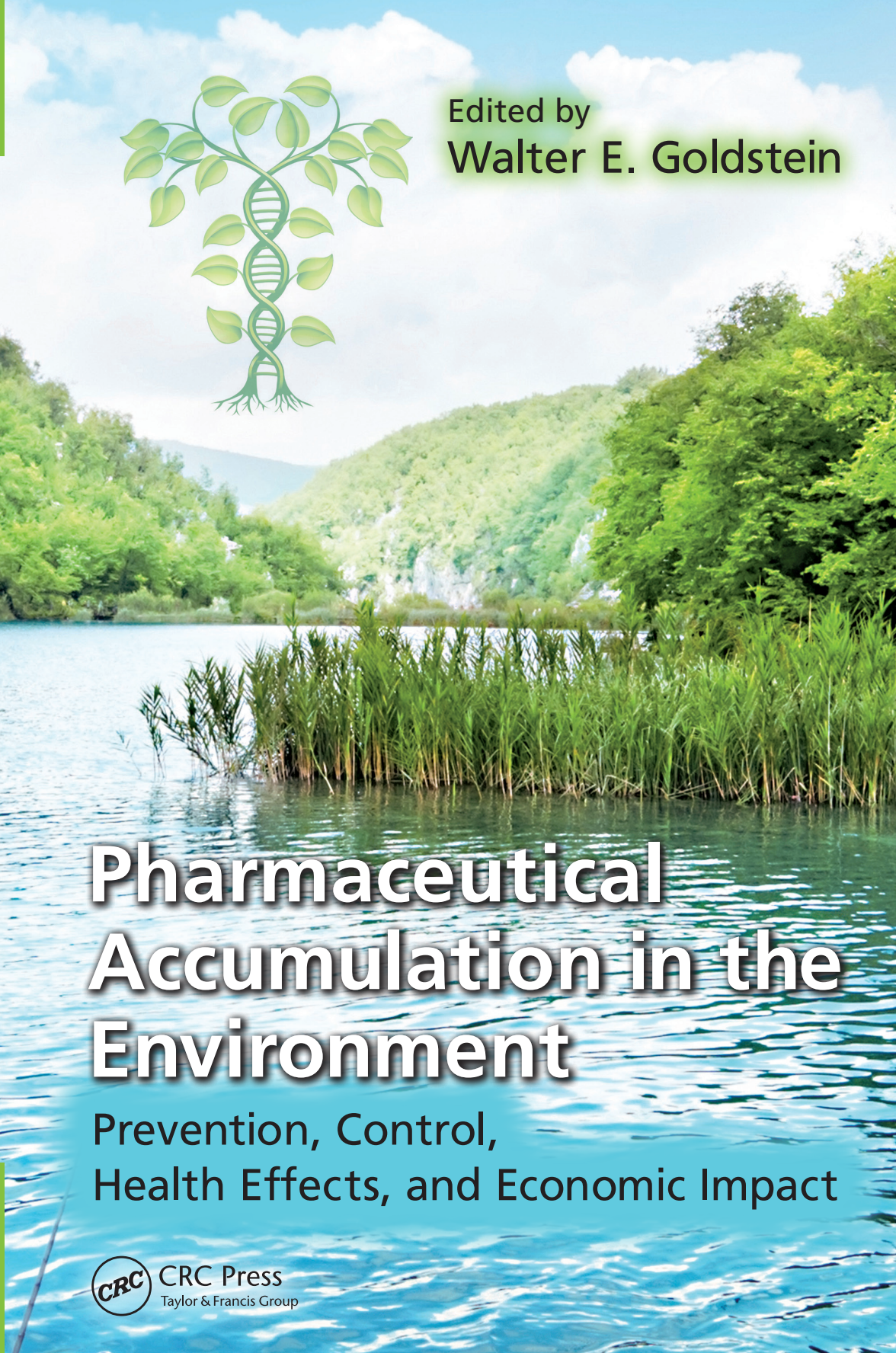
Edited by
Walter E. Goldstein
Pharmaceutical Accumulation in the Environment
Prevention, Control, Health Effects, and Economic Impact
CRC Press
Taylor & Francis Group

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20140403

International Standard Book Number-13: 978-1-4665-1775-2 (eBook - PDF)

This book is dedicated to those who search for solutions to minimize harmful effects of environmental contaminants so as to improve the health and well-being of all living things.

The authors of this work are hopeful that their efforts will contribute to implementation of scientific and engineering advancements that improve the environment.

To my wife, Paula, for her love and support of my professional efforts.

To our wonderful children (Susan and Marc) and grandchildren (Alex, Noah, Reena, and Daniel).

Walter E. Goldstein

Contents

Preface

The intent of this book is to advance knowledge and suggest ways to obtain solutions to contamination of the environment by pharmaceuticals (and implicitly, personal care products). This book provides the following:

- An updated history and status of the sources and fates of pharmaceuticals.
- Updates on particularly important environmental contaminants that include pharmaceuticals, personal care products, and some special products, such as those that are contrast agents and illicit drugs.
- A suggested way to use some of the environmental contaminants as markers of pharmaceutical contamination (particularly those that may not change much as they pass through one phase of the environment to the other).
- Presentation of the status of key analytical methods and how to best use them in detecting low levels of environmental contaminants.
- Examination of current methods to evaluate risks of environmental contamination from the standpoint of what workers and authorities associated with the field suggest. In addition, suggestions are presented from the standpoint of what more can be done to assess risk and minimize negative effects on health through medical and process research and analysis. Through such minimization of negative effects, it is expected that discoveries will be made to benefit the health and well-being of society.
- An extensive look has been taken at antibiotics and how their presence in waste can have predicted and unpredicted results in wastewater treatment operations.
- Examination of ways to potentially effect reduction of such environmental contaminants in wastewater treatment and in the soil.
- Consideration of the cost of contaminant elimination and what may be gained by developing commercial opportunities based on research into methods to effect reduction of pharmaceutical contamination of the environment. This can thereby turn a challenge into a series of profitable opportunities.
- Suggestions for the mobilization of private and public resources to address the challenge in a practical and economic manner. Such cooperative effort can have political and diplomatic benefits.

A *pharmaceutical* is a substance used in healing, relieving pain, or treating disease. Pharmaceuticals have likely been in the environment as long as humans or other species have been on the Earth. People have accessed and used pharmaceuticals present in natural products such as plants.

Humankind learned to collect, harvest, and process entities that occur in the environment to provide a controlled source of pharmaceuticals for many purposes. Humankind also learned to create such entities to form pharmaceuticals that do not otherwise occur in nature. Progress in the creation and control of pharmaceuticals to the present day to cure and prevent ever-changing and newly discovered ills has dramatically changed and improved society.

Pharmaceuticals that occur in the environment in an unexpected or uncontrolled manner become a problem if they cause harm. If pharmaceuticals occur in the environment in a less controlled manner and are presented in a way that affects large segments of the population or components of nature such as plants, animals, or insects, then they pose a problem. In effect, they contaminate the environment.

So, how big is the problem? Well, we are not quite sure. You will read in this book that problems with wildlife (fish, for example) can be traced to the occurrences of environmental pharmaceuticals (and also personal care products that can have pharmaceutical effects). By and large, environmental pharmaceuticals are present in relatively small quantities, and have not yet been shown to definitively cause problems in humans.

However, for many reasons, we are not sure if pharmaceuticals that occur in the environment can cause problems for certain people, or perhaps many people, since the problem may be undiscovered. Basically, for many of us, it is not worth taking the chance that a problem exists that will become apparent in the future. Certainly, the fact that problems with wildlife are traced to contaminant pharmaceuticals in the environment causes concern. This is, in effect, a weak signal, perhaps telltale of a problem that is on the verge of occurring. It does make us wonder if a problem for humanity will also be discovered at some point due to pharmaceuticals present in the environment. Therefore, a main reason for this book is that we simply do not yet know enough to be unconcerned. For example, if a pharmaceutical entity can accumulate somehow in the tissue of a living entity, then at some point, a problem can occur.

Those who say that pharmaceuticals that occur in the environment have not been conclusively shown to affect humans are correct. Some presented evidence that cites this statement notes that the entity is present in very small amounts, for example, nanograms or less. That does sound small. However, entities in such small quantities can be a problem if they are catalytic in nature (accentuate reactions occurring, particularly biological ones). Also, small quantities can be surface active and work to effect surface changes and transport into cells at very small quantities, in molecular layers, where much is not needed.

One might then ask, if these substances are present in small quantities and used widely, what can we do about it? What we can do, as described in this book, is to minimize their presence by learning how to control them, discover new technology to deal with small quantities that may be of concern in nature, and prepare for the day when someone discovers that there is a problem.

Parties that will benefit from this book include the following:

- Those with an invested interest in improving and protecting the environment, which essentially includes all of us (consumers, industries, government, and academia)
- Those with an expressed professional interest in maintaining the purity of our environment and water supply
- Employees of pharmaceutical and personal care product industries
- Those in environmental protection agencies worldwide
- Those in process equipment, process plant construction, wastewater treatment, and water purification industries, plus consulting scientists and engineers providing services to those industries
- Parties who want to see a reduction in environmental contamination in a manner that preserves the soundness and health of businesses
- Those physicians and medical personnel who conduct research on the effect of environmental contaminants on health or treat patients susceptible to environmental pollutants
- Those members of the legal profession who must deal with environmental contamination litigation as part of their professional work
- Members of the insurance industry covering environmental contamination
- Those professional politicians and diplomats seeking ways to secure international cooperation in the environmental area

Walter E. Goldstein

Acknowledgments

To James S. Smith, PhD, president/chemist of Trillium, Inc., for his helpfulness in regard to suggesting coauthors for this work.

To those scientists who were unable to participate in this undertaking, for their suggestions and referrals.

To Taylor & Francis/CRC Press publishers, for originally suggesting that I undertake this project and for issuing this book. In particular, the efforts of Jennifer Ahringer, project coordinator, and Joseph Clements, acquisitions editor, are very much appreciated.

To my colleagues and coauthors, all experts, who followed through and provided their contributions that, in total, deliver what we believe to be important information that will lead to advances in this area.

About the Editor

Walter E. Goldstein, PhD, PE, is president of Goldstein Consulting Company, offering services in chemical engineering and biotechnology (see http://www.goldconsul.com). He is called upon to improve processes and products in health care, consumer products, food, pharmaceuticals, chemicals, and biofuels. He provides expertise to model and analyze product and process components, changes, and defects; construction practice challenges; and alterations to materials, valuable artifacts, and memorabilia. Many of his projects involve biotechnology processes that include mammalian cell, bacterial, and mold propagation.

Dr. Goldstein has an extensive background in fermentation technology and development of products and processes in this field. He is also president and cofounder of a research and development firm with an active patent. Its objective is to produce universal blood from stem cells in a bioreactor process, thereby avoiding use of donor blood for transfusion (see http://www.ivrbc.com).

He has been involved in environmentally important projects throughout his career. He is interested in applying research to benefit society while creating economic value. His involvement in this book stems from his desire to preserve the environment as a means to improve health and well-being.

Dr. Goldstein was vice president for Biotechnology Research for Miles, Inc., a former division of Bayer, Inc., from 1982 to 1987. He was also vice president and director of research for ESCAgenetics Corporation, a plant sciences biotechnology company, from 1988 to 1994. He founded Goldstein Consulting Company in 1994 and has been engaged in several entrepreneurial enterprises since that time. He founded and developed a forensic sciences DNA profiling laboratory at the University of Nevada–Las Vegas from 2003 to 2008. It was shortly after this that his first book for Taylor & Francis was published (*Sick Building Syndrome and Related Illness: Prevention and Remediation of Mold Contamination*).

Dr. Goldstein holds a BS in chemical engineering from the Illinois Institute of Technology (1961), and MS and PhD degrees in chemical engineering from the University of Notre Dame (1973). He also holds an MBA from Michigan State University (1968), and is a Registered Professional Engineer. He is a member of the American Academy of Forensic Sciences, the American Institute of Chemical Engineers, and Sigma Xi.

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Introduction

Walter E. Goldstein

CONTENTS

1.1 Background

A pharmaceutical is a substance used in healing, relieving pain, or for treating disease. Pharmaceuticals have likely been in the environment since humans or other species have been on the earth. People have accessed and used pharmaceuticals present in natural products such as plants. Ancient to recent history provides examples (or likely often correct assertions) that pharmaceuticals were used by early peoples and were present in plants (Ji et al. 2009; Dias et al. 2012; Newman et al. 2000; Cragg et al. 2005). Paracelsus tried to assess the potency of pharmaceuticals in the 16th century (Sonnedecker 1976). There is a report of Neanderthals possibly using pollen containing medicinals to treat themselves approximately 60,000 years ago (Ji et al. 2009). Monographs and books document the uses of natural products as pharmaceuticals (Blumenthal et al. 1998, Roberts et al. 1999).

Present-day pharmaceuticals have their origins in the environment as documented in regard to their sources from plants. Humans and animals discovered healing substances were in plants since they must have sensed that eating such plants, smelling them, or applying them to the skin helps cure or prevent a malady. They likely also discovered that eating insects, or consuming a species, or a particular food, may have also cured an ailment or otherwise maintained health.

Later, humans learned to collect, harvest, and process entities that occur in the environment to provide a controlled source of pharmaceuticals for many purposes. Humans also learned to create such entities to form pharmaceuticals that do not otherwise occur in nature. Progress in the creation and control of pharmaceuticals to the present day to cure and prevent ever-changing and newly discovered ills is astounding and a wonderful contribution to society.

Problems with pharmaceuticals appearing in the environment do not seem to be significantly reported historically prior to such reporting in the latter part of the 20th century, though one might expect that such events did occur in locales. Compared to the present-day reporting of pharmaceuticals in the environment, in past times, the paucity of such reporting is perhaps due to a combination of (1) relatively sparser population, (2) relatively little widespread communication, (3) much less concentration of population, (4) more containment of the pharmaceuticals in sources such as plants until the plants were used, (5) relatively much less overall production of pharmaceuticals, (6) nonfeeding of pharmaceuticals to animals where the pharmaceuticals may subsequently appear in some form in animal waste, and (7) less disposal causing pharmaceutical contamination to be much less in magnitude.

Pharmaceuticals that occur in the environment in an unexpected or uncontrolled manner become a problem if they cause harm. One may not anticipate such harm. However, one may sense such harm and avoid the entity. Animals or humans may know to avoid eating a certain entity that may contain a toxin. A toxin or poison may be a pharmaceutical in other circumstances. For example, *Atropa belladonna* is a deadly toxin if taken in excess. Proper isolation of a compound in this plant species and controlled use can result in a valuable drug (pilocarpine) from this plant to treat glaucoma (Dias et al. 2012). *Papaver somniferin* is a source of many important drugs such as morphine and opium (Newman et al. 2000). Taken in excess, drugs from this plant are (of course) harmful.

1.2 Challenge of Pharmaceutical Accumulation in the Environment

If pharmaceuticals occur in the environment in a less controlled manner and are presented in a way that they affect large segments of the population or components of nature such as plants, animals, or insects, then they pose a problem. In effect, they contaminate the environment.

So, how big is the problem? Well, we are not quite sure. You will read in this book that problems with wildlife (fish, for example) can be traced to the

occurrences of environmental pharmaceuticals (and also personal care products that can have pharmaceutical effects). By and large, as the Pharmaceutical Research and Manufacturers Association purports, environmental pharmaceuticals are present in relatively small quantities, and have not yet been shown to definitively cause problems in humans (Pharmaceutical Research and Manufacturers Association 2013).

However, for many reasons, we are not sure if pharmaceuticals that occur in the environment can cause problems for certain people, or perhaps, many people, since the problem may be undiscovered. Basically, for many of us, it is not worth taking a chance that a problem is there that will become apparent in the future. Certainly, the fact that problems with wildlife are traced to contaminant pharmaceuticals in the environment causes concern (Adams et al. 2008; Swartz et al., 2006; Stokstad 2013). This is, in effect, a weak signal, perhaps telltale of a problem that is on the verge of occurring. It does make us wonder if a problem with humans will also be discovered at some point due to pharmaceuticals present in the environment. Therefore, a main reason for this book is that we simply do not yet know enough to be unconcerned. For example, if the pharmaceutical entity can accumulate somehow in tissue in a living entity, then at some point a problem can be caused.

Pharmaceutical accumulation in tissue may often be a preferred mode of therapy if the accumulation is specific (Tsai et al. 2011). However, if the accumulation is nonspecific and unintended, then such accumulation, when and if it occurs, is undesired and perhaps harmful. The challenge then is that we have not looked sufficiently at the problem. Perhaps, this is because we do not yet have the capability to identify the problem and its magnitude, or we may not have thought to do so in a particular manner.

Those who say that pharmaceuticals that occur in the environment have not been conclusively shown to affect humans are correct. Some evidence presented that cites this statement notes that the entity is present in very small amounts, for example, nanograms or less. That does sound small. However, entities in such small quantities can be a problem if they are catalytic in nature (accentuate reactions occurring, particularly biological ones). Also, small quantities can be surface active and work to effect surface changes and transport into cells at very small quantities, in molecular layers, where much is not needed.

Examples of such surface-active agents are alkyl phenol ethoxylate compounds. These are compounds used in common personal care products that are surfactants and have been shown to affect wildlife (Committee on the Assessment of Water Reuse as an Approach to Meeting Future Water Supply Needs 2012). Also, as another example of a compound essential to life, acetyl choline is required in nerve transmission and inherent to our bodily function (Toda et al. 1997). What is often not recognized is that this essential compound has the structural characteristics of an excellent surface-active agent that works at tiny levels in the body. We do need it in our bodies. We do not, for example, need it in excess, in our water or in our soil, and therefore in the

environment. So a key point may be that a substance is important because it makes surfaces accessible or is catalytic. So, having something present in small quantities does not necessarily excuse an entity since, at least, it can potentially cause a health problem.

1.3 Objectives of This Book

One might ask then, if these substances are present in small quantities and used widely, what can we do about it? What we can do is to minimize their presence by learning how to control them, discover new technology in dealing with small quantities that may be of concern in nature, and prepare for the day when someone discovers that there is a problem. Being able to deal with small quantities that occur is important in our society, for example, in integrated circuits that power our computers, and in nanotechnology, which holds such promise if we control it well. If you like, the presence of pharmaceuticals in the environment is an item that may be relegated to nanotechnology science and discovery. Nanotechnology is a burgeoning area of discovery that can benefit health and medicine if it is properly controlled (Booker and Boysen 2005). So, as the title of this book suggests, research and discovery in the area of pharmaceutical presence in the environment can provide a "flip side" leading to an opportunity that can benefit society and be lucrative. Part of this book deals with the beneficial opportunistic side of this subject matter.

If the pharmaceutical occurs, where might it occur? As one example, it can occur in the air we and other life-forms breathe. However, since most pharmaceuticals are not that volatile, meaning, they do not evaporate, that is a much lesser problematic area (perhaps). That is, it is not a problem area until we discover that some breakdown product of a pharmaceutical in the environment is volatile (or carried by a volatile substance) and can therefore affect our air supply.

Pharmaceuticals (if released into the environment) can certainly appear in (and bind to) soil. That is a concern. Also a concern, for example, is if the pharmaceutical washes out of the contaminated soil and gets into our water supply. If an entity is in soil, to just leave it there to create unknown harm does not make sense.

In this book, we will examine what may be done about things such as contaminated soil and, for example, landfills, where waste is sent and dumped for storage. In this book, among other objectives, we want to suggest ways to get rid of contaminants in soil in a consistent and sensible manner. Ridding the soil of pharmaceutical contamination should impact in a positive manner on dealing with a huge accumulation of waste that is dumped in a landfill and just sits there over time. Doing something about this is certainly reasonable,

given our appreciation of doing what we can to protect our environment and our planet. In dealing with solutions to this matter, we do not want to create a secondary problem due to the accumulation that is a nuisance or harmful. The solution must be engineered, so to speak.

Water is a precious resource. Our water supply is finite, and we do have concern about its availability and our sustenance for a growing population of this planet (Committee on the Assessment of Water Reuse as an Approach to Meeting Future Water Supply Needs; National Research Council 2011). Since pharmaceutical accumulation affects the availability of this resource, this has to be an important part of dealing with pharmaceutical presence that can affect this precious resource and impact on our health.

As an example, if we can nearly eliminate pharmaceutical contamination in wastewater, we then allow water reuse, which is important to conserve the water supply. Water reuse is a strategic initiative that is becoming more and more important in view of the increasing concerns with water scarcity worldwide.

Water that is presented for purification at a wastewater treatment facility has entities that are undesirable for consumption and drinking. These are removed in waste treatment, to the extent possible, depending on the treatment facility. This technology is as modern as possible for the locale involved, and preferably monitored carefully, according to the best methods and science available, again depending on the facility. Sometimes, of course, wastewater is released and it is not possible to treat it in a facility. In these cases, for example, in rural areas, it may be processed through a septic system. In private septic systems, as in large-scale municipal wastewater treatment systems, the waste elimination is dependent on bacteria that naturally grow to process waste before it is released (Marx et al. 2010).

Waste elimination in municipal facilities is thus dependent on such bacteria, and perhaps other microbial forms (Jin-sing and Yu-feng 2011). The quality of the septic system may be quite variable. Of course, if pharmaceuticals are dumped into the septic system, they may not be degraded properly before effluent flows into the environment (Gielen 2007). In turn, they may have a role in rendering a septic system ineffective, depending on what and how much is released into the septic system.

Some entities do slip through untreated from wastewater treatment. This includes some pharmaceuticals that are small in concentration and end up getting passed through a system. We don't know for sure that this slippage is a problem, as discussed previously.

1.4 Book Organization and Description

For the many reasons above, this book has been written, and previous books on this subject have been written (Adams et al. 2008; Jjemba 2008). Both of

these referenced books provide a good treatment of the subject with their own emphasis. In this book, the intent is to describe what is happening in this field, give some history, and also importantly, craft some suggestions for corrective actions that include research to try and address this issue. We will deal with how much we can correct and control this situation, what can be said at this point on medical impact and risk, and what we can do in the future to try and ensure that this problem is minimized. We will also address the costs of this attempt to minimize this problem. Plus, since there are some opportunities that can arise out of addressing this problem to optimizing the environment for our betterment, we will address what these opportunities can be worth, since that can be a way to defray costs inherent in improving how we can eliminate pharmaceuticals from the environment, as well as to promote new business and create employment. Doing what we can to turn a problem into an opportunity should make parties more inclined to solve the problem through technological means.

With this in mind, the book is organized with chapters authored by specialists who are experts in their fields to cover each area. We include contributions on the history of pharmaceuticals in the environment and what is known so far. Indeed, specific chapters deal with aspects of this history. Some case histories are included. The historical reviews are international in scope, since this is a matter to be dealt with globally.

Since the sources of pharmaceuticals in the environment are varied, we deal with that as well in this book (each origin of the pharmaceutical that appears in the environment has to be handled in a specific manner). Further, since we need to know where the pharmaceuticals are headed, and where they may end up, the fate of such pharmaceuticals is noted.

Pharmaceuticals can break down to form other products, which in themselves are not innocuous, so we have to examine these as well. The only time we may not worry about an entity is if it forms a natural product not known to be harmful or likely to be harmful unless it is present in excess (USFDA 2013a). Some natural products are dietary supplements noted by the FDA as requiring good manufacturing practice (GMP). However, these are not otherwise regulated unless a problem occurs (USFDA 2013b).

Further, since this is a subject dealing with chemistry and measurement of pharmaceuticals (which can include personal care products, which can sometimes behave like pharmaceuticals), analytical pharmaceutical chemistry is dealt with sufficiently so we understand with what we are dealing in order to assess its impact on the environment.

Since we need to know how much of something is present to be able to deal with it, we have to measure the entity by the best scientific means so that is covered, since the measurement means are specific to areas of the field of pharmaceuticals that occur in the environment. For example, measurement methods specific to antibiotics and illicit drugs are described.

Entities entering into the environment may be changed by this passage to different degrees. Since monitoring of these entities is desired, Chapter 5