Daniel R. Dietrich*, Simon F. Webb†, and Thomas Petry‡

*Environmental Toxicology
University of Konstanz, Germany

†Procter & Gamble
Bruxelles, Belgium

‡The Weinberg Group
Bruxelles, Belgium

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Hot Spot Pollutants: Pharmaceuticals in the Environment

Pharmaceuticals are important and indispensable elements of modern life. They are employed in human and veterinary medicine, agriculture, and aquaculture. Until the 1990s, however, relatively little consideration was given to the likely fate, occurrence, or effect of pharmaceuticals on the environment following normal use. This apparent lack of scientific interest in pharmaceuticals as contaminants of the aquatic environment is somewhat puzzling. Common over-the-counter (OTC) drugs such as paracetamol or aspirin are sold in quantities comparable to high production volume (HPV) materials, close to or exceeding 1000 tons/year in European countries such as the UK and Germany (Ternes, 2001a; Webb, 2001). Total use of human prescription drugs in such countries is even greater (Webb, 2001). Drugs are also inherently biologically active and often exquisitely potent. They are often resistant to biodegradation, as metabolic stability is necessary to pharmacological action. Certain pharmaceuticals or their metabolites are also highly water soluble. When combined with a lack of biodegradation, removal during wastewater treatment will consequently be limited for such compounds. These compounds will then enter the aquatic environment, resulting in exposure of aquatic biota.

Contributions to our knowledge of pharmaceuticals in the environment (PIE) that predate this period include the observations by Aherne *et al.* (1985) on compounds such as ethinyl oestradiol, diazepam, theophylline, erythromycin, tetracycline, and methotrexate in various environmental matrices as a consequence of normal patient use. Richardson and Bowron (1985) likewise report on analytical studies. They also detail the development of simple modeling techniques aimed at predicting likely concentrations in surface waters following normal use by the patient. This pioneering work included a consideration of national usage patterns, human metabolism, fate during wastewater treatment, and surface water dilution of effluents.

The last decade has seen a marked growth in the literature relating to observations of PIE at concentrations that result from normal use by the patient. At least 60 compounds have now been reported from aquatic matrices (Heberer and Stan, 1997; Hirsch *et al.*, 1999; Stumpf *et al.*, 1996a,b; Ternes, 1998, 2001a,b). Such observations necessitate a consideration of any potential risk. This in turn requires knowledge of the effects of pharmaceuticals upon relevant aquatic biota. This requirement is now being addressed for many classes of compounds such as selective serotonin reuptake inhibitors (SSRIs) (Brooks *et al.*, 2003; Fong *et al.*, 1998), steroids (Länge *et al.*, 2001) and antihyperlipoproteinemics (Köpf, 1995). Concurrently, there have been various regulatory developments in the United States and Europe relating to requirements for risk assessment of new actives as part of their registration process, as elegantly presented by Straub in Chapter 19. The risk assessment of existing pharmaceuticals has also been attempted (Halling-Sørenson *et al.*, 1998; Stuer-Lauridsen *et al.*, 2000; Webb, 2001).

Of particular concern is speculation that the presence of pharmaceuticals in the environment may be leading to subtle but hitherto unrecognized or undetected effects leading to irreversible damage of the ecosystem (Daughton, 2001, 2003a,b; Daughton and Ternes, 1999). This requires empirical research aimed at thoroughly understanding the effects of these biologically active materials at the low exposure levels occurring in the environment (Pfluger and Dietrich, 2001). Equally important is the need to develop solid and scientifically sound approaches to assess the associated risks.

This book contributes in our efforts to extend our knowledge vis-à-vis the occurrence and fate of pharmaceuticals in the environment, their effects, and potential risks. It represents a concerted effort of academic, regulatory, and industry scientists to bring greater understanding to the PIE issue. Together, these 18 papers reflect the state-of-the-art as presented at the Statuskolloqium in Environmental Toxicology in Konstanz, Germany (November 2001), the Special Session at the Society of Environmental Toxicology and Chemistry (SETAC) Europe Annual Meeting in Vienna, Austria (May 2002), and the 11th European Congress on Biotechnology in Basel, Switzerland (August 2003).

In the section "Occurrence and Fate," the first three contributions from Heberer and Adams Boxall *et al.*, and Straub all reflect analytical

studies on the presence and fate of pharmaceutical residues in the environment. These include compounds such as antibiotics and UV filters. Chapter 5 by Schowanek and Webb details exposure modeling of common pharmaceuticals using the GREAT-ER software, while Chapter 6 by Webb *et al.* deals with the probability of human exposure to pharmaceuticals via drinking water.

Within the "Effects" section, the four papers from Zerulla *et al.*, Schmid *et al.*, Brooks *et al.*, and Köllner *et al.*, detail work on the responses of fish species to endocrine modulators (including steroids), immune modulators, and other compounds. Hutchinson presents work on the *in vivo* and *in vitro* responses of invertebrate species. In addition and in contrast to the more singular effect assessment of the previous authors, Cleuvers presents data on the combinatorial effects of pharmaceuticals.

The first of the three contributions in the section "Principle Considerations" is by Länge and Dietrich, who deal with various conceptual aspects of environmental risk assessment as it relates to pharmaceuticals. In the second, Seiler speculates on whether the established knowledge relating to the pharmacodynamic activity of pharmaceuticals can be of use in ecotoxicologial risk evaluation. The third of this group is a critique of the proposed sediment quality guidelines under the European Water Framework Directive by Crane.

Until recently, pharmaceuticals were not subject to environmental risk assessment as part of the registration process. In the last section, "Risk Assessment," there are four papers by Boxall *et al.*, Montforts and Knecht, Long and Crane, and Straub dealing with developments regarding EU regulatory requirements for the environmental risk assessment of new veterinary and human pharmaceutically active compounds.

Overall, this book aims to critically discuss the knowledge on PIE, their potential impact on the environment, and consequently, the most proper and sensible steps for risk assessment. In combining the views from academic, industry, and regulatory scientists, a balanced presentation of the most pressing issues and gaps of knowledge is emphasized. This is especially important in view of the efforts in regulating environmental testing and risk assessment within the EU. We hope that this book will help the interested scientist gain easy entry to this hot spot of current research, foster discussion among scientists, stimulate additional efforts in addressing the knowledge gaps identified, and thus provide for a better scientific basis of dealing with pharmaceuticals in the environment.

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