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Integrated approach to the problem of pharmaceutical products in the environment: an overview

Clemence Coetsier, Liming Lin,
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Introduction

There is an increasing need to monitor water quality across Europe. Pharmaceutical products (PPs), as emerging contaminants, should receive particular attention. There are, currently, no regulations or norms to limit their use, nor are there any types of survey or control to prevent exposure. According to European guidelines, predicted environmental concentrations (PECs) of PPs in water must be equal to or more than $0.01 \mu\text{g L}^{-1}$ before further environmental risk assessment (ERA) is necessary [1]. Some PPs and their metabolites are not removed from water during conventional biological treatment and enter the water supply via wastewater-treatment plants (WWTPs) [2]. These compounds can be biologically active even at environmental concentrations (sub-ng L^{-1} to ng L^{-1}) [3] and could, hence, be harmful to aquatic species. Their persistence is of particular importance, because it increases the risk of long-term exposure which could be responsible for chronic toxicity and subtle effects in animals and plants (endocrine disruption, growth inhibition, disruption of microbial ecosystems, cytotoxicity, mutagenicity, teratogenicity ...). Spatial and temporal variation of the chemicals in water also make PEC determination difficult and uncertain.

In recent years, research and studies on PPs in the environment have increased; the research has, however,

been fragmentary, dealing with only part of the issue (occurrence, treatment, fate, or toxicity), resulting in weak connection between the different data. To improve environmental impact assessment there is, therefore, a need to take into account the whole life-cycle of PPs.

This article presents the concept of an integrated approach enabling better comprehension of the issue of PPs in the environment as a whole. Specific attention is devoted to some of the main analytical tools required in implement this approach.

Integrated approach

The proposed integrated approach relies on the whole life-cycle of PPs (from manufacture to exposure) and requires, as a first step, collection of representative and reliable data (Fig. 1). In particular, these data would help to establish a list of the most relevant PPs in terms of occurrence, degradation/transformation, exposure effects, etc.

The second step is to interconnect all these data to enable better understanding of the fate and behaviour of selected PPs since their manufacture. It would make it possible to identify the main pressure points along the life-cycle of PPs and to propose relevant action aimed at reducing their occurrence and their impact on the aquatic environment.

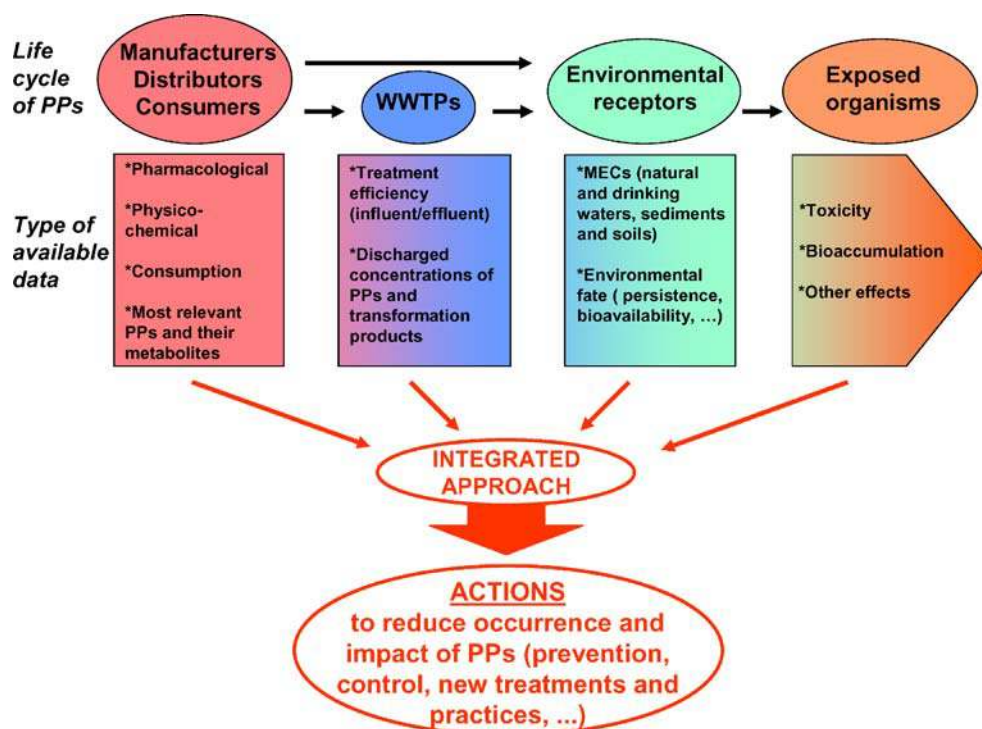
Several actions, which could be taken at the different pressure points of the life-cycles of PPs, can already be proposed:

- use of environmental PP indicators to elucidate the sources of contamination;
- monitoring of relevant PPs at identified pressure points;
- changes in or improvement of current treatment technology which could lead to cleaner technology; and
- prevention, by informing manufacturers, prescribers, and consumers about the risk caused by release of PPs

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Fig. 1 Integrated approach considering the whole life-cycle of PPs



in the environment, and suggestions about better practices.

Complete fulfilment of this integrated approach could be a decision-making tool for those involved in the issue of PPs.

This integrated approach first requires a set of data about the occurrence and fate of PPs in the different water compartments. These data can only be obtained by using sensitive and selective methods able to detect PPs, their metabolites, transformation products, and degradation products at environmental concentrations.

Liquid chromatographic and spectrometric analysis

LC-MS-MS seems to be an ideal technique for the proposed integrated approach, because it can be used to screen for the presence of a broad spectrum of PPs. Indeed, because of important technological progress the selectivity and sensitivity of LC-MS-MS have increased substantially and the techniques has become the reference method both for pharmacokinetic studies and for environmental monitoring of PPs. In a recent review article, Petrovic et al. [4] reported the use of LC-MS-MS for the analysis of 74 human pharmaceuticals, in five classes (anti-inflammatory/analgesics, lipid-regulating agents, β -blockers, antibiotics, and psychiatric drugs), in environmental samples. Because of improvements in LC-MS-MS it is now possible to analyse a total of approximately 150 pharmaceutical

compounds in the environment, most of which can be detected using multi-residue methods [5–10].

The analytical performance of LC-MS-MS (higher selectivity and specificity), especially in the analysis of complex matrices, can be increased by improving:

1. Pretreatment and extraction. Several strategies have been proposed and tested to compensate and/or reduce matrix effects and to improve sensitivity: the establishment of calibration plots by using similar matrices, the use of stable-isotope-labelled internal standards [5, 9], adjustment of the ionic strength and pH of the sample [6], and sample clean-up [12] and extraction. Solid-phase extraction (SPE) is widely used to preconcentrate targeted PPs to a detectable level (from low ng L^{-1} to $\mu\text{g L}^{-1}$) [4]. New strategies in SPE development include use of tandem [5] or mixed-mode extraction adsorbents with ion-exchange capability [8] to make multi-class methodology easier. The concentration factor of the whole SPE process is usually approximately 100 to 1000 and enables the limit of quantification (LOQ) of PPs in effluents to be reduced from $1 \mu\text{g L}^{-1}$ to 1ng L^{-1} . Use of modern variants of SPE, including solid-phase micro-extraction (SPME) and membrane-imprinted SPE (MISPE) [14] result in increased sensitivity and reduced sample handling. On-line and automated SPE techniques [13] have the advantages of higher sample-throughput and faster analysis, which are indispensable in routine analysis. Immunosorbents could also be used for extraction and

preconcentration [15]. New sampling systems, which can be used to extract PPs directly in the field, offer interesting possibilities—a passive sampler such as the Polar Organic Chemical Integrative Sampler (POCIS) can be used to concentrate polar PPs in waterways over a period of deployment ranging from weeks to months [16].

2. Separation efficiency. Use of ultra-performance LC (UPLC) for analysis of PPs has recently been reported. This new technology enables substantial improvement of separation efficiency (by reducing column-packing particle size) and reduction of run time, because of the use of shorter columns, increased flow rates, and faster gradients [9].
3. Spectrometric detection. The development of mass spectrometric technology such as triple quadrupole (QqQ), quadrupole time of flight (Q-TOF), and ion-trap (IT) tandem mass spectrometers has improved detection of PPs in multi-residue analysis. Only high-resolution hyphenated techniques can be used for accurate mass determination and unequivocal identification of target compounds and their degradation products [9–11].

Because of this analytical performance, LC–MS–MS is an appropriate tool which can be useful in an integrated approach. Nevertheless, because of its main drawbacks:

1. it is time-consuming;
2. the cost per analysis is high; and
3. an experienced operator is needed

complementary methods which are more rapid, cost-effective and easier to use, for example biological methods, must be envisaged.

Immunoassays/bioassays

For analysis of trace contaminants in the aquatic environment, immunochemical techniques seem to be more or less selective for a particular analyte, and some are class-specific only [17]. This could be an advantage in the detection both of specific PPs and of families of compounds (similar in structure). Immunoassays are, moreover, excellent tools for screening large numbers of samples in a short time. In environmental analysis, commercially available immunoassays have been readily adopted, mainly to detect pesticides. Few immunochemical methods have been used to detect PPs in water samples, however (Table 1) [11].

Enzyme-linked immunosorbent assays (ELISAs) are, occasionally, not sufficiently sensitive to reach environmental levels; improvement of the detection limit can, however, be achieved by coupling to surface plasmon resonance (Biacore, Spreeta) [22].

Table 1 Main quantitative and semi-quantitative immunoassays developed for environmental analysis of PPs

Analyte	Detection technique	Sensitivity (LOD)	Ref.
Antibiotics	RIA Charm II	1–10 $\mu\text{g L}^{-1}$	[18]
	SPE/RIA	0.05 $\mu\text{g L}^{-1}$	[19]
Sulfonamides	RIANA AWACSS	10 ng L^{-1}	[20]
Methotrexate	RIA	6.25 $\mu\text{g L}^{-1}$	[21]
Ibuprofen	ELISA–SPR ^a	0.02 $\mu\text{g L}^{-1}$	[22]
Naproxen	ELISA	3.5 mg L^{-1}	[22]
Diclofenac	ELISA	6 ng L^{-1}	[23]

^a Surface plasmon resonance

Use of the semi-quantitative radioimmunoassay Charm II RIA test to analyse antibiotic residues in water has been reported [18]. RIA enables rapid, sensitive, and inexpensive screening of many samples but has the major disadvantage of requiring radioisotopes and scintillation fluids [17]. This method was only effective for measurement of high levels of all antibiotic families in water near a farm (large-scale animal feeding operations AFOs) and was not suited to measurement of specific individual antibiotic compounds. To improve the detection limits of the RIA method it has been tested in combination with SPE [19].

Progress in array-based technology for multi-analyte detection recently led to the development of two multi-analyte immunoassay-based prototypes in the EU projects river-analyser (RIANA) and AWACSS (automated water analyser computer supported system) [20]. AWACSS was building on the achievements of the RIANA device (functional model) with major improvements:

1. expansion to multi-analyte detection;
2. miniaturisation of the design; and
3. equipment with intelligent remote control and surveillance facilities for unattended continuous monitoring.

Complementary to immunochemical methods, bioassays are of interest in an integrated approach to estimation of the impact of PPs in the environment. They give semi-quantitative or qualitative information about the toxicity of a single PP or of a mixture of PPs in laboratory tests, and global toxicity in environmental samples. As an example, growth-inhibition tests based on antibacterial activity have been used to detect antibiotics [17]. A screening test battery, including the yeast oestrogen screen (YES), the bioluminescence inhibition test with *Vibrio fischeri*, and the chlorophyll fluorescence test with green algae, has been used to identify the pharmaceutical hazards of a mixture of PPs and to assess the efficiency of wastewater treatment [24]. It cannot, however, be used to determine the specific source of pollution from the contaminants present in samples. An alternative approach is bioassay-directed fractionation that, coupled with biological and chemical

analysis, may enable isolation and identification of the causative toxic agent in a mixture [25].

Immunochemically based techniques and, more generally, biological methods are alternatives or complements to standard chromatographic methods. Their specificity, sensitivity, and speed of analysis make them suitable candidates for PPs monitoring. Their ability to selectively analyse target analytes, or a family of compounds (RIA test) in complex matrices [18], their possibility of automation and of direct measurement in the field offer new opportunities to design monitoring strategies in the framework of an integrated approach. Some of these techniques are commercially available but data describing cross-reactivity of target analytes and matrix effects are missing, the availability of antibodies is limited, and multi-analyte analyses are difficult to perform.

Conclusion

“Pharmaceuticals in the Environment” is an issue which is receiving growing attention because of the increasing consumption of PPs, their occurrence/persistence in the environment, and their described effects. Implementation of control of these products cannot be achieved solely by use of classical analytical procedures. Information about the whole life-cycle of PPs must, moreover, be taken into account by using an integrated approach, to emphasize the main problems and to lead to proposal of relevant actions to limit their occurrence and impact in the environment. This approach must be supported by a set of screening tools.

LC–MS–MS and biological methods are of complementary interest in this approach. Although immunoassays are rapid, cost-effective and easy to use for identification of relevant PPs, they do not cover the whole wide range of PPs; they are, however, in constant development and improvement. LC–MS–MS can enable selective analysis of PPs in complex matrices and can be used to screen for the occurrence, behaviour, and fate of a wide spectrum of PPs and their metabolites. The method is, however, time consuming, costly, and requires an experienced user. Bioassays furnish information in the field about global toxicity and can also be used in laboratories for individual PPs.

The screening techniques described, by combining all the data, are essential for successful implementation of the proposed integrated approach. This approach should

emphasize the most important questions and issues related to PPs in the environment, enabling the design of more effective environmental risk assessment procedures.

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