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The leaching behavior of cyclophosphamide and ifosfamide from soil in the presence of co-contaminant — Mixture sorption approach

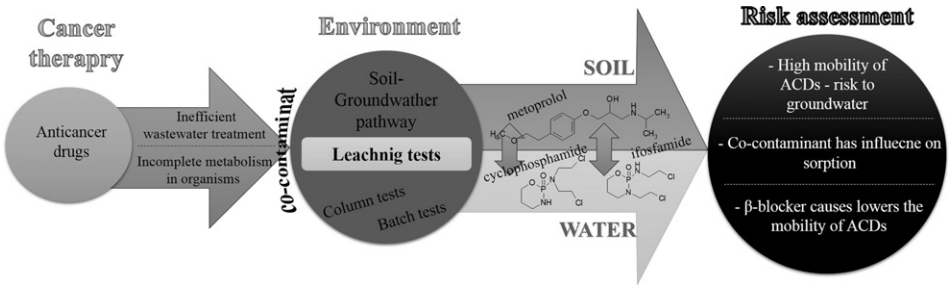
Katarzyna Mioduszewska [a,*], Joanna Maszkowska [a], Anna Białk-Bielińska [a], Oliver Krüger [b], Ute Kalbe [b], Beata Liberek [c], Paulina Łukaszewicz [a], Piotr Stepnowski [a]

[a] Department of Environmental Analysis, Faculty of Chemistry, University of Gdańsk, ul. Wita Stwosza 63, PL-80-308 Gdańsk, Poland
[b] BAM Federal Institute for Materials Research and Testing, Unter den Eichen 87, 12205, Berlin, Germany
[c] Department of Organic Chemistry, Faculty of Chemistry, University of Gdańsk, ul. Wita Stwosza 63, PL-80-308 Gdańsk, Poland

HIGHLIGHTS

- Anticancer drugs show high mobility in soils thus pose a risk to groundwater.
- Metoprolol may diminish leaching of cyclophosphamide and ifosfamide to soils.
- Column tests are more appropriate to model the environmental behavior of the soils.
- Accompanying parameters of the leachates from the leaching tests are presented.

GRAPHICAL ABSTRACT



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ABSTRACT

Anticancer drugs (ACDs) exhibit high biological activity, they are cytotoxic, genotoxic, and are constantly released into the environment as a result of incomplete metabolism. Consequently they pose a serious threat to the environment and human health due to their carcinogenic, mutagenic and/or reproductive toxicity properties. Knowledge of their bioavailability, including their sorption to soils and their impact on the soil–groundwater pathway, is crucial for their risk assessment. Laboratory batch and column leaching tests are important tools for determining the release potential of contaminants from soil or waste material. Batch and column tests were carried out with soils differing in physicochemical properties, each spiked with cyclophosphamide (CK) or ifosfamide (IF). Moreover, due to the fact that environmental pollutants may occur as coexisting compounds in the soil the mobility evaluation for ACDs in the mixture with metoprolol (MET; β-blocker) as a co-contaminant was performed. In order to assess appropriateness, the batch and column tests were compared. The release depended on the properties of both the soil and the presence of co-contaminants. The faster release was observed for coarse-grained soil with the smallest organic matter content (MS soil: 90% decrease in concentration until liquid-to-solid ratio (L/S) of 0.3 L kg^{-1} for all tests' layout) than for loamy sand (LS soil: 90% decrease in concentration until ratio L/S of 0.75 L kg^{-1}). ACDs are highly mobile in soil systems. Furthermore, the decrease of mobility of ifosfamide was observed with the presence of a co-contaminant (metoprolol) in both of the soils (in MS soil a decrease of 29%; in LS soil a decrease of 26%). The mobility of cyclophosphamide does not depend on the presence of a contaminant for MS soil, but also exhibits a decrease of 21% in LS soil.

* Corresponding author.
E-mail address: katarzyna.mioduszewska@ug.edu.pl (K. Mioduszewska).

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1. Introduction

Chemotherapy is the method of choice for cancer treatment. Along with an increasing number of new cancer cases, a subsequent increase in anticancer drug (ACD) consumption is observed. Although the use of ACDs is difficult to assess, the total number of cancer cases in Europe in 2012 was estimated to be 3.45 million new cases of cancer and 1.75 million deaths from cancer. Hence, cancer has become one of the most important public health problems not only in Europe but worldwide (Lutterbeck et al., 2015; Toolaram et al., 2014; Ferlay et al., 2013).

Cyclophosphamide (CK) is a nitrogen mustard alkylating agent. It has been widely used in anticancer therapy for more than 50 years (Lutterbeck et al., 2015; Balcerzak and Rezka, 2014). Ifosfamide (IF) is an analog of CK, with a similar spectrum of antitumor activity but higher toxicity potential and financial costs than CK. Nevertheless it is extensively used nowadays due to greater efficacy (Weiss, 1991). More than 400 kg/a of these cytostatic drugs are used in Germany (Kümmerer, 2001). The consumption in France is above 300 kg/a CK and above 100 kg/a IF, and more than 1 t/a CK and 350 kg/a IF in Spain (Ortiz de García et al., 2013). Furthermore, both ACDs have been used not only in cancer treatment, but also for example for immunosuppression after organ transplantation (Balcerzak and Rezka, 2014). Since the effect of cytostatic drugs is based on their toxicity for rapidly dividing tumor cells, they can be harmful for other cells too. In general, they pose environmental hazards due to carcinogenic, mutagenic and teratogenic properties. Even though these drugs are mostly administered in hospitals (as much as up to 5 kg of a single substance annually in large hospital (Kümmerer, 2001), an increasing number of out-patients consumes them at home (Johnson et al., 2008). Hence, large amounts of ACDs wastes can reach not only hospital treatment plants but also municipal wastewater treatment plants, which very often do not possess the appropriate technology for the efficient removal of such pollutants from domestic sewage.

Alkylating cytostatics like CK and IF are only partially metabolized and thus excreted to a relatively great extent with urine (21% and 26%, respectively). Their biodegradability in activated sludge is exceptionally low (Buerge et al., 2006). Thus, these ACDs are very likely to reach aquatic environments where they are found to be extremely stable (Balcerzak and Rezka, 2014). The occurrence of biologically active compounds such as ACDs is in the range of ng L^{-1} to μg L^{-1} (Nussbaumer et al., 2011; Parrella et al., 2014; Zhang et al., 2013).

The bioavailability of ACDs in surface waters is directly related to their mobility in the terrestrial environment. Sorption – in addition to other processes – is one of the key features affecting the fate of micropollutants in the environment (Kümmerer, 2010; Zuo et al., 2013). It has been shown that interaction between colloids and pharmaceuticals may provide long-term storage of pollutants, hence increasing their persistence in the environment and simultaneously reducing their bioavailability.

Little is known about ACD sorption onto soils and their mobility in the environment (Zhang et al., 2013). So far, only a few studies have been conducted concerning the adsorption of anticancer drugs onto activated sludge as a way of eliminating these micropollutants from wastewater. Lenz et al. (2005) showed that cancerostatic platinum compounds (CPCs) have a potential to sorb onto activated sludge.

The recent study about adsorption of CPCs in the presence of the natural estuarine sediment indicates the high adsorption potential of these pharmaceuticals (K_d values in the range of 10^2 and 10^3 L kg^{-1}) (Turner and Mascorda, 2015). However the investigation has been performed using batch test procedure (static conditions) whereas dynamic test conditions are crucial for an assessment of the possible leaching/release potentials of contaminated materials concerning the soil–groundwater pathway. Static tests like batch tests show only a snapshot of a particular liquid-to-solid ratio. Column leaching tests provide information about time-dependent contaminant release with respect to local equilibrium times and advection conditions (Lopez Meza et al., 2008). Moreover the mobility of ACDs in soil, not only in sediments, needs to be tested, since this matrix is potentially threatened by pollution from using sewage sludge as fertilizer (Smith, 1996).

Reliable understanding of the mobility of any chemical compound in the soil environment is difficult to achieve due to possible and very likely presence of coexisting contaminants (co-contaminants). In the case of pharmaceuticals, only a few studies to date have considered these effects. These include, for example, sulfonamides in the presence of herbicides or steroid hormones (Accinelli et al., 2006; Srinivasan et al., 2013) and 17-β-estradiol in the presence of veterinary antibiotics (Chun et al., 2005). These studies revealed that co-contaminants affect both the sorption and the persistence of the investigated compounds.

Taking all of the above into account, the main aims of this presented study were (i) to assess the mobility of CK and IF in soils varying in their physicochemical properties and (ii) to investigate the influence of exemplary pharmaceutical co-contaminant on the sorption behavior of both ACDs. Metoprolol was selected for this purpose. This drug is one of the most commonly consumed and detected pharmaceuticals in the environmental, and is considered to be harmful to aquatic organisms also (Maszkowska et al., 2014a, 2014b).

2. Materials and methods

2.1. Chemicals

Standards of cyclophosphamide monohydrat (CK), ifosfamide (IF), metoprolol (MET) were purchased from Sigma-Aldrich (Steinheim, Germany). Deionized water was produced by the HYDROLAB System (Gdańsk, Poland) and acetonitrile (ACN) was obtained from POCH (Gliwice, Poland) (Table A.3).

2.2. Preparation of test materials

Two soil matrices differing in particle size distribution and organic matter content were used. A reference soil, characterized as loamy sand (LS) was obtained from the Fraunhofer Institute for Molecular Biology and Applied Ecology, Schmallenberg, Germany and a second, characterized as medium sand (MS) from a construction site at BAM Federal Institute for Materials Research and Testing, Berlin, Germany. Selected properties of the test materials are presented in Table A.1.

6 kg of the respective air-dried soils were mixed with 60 mg of anticancer drug with or without addition of 60 mg beta-blockers. Mixing

Table A.1
Physicochemical properties of the soils matrices used in the experiments.

	LS	MS
pH	5.41	8.66
C_{org} [%]	2.84	0.64
CEC_{ef} [$cmol_c$ kg^{-1}]	7.20	0.83
Particle size distribution		
>2 mm [%]	–	7
2–0.063 mm [%]	78	92
0.063–0.002 mm [%]	14	1
<0.002 mm [%]	8	–
The inorganic constituents		
K [mg kg^{-1}]	618	1217
Na [mg kg^{-1}]	239	142
Ca [mg kg^{-1}]	1420	6295
Mg [mg kg^{-1}]	245	661
Fe [mg kg^{-1}]	1524	4899
Al [mg kg^{-1}]	3542	4245
Residual moisture content [%] DIN ISO 12880	1.6	0.5