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Prioritising anticancer drugs for environmental monitoring and risk assessment purposes

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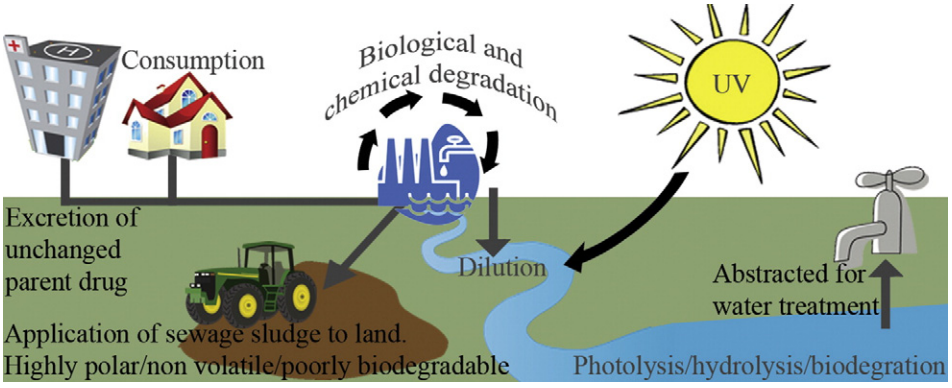
HIGHLIGHTS

- We surveyed regional hospitals to get accurate consumption data for anticancer drugs.
- Drugs were systematically ranked based on consumption, behaviour and fate.
- A shortlist of 18 drugs is likely to be of environmental concern.
- 12 anticancer drugs can 'breakthrough' to receiving waters.
- 6 anticancer drugs partition appreciably to sewage sludge and may persist.

GRAPHICAL ABSTRACT



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ABSTRACT

Anticancer drugs routinely used in chemotherapy enter wastewater through the excretion of the non-metabolised drug following administration to patients. This study considers the consumption and subsequent behaviour and occurrence of these chemicals in aquatic systems, with the aim of prioritising a selection of these drugs which are likely to persist in the environment and hence be considered for environmental screening programmes. Accurate consumption data were compiled from a hospital survey in NW England and combined with urinary excretion rates derived from clinical studies. Physical–chemical property data were compiled along with likely chemical fate and persistence during and after wastewater treatment. A shortlist of 15 chemicals (from 65) was prioritised based on their consumption, persistency and likelihood of occurrence in surface waters and supported by observational studies where possible. The ecological impact of these 'prioritised' chemicals is uncertain as the measured concentrations in surface waters generally fall below standard toxicity thresholds. Nonetheless, this prioritised sub-list should prove useful for developing environmental screening programmes.

1. Introduction

There is growing concern about the presence of pharmaceuticals in the wider aquatic environment. Common 'over the counter' and prescription medicines as well as veterinary medicines are increasingly reported in waste and surface waters in the scientific literature (Jones

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et al., 2005; Buerge et al., 2006; Moldovan 2006; Yin et al., 2010; Martín et al., 2011; Gómez-Canela et al., 2012). However, anticancer drugs used in chemotherapy have received less attention but have high pharmacological potency and possess fetotoxic, genotoxic and teratogenic properties and can induce subtle genetic and cell cycle changes in aquatic fauna and flora under chronic exposure (Johnson et al., 2008; Rowney et al., 2009).

Due to the improvement in detection limits (from <10 ng/L in 1998 to >1 ng/L in 2011) to quantify anticancer drugs with liquid chromatography tandem mass spectrometry (LC–MS/MS) some of these chemicals have been reported in hospital waste effluents, influents/effluents in sewage treatment plants (STPs) and river water, in a small but growing number of studies (Aherne et al., 1990; Castiglioni et al., 2005; Buerge et al., 2006; Mahnik et al., 2006; Garcia-Ac et al., 2009; Kovalova et al., 2009; Yin et al., 2010; Llewellyn et al., 2011; Martín et al., 2011). The concern over these substances is their occurrence in freshwater systems which are then abstracted as a potable water supply, hence presenting a risk of human exposure, as well as posing a wider risk to freshwater and estuarine habitats (Rowney et al., 2009).

Anticancer drugs are classified under antineoplastic and immunomodulating agents (class L) using the Anatomical Therapeutic Classification (ATC) system. Based on the chemical structure and therapeutic properties they are further subcategorised into five groups; L01A: alkylating agents; L01B: antimetabolites; L01C: plant alkaloids & other natural products; L01D: cytotoxic antibiotics & related substances, and L01X: other antineoplastic agents which relate to their mode of action. Chemotherapy is correctly described as cytotoxic therapy, and refers to the use of drugs to kill or inhibit the growth of cancer cells. Most chemotherapy drugs act as cytotoxic agents by causing damage to deoxyribonucleic acid (DNA) or prevent chromosomal replication by disrupting critical cell processes, which leads to cell death (apoptosis) (Caley and Jones 2012). There are other treatments (cytostatic agents) that do not kill cancer cells and work by stopping cancer cell replication/division and arresting cells in a specific phase of their cell cycle. Trastuzumab (common name: Herceptin) is an example of a cytostatic agent that has high consumption, in France (Besse et al., 2012). Once cancerous cells are arrested and synchronised they can be targeted with a cytotoxic agent (Caley and Jones 2012).

Currently, there are over fifty anticancer drugs being used routinely in chemotherapy in the UK. In general, many of these compounds are polar, water soluble and non-volatile with principle sources including wastewater through point release as hospital effluents as well as diffusive release from domestic dwellings from cancer patients (non-hospital bound or 'outpatients') undergoing chemotherapy medication. Therefore, STP discharges are considered as the main source of anticancer drugs to the aquatic environment (Kummerer 2001; Rowney et al., 2009). However, in countries where on-site wastewater treatment systems (i.e. septic systems) are extensively used the diffusive release from domestic dwellings may provide significant entry of anticancer drugs into the environment (Stanford and Weinberg 2010; Du et al., 2014).

Some of these drugs are not fully metabolised and are poorly biodegradable and therefore can resist biological as well as physical removal processes during wastewater treatment (Johnson et al., 2008). Some of these chemicals could be considered to be semi-persistent with ongoing release into the environment (Daughton 2002; Jones et al., 2005). Given that many of the drugs possess a similar pharmacology then it is plausible that they may act additively once in the environment, possibly enhancing their overall cytotoxicity and increasing the risk to aquatic organisms (Lambert and Lipscomb 2007).

The aim of this study was to generate a shortlist of anticancer drugs (from the many drugs in use) that are likely to have relevance with regard to their actual occurrence and impact on the wider environment. By following a systematic methodology examining consumption, excretion and chemical fate we are able to generate a shortlist of priority chemicals that can then be used to inform future screening programmes and/or targeted risk assessments.

2. Methods

To generate a shortlist of priority anticancer drugs, a systematic, stepwise approach was taken which is outlined in Fig. 1. Contemporary use and consumption data of anticancer drugs were obtained for 31 hospitals operating a range of specialist and/or non-specialist oncology units in NW England. Drugs were ranked according to their annual use and then grouped according to their rates of metabolism. Low metabolism assumes that a high percentage of the consumed parent drug is lost via excretion (via urine and faeces) to the wastewater system. Chemical fate in wastewater was then undertaken using chemical property estimation and fate models including the use of SPARC (http://archemcalc.com/sparc/) and the EPI-Suite models (http://www.epa.gov/oppt/exposure/pubs/episuite.htm) and supported by empirical studies to ascertain partitioning (i.e. between the dissolved aqueous phase and suspended particulate matter) and the susceptibility of a drug to undergo transformation/degradation. For this step efforts were made to assess and select the most appropriate physical–chemical property data, particularly aqueous solubility and K_{ow} or D_{ow} values. Furthermore, estimates of key abiotic or biotic loss processes were undertaken. Drugs could then be grouped according to those most likely to exist in the dissolved phase but with sufficient persistency to reach surface waters (via treated effluent) and those partitioned strongly to particle matter and sufficiently persistent to be retained in sewage sludge. Those drugs considered to be present in the final effluent were then assessed with regard to their likely release to receiving water

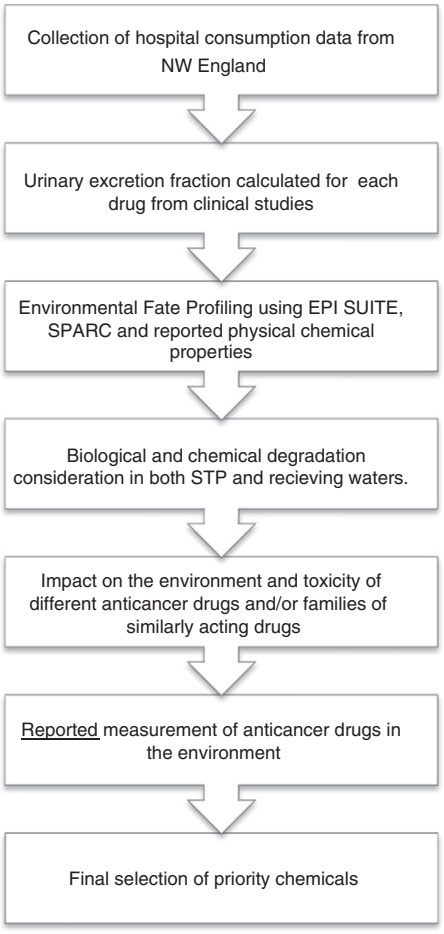

Fig. 1. Schematic representation of the methodology used to select priority chemicals.