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Review

Environmental risk assessment of anti-cancer drugs and their transformation products: A focus on their genotoxicity characterization-state of knowledge and short comings

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ABSTRACT

Anti-cancer drugs are chemotherapeutic agents that are designed to kill or reduce proliferating cells. Often times, they interfere directly or indirectly with the cell's deoxyribonucleic acid (DNA). Some of these drugs can be detected in the ng/L concentration range in the aquatic environment and have the potential to be very persistent. Environmental risk assessment is available for only a few anti-cancer drugs, derived mainly from predicted data and excluding information on their metabolites and transformation products (TPs). Notably, there is no defined strategy for genotoxicity risk assessment of anti-cancer drugs, their metabolites and TPs in the environment. In fact, the presence of anti-cancer drugs in hospital and municipal wastewaters has not been clearly related to the genotoxic nature of these wastewaters. The few available studies that have sought to investigate the genotoxicity of mixtures derived from treating anti-cancer drugs prior to disposal seem to share the commonality of coupling analytical methods to measure concentration and genotoxic bioassays, namely the Ames test to monitor inactivation. Such limited studies on the environmental fate and effects of these drugs presents an area for further research work. Most importantly, there is a need to characterize the genotoxic effects of anti-cancer drugs towards aquatic organisms. Given current environmental risk assessment strategies, genotoxicity risk assessment of these drugs and their TPs would have to include a combination of appropriate analytical methods, genotoxicity bioassays, (bio) degradability and computer based prediction methods such as QSAR studies.

Contents

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1. Introduction

Cancer is credited with been the leading cause of human deaths worldwide, accounting for 7.6 million deaths in 2008 and is expected to rise to 13.1 million deaths in 2030 [1]. Antineoplastic or anti-cancer drugs are one of the main chemotherapeutic agents used in the fight against cancer. Most of these drugs kill or control the proliferating cells by mainly interfering with deoxyribonucleic acid (DNA) through various mechanisms [2]. These drugs can also exhibit unwanted effects to normal cells and are potentially immunosuppressive to humans and animals. Some anti-cancer drugs have shown potential to act as carcinogen, teratogen and/or mutagen [3,4]. Evidence of their genotoxic effects has so far been established in situations where there is likelihood of higher exposure such as in a health care setting [5–9].

Anti-cancer drugs are administered under controlled situations at hospitals and now at increasing levels at home by out-patients' consumption [10]. The main environmental source of anti-cancer drugs comes from excretion in the form of urine and faeces from chemotherapeutic patients. An ongoing move towards out-patient treatment and the fact that hospital effluent often time leads into the municipal sewer system would now make municipal wastewater an important source for the introduction of these drugs into the environment. There is some knowledge on the presence of these compounds in the aquatic environment but rather limited knowledge on their effects on humans and wild life once they enter the environment.

Thus far, there have been some efforts in characterizing the potential risk of anti-cancer drugs in the environment. Publications on detection of these compounds in the aquatic environment started since the late 1980s with the works of Richardson and Bowron [11] and Ahrene et al. [14], among others. Since then it has been found that different anti-cancer drugs usually occur in ng/L or below in the environment [11–13]. Recently, a number of reviews have chronicled the efforts of researchers in characterizing the presence and fate of these drugs in the environment [13,15–17]. The review of Kosjek and Heath discussed the state of analytical procedures for detecting anti-cancer drugs in the aquatic environment [13]. Zhang et al. focused on methods of removal of anti-cancer drugs from wastewaters [17]. Many authors including Kümmerer et al. [18–20], Kümmerer and Al-Ahmad [21], Al-Ahmad et al. [22], Steger-Hartmann et al. [23,24] and Al-Ahmad and Kümmerer [25] have investigated the environmental fate of some anti-cancer drugs. Besse et al. provided extensive data on exposure of several anti-cancer drugs for surface waters in France [15]. The review of Xie additionally contained data on ecotoxicity and approaches for effluent treatment [16]. Presently, there are two ongoing projects, funded by the European Union (EU), namely the Pharmas (http://www.pharmas-eu.org) and Cytothreat (http://www.cytothreat.eu/) projects that are focused on determining the risks from the presence of anti-cancer drugs, their metabolites and their transformation products in the aquatic environment.

So far we know some of these drugs are present and stable in the aquatic environment [11–24]. Data on acute toxicity testing usually suggest that anti-cancer drugs are toxic at 3 fold or higher concentration than their known environmental concentrations [16,17]. Most of the reviews mentioned above conclude that there is a need for more chronic ecotoxicity testing of these drugs since they are present in low concentrations and are rather persistent in the aquatic environment. Only a few rough risk assessments are available and only for a few compounds such as Cyclophosphamide (CPA) and Ifosfamide (IF). Moreover, though it is known that many of these compounds are transformed through human metabolism, limited studies have sought to identify and characterize their human metabolites. Furthermore, additional transformation products (TPs) can result from various treatment processes or from abiotic and biotic environmental processes such as biotransformation, hydrolysis or photolysis. For them even less is known.

In this paper, emphasis is not placed on the occurrence and fate of these compounds. In this respect, we aim to simply highlight the presence of these compounds as contaminants in the aquatic environment. The main focus of this work is on determining the status of current research on genotoxic and mutagenic potentials of these drugs, their human metabolites and their TPs as part of their environmental risk assessment. Emphasize is placed specifically on the current methods used for genotoxicity risk assessment and their suitability to assess the effects of anti-cancer compounds and their TPs in the aquatic environment.

2. Understanding the potential risk of anti-cancer drugs as environmental micro-pollutants

Anti-cancer drugs are classified by the Anatomical Therapeutic Classification (ATC) system according to their chemical structures and therapeutic properties as class L, Antineoplastic and immunomodulating agents [26]. Table 1 shows the classes of antineoplastic drugs as defined by the ATC and a general description of their mode of action. Understanding the different modes of action can support the idea that by design, these drugs can interact directly or indirectly with DNA causing DNA damage and/or inhibit DNA synthesis as well as affecting mitosis and inhibiting cell proliferation. These actions can be unspecific inhibiting normal cells thereby presenting a danger to environmental organisms.

2.1. Usage and physico-chemical properties as an indicator of environmental fate

To understand the potential risk of these drugs to the environment, a closer look at the consumption patterns and the physico-chemical nature of the drugs are the least of requirements. According to Bergmann et al., Germany has experienced an increase of 58% in the consumption (mass) of active ingredients of various anti-cancer drugs from 2002 to 2009 [30]. Even though not all drugs are consumed equally, the gross effect is likely to be an increased input into the environment. Kosjek and Heath in their review mentioned that 5-Fluorouracil (5-FU) followed by Gemcitabine (GEMc), IF, CPA, and Methotrexate (MTX) were the most widely administered cytostatic drugs globally [13]. Interest should also be given to the newly formulated anti-cancer drugs such as Imatinib (IB) since little to no information exists on their environmental fate. In Germany, there was a 478% increase in consumption of IB from 2002 to 2009 [30] while in France, there was a 50% increase between 2004 and 2008 [15]. Furthermore with increasing life expectancy and increasing standard of living on a global scale it has to be expected that the input of anti-cancer drugs into the environment will increase further. Some drugs are used for anti-cancer treatment but also for other treatments. MTX, for example, is used in anti-cancer treatment and the treatment of rheumatism. There seems to be also a trend of increasing usage of anti-cancer drug treatment for pets such as dogs and cats in several countries. This has to be accounted for when data of usage are assessed.

Physico-chemical parameters such as the dissociation constant (pK_a), bioconcentration factor (BCF), octanol–water partition coefficient (K_{ow}), organic carbon partition coefficient (K_{oc}), atmospheric OH reaction rate, solubility, Henry's coefficient and the vapour pressure are all instrumental in risk assessment analysis. Since many reviewers [13,15–17] have provided extensive data on the physico-chemical nature, the occurrence and fate of these compounds, only data pertaining to the five main

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