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PBT assessment and prioritization of contaminants of emerging concern: Pharmaceuticals ☆

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ABSTRACT

The strong and widespread use of pharmaceuticals, together with incorrect disposal procedures, has recently made these products contaminants of emerging concern (CEC). Unfortunately, little is known about pharmaceuticals' environmental behaviour and ecotoxicity, so that EMEA (European Medicines Agency) released guidelines for the pharmaceuticals' environmental risk assessment. In particular, there is a severe lack of information about persistence, bioaccumulation and toxicity (PBT) of the majority of the thousands of substances on the market. Computational tools, like QSAR (Quantitative Structure Activity Relationship) models, are the only way to screen large sets of chemicals in short time, with the aim of ranking, highlighting and prioritizing the most environmentally hazardous for focusing further experimental studies.

In this work we propose a screening method to assess the potential persistence, bioaccumulation and toxicity of more than 1200 pharmaceutical ingredients, based on the application of two different QSAR models. We applied the Insubria-PBT Index, a MLR (Multiple Linear Regression) QSAR model based on four simple molecular descriptors, implemented in QSARINS software, and able to synthesize the PBT potential in a unique cumulative value and the US-EPA PBT Profiler that assesses the PBT behaviour evaluating separately P, B and T. Particular attention was given to the study of Applicability Domain in order to provide reliable predictions. An agreement of 86% was found between the two models and a priority list of 35 pharmaceuticals, highlighted as potential PBTs by consensus, was proposed for further experimental validation. Moreover, the results of this computational screening are in agreement with preliminary experimental data in the literature. This study shows how *in silico* models can be applied in the hazard assessment to perform preliminary screening and prioritization of chemicals, and how the identification of the structural features, mainly associated with the potential PBT behaviour of the prioritized pharmaceuticals, is particularly relevant to perform the rational *a priori* design of new, environmentally safer, pharmaceuticals.

1. Introduction

In the last decades the improvement of welfare and life style has changed some demographic keys aspects leading to a population growth and also to a change in the age class ratio to benefit of the older age groups. The consequent increased demand for food and health care provisions has led to an enhancement in the use of human and veterinary drugs (United Nations, 2007; WHO, 2011).

Unfortunately, nowadays the pharmaceuticals are too frequently overused. The irrational use of pharmaceuticals products was well documented (Busfield, 2015; WHO, 2011), while overuse of medicine was assessed to push up health care costs and have negative consequences for societies and individuals (Busfield, 2015). The main example is the increased resistance of infectious microorganisms to many antibiotics due to the overuse of such pharmaceutical products in human and veterinary (WHO, 2011).

Abbreviations: AD, Applicability Domain; API, Active Pharmaceutical Ingredient; B, Bioaccumulative; BCF, BioConcentration Factor; bor AD, borderline Applicability Domain; CAS, Chemicals Abstracts Service; CEC, Contaminants of Emerging Concern; EMEA, European Medicines Agency; EPI, Estimation Program Interface; ERA, Environmental Risk Assessment; EV, Explained Variance; HVP, High Production Volume; in AD, inside Applicability Domain; MLR, Multiple Linear Regression; NCCOS, National Center for Coastal Ocean Science; NOAA, National Oceanic and Atmospheric Administration; NSAID, Non-Steroidal Anti-Inflammatory Drugs; OECD, Organization for Economic Co-operation and Development; OLS, Ordinary Least Square; OSPAR, Oslo PARis; out AD, outside Applicability Domain; P, Persistent; PB, Persistent Bioaccumulative; PBT, Persistent Bioaccumulative and Toxic; PC, Principal Component; PCA, Principal Components Analysis; POP, Persistent Organic Pollutant; QSAR, Quantitative Structure Activity Relationship; QSARINS, QSAR-Insubria; SMILES, Simplified Molecular Input Line Entry System; T, Toxic; US EPA, United State Environment Protection Agency; vPvB, very Persistent very Toxic; WWTP, Waste Water Treatment Plant

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The expansion of medicine use is a clear phenomenon, so that some authors talk about society pharmaceuticalisation: "the process by which social, behavioural or bodily conditions are treated or deemed to be in need of treatment, with medical drugs by doctors or patients pharmaceuticals are now used not only to treat existing sickness state" (Abraham, 2010; Busfield, 2015).

This strong worldwide increased use of drugs has brought to a consequent increasing levels of detected and measured medicine residues in the environment, so now pharmaceuticals are widely recognized environmental contaminants of increasing concern, since they have been recently detected in more than 71 countries all over the world (IWW, 2014). More than 600 Active Pharmaceutical Ingredients (APIs) (or their metabolites and transformation products) have been identified in the environment, mainly in surface water and sewage effluent, but also in groundwater, soil, and other environmental matrices (Kümmerer, 2013; Weber et al., 2014; Zuccato et al., 2000, 2010).

In a recent review, (Hughes et al., 2013) collected monitoring and detection data: more than 200 APIs were frequently detected all over the world, within a range of concentration that varies from few ng/L to hundreds μg/L. The main detected therapeutic groups were: antibiotics, analgesic and painkillers, cardiovascular drugs or blood lipid regulators and *anti*depressants, with carbamazepine as the single most commonly identified compound.

Waste Water Treatment Plants (WWTPs) are considered the main environmental source of pharmaceuticals, since they collect and accumulate APIs from waste water of urban and industrial discharges, but the ordinary treatment procedures are not able to reduce efficiently this kind of contamination load (Batt et al., 2006; Kümmerer, 2009; Verlicchi et al., 2012).

Moreover, veterinary pharmaceuticals, used in intensive farming and aquaculture to increase livestock production, are often directly released in surface waters and soils, increasing the worldwide contamination (Boxall et al., 2003).

The capability of pharmaceutical ingredients to be absorbed and to interact with living organism makes them a potential hazard for the whole ecosystem. Pharmaceuticals are specifically designed to be biologically active substances and, when released into the environment, their biological activity may cause adverse effects to the wildlife (so-called non-target organisms) and impair ecosystem health (Barra Caracciolo et al., 2015; Fent et al., 2006; Fong and Ford, 2014; Oaks et al., 2004; Sumpter et al., 2006).

Environmental presence of pharmaceutical products represents a scientific, technical and regulatory challenge and, in order to prevent the rise of negative impacts and to preserve good quality standards, environmental behaviour and effects of drugs need to be carefully assessed.

For these reasons the Environmental Risk Assessment (ERA) for human and veterinary products was taken in account by the European legislation and became effective with two EC Directives 2004/27/EC and 2004/28/EC. Currently, the ERA is performed according to the European Medicines Agency (EMEA) guidelines (EMEA, 2006) in the pre-approval phase for the marketing authorisation of new human medicinal products and for existing substances used in generic applications. The most common remark on these guidelines is that they cover only pharmaceuticals marketed after their introduction in 2006, neglecting the majority of APIs marketed before that date. Some authors suggest to enlarge ERA procedure also for so called "existing pharmaceuticals" because "there are no reasons to believe that the risks posed by a substance, or the need for a risk assessment, would depend on the date of market approval" (Ågerstrand et al., 2015).

The guidelines for ERA of human medicines require, in the first preliminary phase, the PBT assessment to verify if a pharmaceutical ingredient may be Persistent, Bioaccumulative and Toxic (PBT) at the same time. PBT chemicals are priority pollutants due to the potential risk they pose to human's health and ecosystems. They can resist to biotic and abiotic degradation and, persisting unchanged for long time, they can interact with humans and wildlife, accumulating in living organisms and also causing toxic effects. It has been already demonstrated that some pharmaceuticals are unaffected by microbiological and other degradation process and thus can be persistent in the environment (Monteiro and Boxall, 2009; Verlicchi et al., 2012). Some are also lipid soluble and potentially bioaccumulative in organisms, where they could express hazardous biological activity (Brodin et al., 2013; Foster et al., 2010; Parolini et al., 2015; Wu et al., 2010; Zenker et al., 2014).

Approximately 5000 active substances are currently on the market (Kuester and Adler, 2014), of which the majority are without information on their environmental behaviour. The need for an early identification and prioritization of the most environmentally dangerous substances, on which to focus the experimental tests, is thus evident.

In the past years different approaches, based on consumption, experimental toxicological and physico-chemical data and *in silico* predictions, were carried out to screen and identify the most environmentally hazardous pharmaceuticals (Boxall et al., 2003; Di Nica et al., 2015; Howard and Muir, 2011; Kar and Roy, 2012; Ortiz de García et al., 2013; Riva et al., 2015; Sanderson et al., 2004).

In this work we apply to a big data set of pharmaceuticals a screening approach, based on QSAR models, that allows the identification of Persistent, Bioaccumulative and Toxic (PBT) chemicals directly from the molecular structure in absence of experimental data. QSAR(Quantitative Structure-Activity Relationships) modelling is based on the assumption that the molecular structure of a chemical (i.e. its geometric, steric and electronic properties) contains the features responsible for its physical, chemical, and biological properties. Such modelling techniques are the best chemoinformatic approaches to extract the information inherent in the molecular constitution and characterize the intrinsic hazard of any chemical. In fact, good QSAR models, based on theoretical molecular descriptors and validated for their predictivity, can be applied to new chemicals, without experimental data even before their synthesis. In this way it is possible to screen also big data sets of compounds without experimental data, highlighting which have the potentiality to be hazardous for the studied property. Many research groups developed and applied QSAR models for prioritization (Gramatica, 2009, 2012, 2013; Cassani and Gramatica, 2015; Gramatica et al., 2015, 2016; Howard, P.H., Muir, D.C.G. 2010, 2011; Öberg, 2004, 2005, 2006; Papa and Gramatica, 2010; Roy et al., 2015a, 2015b, Sanderson et al., 2004, Sanderson and Thomsen, 2009).

Focusing on PBT assessment, in a recent paper (Gramatica et al., 2015) (Part 1 of this Series) we verified and demonstrated that the comparative application of two different modelling approaches, the Insubria-PBT Index (Papa and Gramatica, 2010), implemented in the QSARINS (QSAR-INSubria) software (Gramatica et al., 2013, 2014) and the US-EPA PBT Profiler (US EPA, 2006), is a reliable method for screening large sets of heterogeneous compounds in order to highlight the potentially PBT chemicals predicted by consensus. The application of this screening approach to Personal Care Products ingredients (Cassani and Gramatica, 2015) (Part 2 of the Series) and to Flame Retardants and their supposed safer alternatives (Gramatica et al., 2016) (Part 3 of the Series) has already allowed to characterize the intrinsic hazard and to prioritize the potentially PBTs into these important classes of environmental CECs. The reliability of the consensus modelling approach was demonstrated by the identification of compounds, in all the screened classes, that are actually PBTs, based on the available experimental evidences.

The pharmaceuticals, which will be prioritized as new potential