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Identification of potential PBT behavior of personal care products by structural approaches ☆

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ABSTRACT

Several organic ingredients in personal care products (PCPs) became recently compounds of increasing environmental concern, being frequently detected mainly in receiving waters. However, there is limited understanding of how these emerging contaminants may affect wildlife communities, as well as humans. In particular, data on persistence, bioaccumulation and toxicity (PBT) are generally lacking and the environmental behavior of PCPs needs to be further investigated. The determination of all the dangerous properties is a long and difficult task, thus it is very important to have tools to quickly screen and highlight the most hazardous compounds, focusing the experiments only on the prioritized compounds. QSAR models can predict missing data for the unknown activities and properties, necessary to prioritize chemicals, directly from the chemical structure. Using QSAR models, in this work we have studied the potential cumulative PBT behavior of hundreds of PCPs. More than 500 chemicals have been screened for their PBT properties by applying different tools: the Insubria PBT Index, a QSAR model included in the QSARINS software, and the US-EPA PBT Profiler. A priority list of the potentially most hazardous PCPs, identified in agreement by both the modeling tools, is therefore proposed: some sun-screens are among the few PCPs identified as PBTs. This study also shows that the PBT Index could be a valid tool to evaluate immediately from the molecular structure safer and more environmentally sustainable chemicals, *a priori* from the chemical design in a benign by design approach of Green Chemistry, avoiding unnecessary synthesis and expensive tests.

1. Introduction

Personal care products and their ingredients (PCPs) are a wide and heterogeneous group of chemicals used in different products of daily use such as cosmetics, soaps, perfumes, and sunscreens. This kind of chemicals is largely used all over the world, in huge quantities, in order to improve the quality of several products and to obtain benefits in everyday life. This great consumption has led to the detection of PCPs with greater frequency and persistence in the environment, mainly in the water compartment including natural water, wastewater, wastewater treatment plants (WWTPs) and marine environment (Brausch and Rand, 2011; Peck, 2006; Tsui et al., 2015). Their wide environmental occurrence is thus of potential concern for both humans and wildlife, also considering the limited information on the toxicity of PCPs, even though the available data indicate that most PCPs are relatively nontoxic to aquatic organisms at expected environmental concentrations. However, there are evidences that some PCPs have the potential to bioaccumulate through the food chain and can be also potential endocrine disruptors, even at relative low concentrations (Brausch and Rand, 2011). In light of these considerations, there is a need to extend knowledge about the PCP properties, to better understand

Abbreviations: PCP, personal care products; WWTPs, wastewater treatment plants; PBT, persistent, bioaccumulative and toxic; QSAR, quantitative structure–activity relationship; OPBT, occurrent, persistent, bioaccumulative and toxic; PPCPs, pharmaceuticals and personal care products; EPI, estimation program interface; QSARINS, qsar-insubria; US-EPA, united states environmental protection agency; DnBp, di-n-butyl phthalate; DEHP, di(2-ethylhexyl) phthalate); EU, european union; DEP, diethyl phthalate; PPD, p-phenylenediamine; PTD, toluene-2,5-diamine; CADASTER, case studies on the development and application of in-silico techniques for environmental hazard and risk assessment; MLR, multi-linear regression; OECD, organization for economic cooperation and development; Q^2_{LOO}, Q^2 leave-one-out; RMSE, root mean squares of errors; RMSEcv, root mean squares of errors in cross validation; PCA, principal component analysis; PC, principal component; vPvB, very persistent very bioaccumulative; AD, applicability domain; in AD, inside applicability domain; bor AD, borderline applicability domain; out AD, outside applicability domain; ECHA, european chemicals agency; PACT, public activities coordination tool; RMOA, risk management option analysis; SVHC, substances of very high concern; EC, european commission; CAS, chemical abstracts service; BCF, bioconcentration factor; PT, persistent, toxic; MSC, member state committee; CORAP, community rolling action plan; SPF, sun protection factor; HPV, high production volume; REACH, registration, evaluation, authorization and restriction of chemicals

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their environmental behavior and sustainability, not only for the immediate impact on the environment, but for the long term implications as well, and their potential environmental hazard, in particular persistence bioaccumulation and toxicity (PBT), handled in this study.

QSAR (Quantitative Structure-Activity Relationships) modeling exploits the fact that any hazardous property of a substance is an inherent property in the chemical structure and, if good QSAR models are developed and applied, it is possible to screen also big data sets of compounds without experimental data, highlighting which have the potentiality to be hazardous for some studied property starting from the chemical structure (Gramatica, 2010; Roy et al., 2015). This screening can be done on any compound with a known chemical structure, even without experimental data, and therefore can be applied also for planning environmentally safer and more sustainable alternatives to those PCPs that are identified as potentially hazardous.

Regarding the PBT behavior, other authors (Ortiz de García et al., 2013) proposed a ranking of concern focused on occurrence, persistence, bioaccumulation and toxicity (OPBT) of a set of pharmaceuticals and few personal care products (overall called PPCPs), more used in Spain, based on the predictions obtained by the EPI Suite models (US EPA, 2012) and applying the Hasse diagram for the ranking (Brüggemann et al., 1995). Our present study is concentrated specifically on PCPs and has the aim to assess the PBT behavior of a very large set of these kind of chemicals, comparing two different QSAR methodologies (i.e. the Insubria PBT Index (Papa and Gramatica, 2010), now implemented in the module QSARINS-Chem (Gramatica et al., 2014) of the QSARINS (QSAR-Insubria) software (Gramatica et al., 2013) and the US-EPA PBT Profiler (US EPA, 2006). The application of both methods for the screening of large sets of heterogeneous compounds has already demonstrated the utility of this consensus modeling approach for highlighting potentially PBT chemicals (Gramatica et al., 2015).

A priority list of the most hazardous PCPs for their PBT behavior, on which the concentration of experimental tests is suggested, is the main output of the present screening study.

The heterogeneous chemical nature of PCPs allows us to consider here the subclasses studied in this work that mainly contains fragrances, sunscreens/UV filters, phthalates, parabens, and hair dye ingredients.

Fragrance substances are a large and structurally heterogeneous group of compounds, used in various everyday products such as perfumes, deodorants, detergents, cleaners, room sprays and other consumer products. Even though, correctly, they should not be considered as a single class of chemicals, since they are represented by 22 major structural classes, exhibiting a wide range of physical-chemical properties (Bickers et al., 2003; Salvito et al., 2004), anyway in this paper, for simplicity, we will consider the fragrance ingredients as a single subclass of PCPs. Nowadays, synthetic fragrances like polycyclic- and nitro-musks are increasingly applied, together with the natural fragrances (Lange et al., 2015). It is mainly the fate of fragrances in the wastewaters that determines their presence in receiving streams or soils (Salvito et al., 2004). Synthetic fragrances, like the musks galaxolide and tonalide, are lipophilic, thus they tend to bioaccumulate in aquatic organism, especially fish and mussels, and in fact they have been detected in various environmental and animal samples, such as water, sediments and aquatic organisms (mainly fish and mussels), and are among the most commonly detected synthetic organic compounds in surface water (Lange et al., 2015).

In the last decades, the usage of UV filters and sunscreens in different products, including skin care, facial makeup and lip care products, is increased to protect skin from UV radiation, due to the growing concern about the effects of ultraviolet radiation in humans, with the possible negative consequences on health. Some PCPs may contain UV filters, as UV absorbers, also to prevent product degradation by light. UV filters can be either organic, that are able to absorb UV, or inorganic micropigments, that are able to reflect UV. In this work, we focused only on organic compounds. UV filters are mainly contaminants of the aquatic compartment, being commonly detected in surface or marine water, alongside the recreational areas and beaches (Tsui et al., 2015). These chemicals have the potential to bioaccumulate in biota and show various adverse health effects, mainly endocrine disrupting activity and cutaneous side-effects (Bachelot et al., 2012; Manová et al., 2013; Ma et al., 2003; Schlumpf et al., 2004).

Phthalates are a class of chemicals that have been widely used in modern society, mainly as additives and plasticizers, and as solvents in cosmetics and perfumes. Due to their large use, in many different fields, phthalates have been detected in the environment (Wormuth et al., 2006), mainly in water compartment (Peijnenburg and Struijs, 2006), as well as in indoor air (Adibi et al., 2008) and food (Benson, 2009), thus they are considered environmental contaminants. Many concerns over health effects of phthalates as a group, particularly on reproduction as endocrine disruptors, are well known (Dodson et al., 2012), drawing attention from different legislations and regulations. For example, the United States and the European Union are currently regulating several phthalates in children's products, and similar action is underway in Canada. Two phthalates (DnBp, di-n-butyl phthalate, and DEHP, di(2-ethylhexyl) phthalate) are banned for their use in cosmetics in the European market (Koniecki et al., 2011), while DEP (diethyl phthalate) is still largely used in perfumes (Guo and Kannan, 2013). However, the phthalates do not appear to be bioaccumulative (Gobas et al., 2003).

Parabens are esters of p-hydroxybenzoic acid, commonly used as preservatives, antimicrobial and antifungal agents in various cosmetic products, where they were found in more than 22,000 products, in a low content (0.4–0.8%) (Andersen, 2008). Guo and Kannan (2013) demonstrate that PCPs are the major sources of paraben exposure in the United States. Despite their biodegradability under aerobic conditions and their removal in WWTPs, parabens are frequently found at the ng/L level in the aquatic compartment, probably due to their high consumption (Haman et al., 2015). Greatest concentrations of parabens have been identified in surface water with concentrations ranging from 15 to 400 ng L^{-1}, depending on paraben (Brausch and Rand, 2011). Continuous exposure to parabens, even at low concentrations, can generate alterations in the endocrine system of several organisms (Dodson et al., 2012; Peng et al., 2014). Given these concerns, many cosmetics brands are avoiding parabens and currently labeling their products as parabens-free, to highlight their safety.

Hair dye ingredients contain aryl-amines, which are considered as the most reactive chemicals used in the cosmetic industry (Nohynek et al., 2010). Clinical experience shows that hair dyes can cause allergic contact reactions, in particular p-phenylenediamine (PPD) and toluene-2,5-diamine (PTD) are extreme sensitizers among the hair dye substances (Danish Environmental Protection Agency, 2013; Søsted et al., 2004). Anyway, the results of studies on genetic and reproductive toxicity and carcinogenicity suggest that modern hair dyes and their ingredients pose no genotoxic, reproductive or carcinogenic or risk (Nohynek et al., 2010). At the present time, there is a lack of information about the occurrence and the persistence of hair dyes ingredients in the environment and their potential bioaccumulation in biota.

Given the significant, and relatively uncontrolled, human and environmental exposure to PCPs, the reported concerns, and the general lacking of information on PBT behavior, these chemicals should be thoroughly evaluated for their safety even before to their marketing (Nohynek et al., 2010), according to the benign by