The potential ecotoxicological impact of pharmaceutical and personal care products on humans and freshwater, based on USEtox™ characterization factors. A Spanish case study of toxicity impact scores.

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Abstract

Pharmaceutical and personal care products (PPCPs) are being increasingly included in Life Cycle Assessment studies (LCAs) since they have brought into evidence both human and ecological adverse effects due to their presence in different environmental compartments, wastewater facilities and industry. Therefore, the main goal of this research was to estimate the characterization factors (CFs) of 27 PPCPs widely used worldwide in order to incorporate their values into Life Cycle Impact Assessment studies (LCIA) or to generate a toxicity impact score ranking. Physicochemical properties, degradation rates, bioaccumulation, ecotoxicity and human health effects were collected from experimental data, recognized databases or estimated using EPI Suite™ and the USEtox™ software, and were subsequently used for estimating CFs. In addition, a Spanish toxicity impact score ranking was carried out for 49 PPCPs using the 27 newly calculated CFs, and 22 CFs already available in the literature, besides the data related to the occurrence of PPCPs in the environment in Spain. It has been highlighted that emissions into the continental freshwater compartment showed the highest CFs values for human effects (ranging from 10^{-9} to 10^{-3} Cases·kg^{-1}), followed by emissions into the air (10^{-9} to 10^{-5} Cases·kg^{-1}), soil (10^{-11} to 10^{5} Cases·kg^{-1}) and seawater (10^{-12} to 10^{-4} Cases·kg^{-1}). CFs regarding the affectation of freshwater aquatic environments were the highest of those proceeding from emissions into continental freshwater (between 1 to 10^{4} PAF·m^3·day·kg$_{emission}^{-1}$) due to the direct contact between the source of emission and the compartment affected, followed by soil (among 10^{-1} to 10^{4} PAF·m^3·day·kg$_{emission}^{-1}$), and air (among 10^{-2} to 10^{4} PAF·m^3·day·kg$_{emission}^{-1}$) while the lowest were the CFs of continental seawater (among 10^{-28} to 10^{-3} PAF·m^3·day·kg$_{emission}^{-1}$). Freshwater aquatic ecotoxicological CFs are much higher than human toxicity CFs, demonstrating that the ecological impact of PPCPs in aquatic environments must be a matter of urgent attention. According to the Spanish toxicity impact score calculated, the PPCPs with the highest impact are hormones, antidepressants, fragrances, antibiotics, angiotensin receptor blockers and blood lipid regulators, which have already been found in other kinds of score rankings. These results, which were not available until now, will be useful in order to perform better LCIA studies, incorporating the micro-pollutants whose CFs have been estimated, or in order to carry out single hazard/risk environmental impact assessments.

Keywords: Characterization Factor, Ecotoxicity, Human toxicity, Life Cycle Impact Assessment, Pharmaceuticals and Personal Care Products.

1. Introduction

In recent years, pharmaceutical and personal care products (PPCPs) have been found at different levels of concentration in all environmental compartments (air, water and soil), and many of their impacts are still unknown or under analysis. The primary routes of pharmaceuticals into the environment are through human excretion, disposal of unused products and through agricultural usage, but high concentrations of pharmaceuticals have also been reported in treated industrial effluents or recipient waters, through direct discharge from manufacturing companies (Larsson et al. 2007; Larsson, 2014a). A wide range of pharmaceutical products have been detected in surface and groundwater, associated with wastewater disposal (Brausch and Rand, 2011; Ebele et al. 2017; Stuart et al., 2012) but can also be found in soil, sediments (Larsson, 2014b; Xu et al. 2009) and to a lesser extent possibly in the air (Larsson, 2014b).

There is a lot of research in this area, some of which was carried out by Ebele et al. (2017) who presented a review of the current state-of-knowledge on PPCPs in the freshwater aquatic environments (water, sediments and biota) of the five continents. Wu et al. (2009) studied the degradation and adsorption of selected PPCPs in agricultural soils, while Gaw et al. (2014) reviewed the sources, impacts and concentrations of pharmaceuticals in marine and coastal environments, among many others. In the specific case of personal care products (PCPs), Tolls et al. (2009) indicated that considerable amounts of these compounds are utilized each day, resulting in large quantities of chemical substances that could potentially reach environmental compartments, particularly water, but also soil and air.

Currently, there are thousands of PPCPs which are available on the market and are used daily, and they can be released into the environment individually, although in most cases they tend to be released in ever-changing mixtures, whose effects can be synergetic or antagonistic, so the possibility of knowing the potential impact that all these compounds and their mixtures might generate in nature is almost impossible, without spending a large amount of money, resources and time.

The effects of PPCPs in the environment are very diverse, these compounds can be persistent, bioaccumulable and can cause acute and chronic human and ecotoxicological damage. Therefore, the interest in knowing the ecotoxicological effects of PPCPs on the environment has increased

in the last years. Some authors (Brausch and Rand, 2011; Cleuvers, 2003, 2004; Daughton and Brooks, 2010; Fent et al., 2006; Sanderson et al., 2004a; Santos et al., 2010; Vasquez and Fatta-Kassinos, 2013) have reported ecotoxicogical data from different types of assays (for single PPCP or their mixtures) including different species (trophic levels), times of exposure (chronic, subchronic or acute) and endpoints (Half maximal effective concentration, EC_{50}; concentration which causes the death of 50% of the sample population, LC_{50}; Non observed adverse effect level, NOAEL; Lowest observed adverse effect level, LOAEL).

Although there is a great variety of analyses and tests to bring into evidence the negative effect of PPCPs on the environment, it is necessary to have different methods of predicting these effects, due to the large number of these types of compounds, and the diverse ways that they can be found in the environment.

A large number of tools for predicting the impact of a process, activity or contaminant in the environment are currently available. One of them is the Life Cycle Assessment (LCA), which allows the estimation of the potential impacts of such compounds on human health, ecosystems and resources. LCA has been extended to many aspects of production and consumption, including eco-design of products, cleaner production, environment labels, green purchase, resource management, wastes management and environment strategy, etc. (Nie et al., 2010), and therefore, LCA is gradually gaining acceptance as an efficient tool for the environmental evaluation of the potential impact of chemicals and chemical processes. LCA does not substitute other methodologies (such as environmental risk assessment, or the ratio between predicted environmental concentration and the predicted no effect concentration etc.) since the different tools fulfill different purposes and they can, in fact, play complementary roles and benefit from each other (Muñoz et al., 2008). Kobayashi et al. (2015) proposed the combination of LCA and quantitative risk assessment (QRA) with different hybridization approaches, taking into account that LCA is useful in the evaluation of global impacts and QRA in local impacts.

The guidelines of LCA studies are established in the standard series of ISO 14040, and more specifically in the ISO 14040:2006 and 14044:2006 standards (ISO, 2006). LCA methodology can be a powerful tool: (i) to identify the type of impact (on renewable or non-renewable

resources, global warming, ozone depletion, toxicity, acidification, energy and water use, among others) of diverse compounds in different environmental scenarios; (ii) to compare these impacts with those from other compounds; (iii) to implement preventive or corrective actions to minimize the potential or real adverse effect caused by them.

The life cycle impact assessment (LCIA) phase of a LCA study requires not only the data from the emissions inventory, but also the characterization factors (CFs, alternatively referred to as equivalency factors) to provide indicators in the context of various impact categories (such as global warming, stratospheric ozone depletion, tropospheric ozone creation, eutrophication/nitrification, acidification, toxicological impacts on humans, and toxicological impacts on ecosystems) (Pennington et al., 2004).

Knowledge of CFs is mainly essential for determining/estimating the human and ecological potential impact of chemicals on different environments (air, freshwater, seawater, natural soil, agricultural soil, etc.) and they must be included in the LCIA stage of LCA studies.

CFs are also used to determine the relative importance of a substance to toxicity related impact categories, such as human toxicity or ecotoxicity in LCA studies. The CFs accounts for the environmental persistence (fate), accumulation in the human food chain (exposure) and toxicity (effect) of a chemical. Fate and exposure factors can be calculated by means of "evaluative" multimedia fate and exposure models, while effect factors can be derived from ecotoxicity data on human beings and laboratory organisms (Huijbregts et al. 2005a).

In this sense, the USEtox™ model, which has been developed as a result of a Task Force on Toxic Impacts under the UNEP-SETAC Life Cycle Initiative, is a powerful tool for calculating CFs. It is a way to characterize human and ecotoxicological impacts in LCIA and comparative risk assessment (CRA) analysis. USEtox™ was designed to describe the fate, exposure and effects of chemicals (Huijbregts et al., 2010a).

USEtox™ provides a parsimonious and transparent tool for human health and ecosystem CFs estimation. Based on a referenced database, it can be used to calculate CFs for several thousands

of substances and forms the basis of the recommendations from UNEP-SETAC's Life Cycle Initiative regarding the characterization of toxic impacts in LCA (Rosenbaum et al., 2008).

Despite the large number of substances that have been considered in the USEtox™ database (more than 3000 in the USEtox™ organic database 1.01), only a small amount of these compounds are PPCPs (approximately sixty compounds of the organic database correspond to PPCPs). Therefore, the CFs of many PPCPs have not yet been calculated.

LCIA conducted in systems with PPCPs may be incomplete or unrealistic if these compounds are not considered. Therefore, the estimation of CFs is a very important issue and a novel contribution in this research field.

For this reason, Alfonsín et al. (2014) provide CFs for the toxicity related impact categories in LCA for 23 PPCPs. Some of the CFs already available in databases were updated (11 compounds) whereas others were implemented for the first time by means of USEtox™ (12 compounds) and USES-LCA 2.0 methodologies. They cited only five previous studies that calculated a limited number of PPCPs' CFs by different methodologies. More recently, Roos et al. (2017), provided a set of 72 CFs, calculated with USEtox™, for some of the most common textile chemicals, in order to include them in LCA studies for this type of industry. This indicates that there is still a lack of data on the CFs of many compounds, which, therefore, cannot be included in LCA studies.

Hence, in this paper, the CFs for 27 PPCPs have been calculated following the USEtox™ methodology, to complement its own database and thus be able to incorporate these compounds into LCIA studies. Six compartments were considered as to which type of emission can take place (continental urban air, continental rural air, continental freshwater, coastal seawater at continental scale, continental natural soil and continental agricultural soil) and toxicity potentials were estimated for two different impact categories: human health and freshwater aquatic environments, according to the scope of USEtox™ design.

Additionally, using the new CFs calculated in this work, those CFs existing in the software database of USEtox™, the new CFs calculated by Alfonsín et al. (2014) and the data of occurrence (emissions) of PPCPs in the aquatic environments in Spain (Ortiz et al., 2013a), the human toxicity and ecotoxicity impact scores (IS) for 49 PPCPs have been estimated. These ISs have

been used to develop and analyze ranking scores from CFs and then, compare the relative toxicity between these compounds and compare with other ranking of concern such as the established in Ortiz et al. (2013b).

2. Materials and methods

The main steps carried out for the realization of this work are summarized below. The procedure for collecting the input parameters, the equations used, the run of the software and the results analysis of the USEtox™ model were carried out according to the published literature (Huijbregts et al., 2005a; 2005b; 2010a; 2010b; Rosenbaum et al., 2008) and are shown in Figure 1

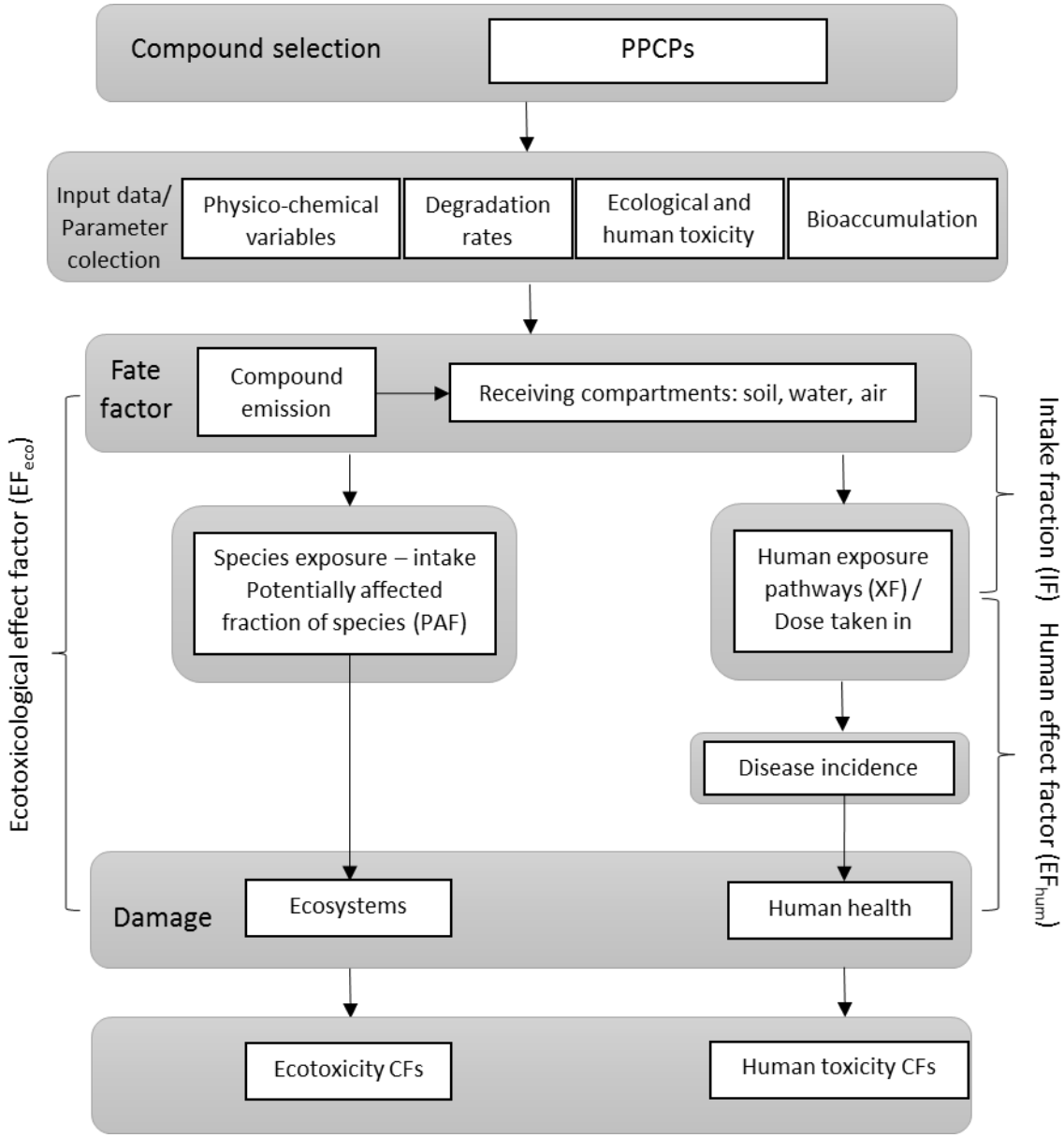

Figure 1. Flow diagram of main steps for the calculation of CFs.
Adapted from Huijbregts et al. (2010)

USEtox™ considers environmental compartments to be well-mixed boxes that contain and exchange contaminant mass. Their total mass, total volume, solid-phase mass, liquid-phase mass and gas-phase mass, describe the compartment. Contaminants move between, and are transformed within compartments through a series of transport and transformation processes that can be represented mathematically by first-order processes, which depend on the physicochemical characteristics of the chemicals modelled. In each compartment, different factors are considered

in the USEtox™ model: persistence, transportation between compartments by cross-media transfers (dispersive, advective as volatilization, precipitation, etc.), transformation by a physical, chemical, or biological degradation process, or the irreversible removal from a compartment by leaching and/or burial (Fantke et al. 2017). All these considerations, and the values and parameters that emerge from them, define the final results of CFs and the differences observed between compartments.

It is necessary to highlight that the USEtox™ program has limitations that should be considered when it is used. The primary outputs of USEtox™ are characterization factors for human toxicity and freshwater ecotoxicity; other impact categories are not considered. This assumes that the compartments are homogeneous. It does not account for speciation or other potentially important specific processes for metals, metal compounds and certain types of organic chemicals. It does not allow for the degradation of vegetation in the exposure model, and there are uncertainties regarding input data (Fantke et al. 2017).

2.1. Selection of PPCPs

Similar to our previous pieces of research (Ortiz et al. 2013a, 2013b; 2014), the PPCPs selected are some of the most worldwidely important pharmaceutical active compounds (PhACs) and PCPs. Their consumption and occurrence in aquatic environments and in wastewater treatment plants (WWTPs) is relevant, and there is evidence of their potential ecotoxicity in the different compartments of the environment.

Ortiz et al. (2013a) found that acetaminophen, amoxicillin, valsartan, omeprazole, clarithromycin, galaxolide, tonalide, iopromide and iohexol (among other compounds) had the highest level of occurrence in the Spanish aquatic environment. Additionally, in Ortiz et al. (2013b) a persistence, bioaccumulation and toxicity ranking score was carried out, and some of the compounds found at the top were: galaxolide, tamoxifen, sertraline, atorvastatin, tonalide, triclosan, irbesartan, fluoxetine, paroxetine and 17-α ethynylestradiol. When occurrence level was considered in the ranking score, tamoxifen was highlighted. In general, Ortiz et al. (2013b) found that fragrances,

hormones, antidepressants, anxiolytics and blood lipid regulators presented the highest levels of risk. On the other hand, an environmental risk assessment of 26 PPCPs were done by Ortiz et al. (2014) with both new and current ecotoxicity values, and at least half of the compounds being studied were cataloged as being harmful to aquatic organisms, among them: triclosan, omeprazole, methylparaben, ethylparaben, propylparaben, clofibrate, ciprofloxacin, clarithromycin, diclofenac, naproxen and norfloxacin. Nevertheless, it is necessary to emphasize that some CFs of the PPCPs are already in the USEtox^{TM} database and are not included in this study because there is no new data (according to our knowledge) that would make it possible to update these values.

Therefore, twenty seven PPCPs were chosen in order to have their first, new CFs calculated, for subsequent use in LCA studies. These compounds can be seen in the first row of Table 1. With the purpose of fulfilling the second goal of this study (to estimate the human toxicity and ecotoxicity ISs in the Spanish case study), twenty two values of CFs (calculated with the same tool, USEtox^{TM}) were taken from the bibliography (Alfonsin et al., 2014 and the database of USEtox^{TM}) in order to make a comparative study of ISs with as many compounds as possible (second and third row in Table 1). Therefore, a total of 49 compounds from 14 different therapeutic classes have been considered in this study: analgesic/antipyretic (1), angiotensin converting enzyme inhibitor (1), angiotensin receptor blockers (2), antibiotics (11), antidepressants (3), antiepileptics (4), anxiolytics (3), blood lipid regulators (3), cytostatics/cancer therapeutic (2), H_2 blocker (1), hormones (4), platelet inhibitor (1), non-steroidal anti-inflammatory drugs (NSAIDs)/antirreumatics (4), X-ray contrast media (3) and PCPs (6).

Table 1. Pharmaceutical and personal care products under study

Compounds	Reference
Acetaminophen, alprazolam, amoxicillin, atorvastatin, azithromycin, bromazepam, cefaclor, ciprofloxacin, clarithromycin, enalapril, ethylparaben, gabapentine, iohexol, iopamidol, irbesartan, ketorolac, levofloxacin, lorazepam, methylparaben, norfloxacin, omeprazole, paroxetine, pregabalin, propylparaben, sertraline, simvastatin and valsartan.	This study*
17α-ethinylestradiol, 17β-estradiol, carbamazepine, diclofenac, erythromycin, estrone, galaxolide, ibuprofen, iopromide, naproxen, roxythromycin, sulphametoxazole, tonalide, triclosan, trimethoprim.	Alfonsin et al. (2014)**
Clofibrate, cyclophosphamide, fluoxetine, salicylic acid, tamoxifen, testosterone, valproic acid.	USEtox^{TM} database**

***** For these compounds, new CFs, human toxicity and ecotoxicity IS have been estimated.
**For these compounds, human toxicity and ecotoxicity IS have been estimated, and CFs have been taken from references.

2.2. Characterization factor

The potential for increasing the ecological and human toxicities is estimated through the CFs of chemicals that are computed as the result of the product of three factors: a fate factor (FF), an exposure factor (XF) and an effect factor (EF) (See Table 2, Eq. 2 and 7). FF, XF and EF are related, as is shown in the methodology presented by Huijbregts et al. (2010a). The FF and EF are combined to reflect the intake fraction (iF) of a chemical, representing the fraction of the emitted mass that enters the human population (Eq. 8, Table 2).

USEtox^{TM} CFs for ecotoxicity are reported for freshwater aquatic ecotoxicological effects, and include the impacts of emissions into urban air, rural air, freshwater and/or agricultural soil in different scales. CFs for human toxicity are estimated for carcinogenic and non-carcinogenic effects, and consider emissions on different scales.

In order to make USEtox^{TM} CFs compatible with the needs of LCA, the units for human toxicity are expressed as cumulative cases of either cancer or non-cancer health outcomes per kg of contaminant emission, (cases·$kg_{emmited}^{-1}$), and, for freshwater aquatic ecotoxicity impacts, as the potentially affected fraction (PAF) of aquatic species integrated over the exposed water volume (m^3), time (day) and per kg emitted (PAF·m^3·d·$kg_{emmited}^{-1}$) (Fantke et al., 2017).

2.2.1. Fate factor

The fate factor (FF) is the same for ecotoxicity and human toxicity. Two geographical scales are specified in the USEtox™ model: (i) the continental scale with the following compartments: urban air, rural air, freshwater, sea, natural soil and agricultural soil; and (ii) the global scale with the following compartments, air, freshwater, ocean, natural soil and agricultural soil. The continental scale is nested in the global scale. "Nested" means that chemicals can be transported from one scale to a higher scale and vice versa (Huijbregts et al., 2010a).

The fate factor is equal to the compartment-specific residence time (in days) of a chemical. The longer the residence time, the longer a chemical remains in the environment. Within the consensus model, the residence time of a chemical depends on (i) the properties of the chemical, (ii) the selected emission compartment, and (iii) the selected receiving compartment.

The fate routine of USEtox™ model calculates the residence time of a chemical, by solving the mass balance under steady state conditions with the help of linear algebra calculation rules, and is based on the quantification of environmental processes such as: (bio) degradation by micro-organisms, transport of the chemical to the sediment, leaching into the groundwater and escape to the stratosphere (removal processes) and intermedia transport processes (advective and diffusive transport).

Table 2. Main parameters and equations used in the USEtox™ model for ecotoxicity[+] and human toxicity.

Life cycle impact assessment for ecotoxicity			
Parameter (Notation)	**Units**	**Equation (Nº)**	**Explanation[+]**
Toxicity impact score (IS_{eco})	$PAF^{++}\cdot m^3\cdot day$ or CTU_e^{+++}	$IS_{eco} = \sum_i \sum_x CF_{x,i} \cdot M_{x,i}$ (1)	IS_{eco}: Impact score for ecotoxicity. $CF_{x,i}$: Ecotoxicity characterization factor of substance *x* released to compartment *i*. $M_{x,i}$: Emission of *x* to compartment *i* (kg). The summation holds for substances and emission compartments.
Characterization factor (CF_{eco})	$PAF\cdot m^3\cdot day\cdot kg_{emission}^{-1}$ or $CTU_e\cdot kg^{-1}$	$CF_{eco} = FF_{eco} \cdot XF_{eco} \cdot EF_{eco}$ (2)	FF_{eco}: Ecotoxicity fate factor (day). XF_{eco}: Ecotoxicity exposure factor (unitless). EF_{eco}: Ecotoxicity effect factor ($PAF\cdot m^3\cdot kg^{-1}$).
Fraction of a chemical dissolved in freshwater ($FR_{w.w}$)	(unitless)	$FR_{w.w} = \frac{1}{1+(K_p\cdot SUSP+K_{doc}\cdot DOC+BCF_{fish}\cdot BIOmass)/10^6}$ (3)	The XF_{eco} for freshwater ecotoxicity is the $FR_{w.w}$. Kp: Partition coefficient between water and suspended solids ($L\cdot kg^{-1}$). SUSP: Suspended matter concentration in freshwater (15 $mg\cdot L^{-1}$ in USEtox™). K_{doc}: Partitioning coefficient between dissolved organic carbon and water ($L\cdot kg^{-1}$). DOC: Dissolved organic carbon concentration in freshwater (5 $mg\cdot L^{-1}$ in USEtox™). BCF_{fish}: Bioconcentration factor in fish ($L\cdot kg^{-1}$). BIOmass: Concentration of biota in water (1 $mg\cdot L^{-1}$ in USEtox™).
Ecotoxicity effect factor (EF_{eco})	$PAF\cdot m^3\cdot kg^{-1}$	$EF_{eco} = \frac{0.5}{HC_{50}}$ (4)	The EF_{eco} reflects the change in the PAF of species due to change in ecotoxicant concentration. In USEtox™, the EF_{eco} is calculated by determining the linear slope along the concentration–response relationship up to the point where the fraction of effected species is 0.5. HC_{50}: Hazardous concentration of chemical at which 50% of the species are exposed above their EC_{50} ($kg\cdot m^{-3}$), based on species-specific EC_{50} data. EC_{50}: Water concentration at which 50% of a population displays an effect (e.g. mortality). Aquatic EF_{eco} is calculated based on geometric means of single species EC_{50} tests data. Chronic values have priority as long as they represent measured EC_{50} values but chronic EC_{50} values are seldom reported. Second-order priority is given to acute data, applying an acute-to-chronic extrapolation factor that is set to a default factor of 2.
log HC_{50} (α)	log ($kg\cdot m^{-3}$)	$\propto = \frac{1}{n_s}\cdot \sum_s logEC_{50_s}$ (5)	n_s: Number of species.

[+]Huijbregts et al. (2005b); Huijbregts et al. (2010a); Huijbregts et al. (2010b); Rosenbaum et al. (2008).

[++]PAF = Potentially affected fraction.

[+++]CTU = Comparative Toxic Units

Table 2. Cont. Main parameters and equations used in the USEtox™ model for ecotoxicity[+] and human toxicity.

Life cycle impact assessment for human toxicity			
Parameter (Notation)	**Units**	**Equation (Nº)**	**Explanation[+]**
Toxicity impact score (IS_{hum})	Cases or CTU_h [+++]	$IS_{hum} = \sum_i \sum_x CF_{x,i,hum} \cdot M_{x,i}$ (6)	IS_{hum}: Impact score for human toxicity. $CF_{x,i,hum}$: Human toxicity characterization factor of substance *x* released to compartment *i* . $M_{x,i}$: Emission of *x* to compartment *i* (kg). The summation holds for substances and emission compartments.
Characterization factor (CF_{hum})	Cases·kg^{-1} or CTU_h·kg^{-1}	$CF_{hum} = FF_{hum} \cdot XF_{hum} \cdot EF_{hum} = = iF \cdot EF_{hum}$ (7)	In USEtox™, chemicals that have a potential to increase human disease have a CF_{hum} that includes a fate factor (FF_{hum}), an exposure factor (XF_{hum}) and an effect factor (EF_{hum}) similar than ecotoxicity. Both the human and ecotoxicity CFs are calculated using standard matrix algebra.
Intake factor (iF)	kg_{intake}·$kg_{emitted}^{-1}$	$iF = FF_{hum} \cdot XF_{hum}$ (8)	iF: Intake fraction, fraction of the emitted mass that enters the human population. Intake through inhalation and ingestion is commonly considered in iF calculations.
Exposure factor via inhalation of air ($XF_{hum,air}$)	day^{-1}	$XF_{hum,air} = \frac{INH \cdot POP}{Volume_{air}}$ (9)	INH: Average inhalation rate of a person (13 m^3·day^{-1} in USEtox™). POP: Population number (e.g. 900 million on the continental scale). $VOLUME_{air}$: Volume of the air compartment (e.g. $5.76 \cdot 10^{10}$ m^3 at the urban scale).
Exposure factor for a specific food or drinking water at a specific scale (e.g. continent) ($XF_{hum,i,r}$)	day^{-1}	$XF_{hum,i,r} = \frac{BAF_{i,r} \cdot PROD_i \cdot POP}{MASS_r}$ (10)	$BAF_{i,r}$: Bioaccumulation factor of the chemical of exposure pathway *i* (e.g. fish) via compartment r (e.g. freshwater) (kg·kg^{-1}). $PROD_i$: Production per person of item i in the exposure pathway (e.g. 0.04 kg·person·day^{-1} for freshwater fish). $MASS_r$: Mass of compartment r (e.g. $6.8 \cdot 10^{14}$ kg for continental freshwater).
Human-toxicological effect factor of a chemical (EF_{hum})	Cases·kg_{intake}^{-1}	$EF_{hum} = \frac{0.5}{ED_{50}}$ (11)	EF_{hum}: Reflects the change in life time disease probability due to change in life time intake of a pollutant. In USEtox™, separate EFs are derived for non-carcinogenic effects and carcinogenic effects. Furthermore, for each effect type (non-carcinogenic and carcinogenic) the two exposure routes, i.e. inhalation and ingestion are addressed separately. The EF_{hum} is calculated under the assumption of linearity in concentration–response up to the point at which the life time disease probability is 0.5.
Daily dose for a chemical per person (human) in its lifetime for carcinogenic and non-carcinogenic effects related to inhalation or oral exposure ($ED_{50h,j}$)	kg·person^{-1}·lifetime^{-1}	$ED_{50_{h,j}} = \frac{ED_{50_{a,t,j}} \cdot BW \cdot LT \cdot N}{AF_a \cdot AF_t \cdot 10^6}$ (12)	$ED_{50a,\,t,j}$: Daily dose for animal *a* (e.g. rat) and time duration *t* (e.g. subchronic) per kg body weight that causes a disease probability of 50% for exposure route *j* (mg·kg^{-1}·day^{-1}). AF_a: Extrapolation factor for interspecies differences*. AF_t: Extrapolation factor for differences in time of exposure (i.e. a factor of 2 for subchronic to chronic exposure and a factor of 5 for subacute to chronic exposure). BW: Average body weight of humans (70 kg·person^{-1}). LT: Average lifetime of humans (70 years·lifetime^{-1}). N: Number of days per year (365 days year^{-1}).

[+]Huijbregts et al. (2005b); Huijbregts et al. (2010a); Huijbregts et al. (2010b); Rosenbaum et al. (2008).
[+++]CTU_h = Human Comparative Toxic Units

Table 2. Cont. Main parameters and equations used in the USEtox™ model for ecotoxicity[+] and human toxicity.

Life cycle impact assessment for human toxicity			
Parameter (Notation)	**Units**	**Equation (Nº)**	**Explanation[+]**
Daily dose for a chemical per person in its lifetime for carcinogenic and non-carcinogenic effects related to inhalation exposure ($ED_{50\ h,inh}$)	kg·person^{-1}·lifetime^{-1}	$ED_{50_{h,inh}} = \frac{ED_{50_{a,t,inh}} \cdot INH \cdot LT \cdot N}{AF_a \cdot AF_t \cdot 10^6}$ (13)	$ED_{50a,t,inh}$: Concentration in air (mg·m^{-3}) which has been exposed to an animal *a* and time duration *t*. INH: Average human inhalation rate (13 m^3·day^{-1}). AF_a[§]: The extrapolation factor for interspecies differences is by default 1 if the ED_{50} is given as concentration in the air. Metabolic activity and inhalation rate are assumed to have the same ratio for all species.
Daily dose for animal *a* and time duration *t* per kg body weight that causes carcinogenic effects of 50% for exposure route *j* ($ED_{50\ a,t,j(cancer)}$)	mg·kg^{-1}·day^{-1}	$ED_{50_{a,t,j(cancer)}} = \frac{1}{q^*_{a,t,j}} \cdot AF_q$ (14)	For carcinogenic effects, the ED_{50} can also be estimated from the carcinogenic, low-dose, slope factor q* by the 1/q*-to-ED_{50} extrapolation factor. $q^*_{a,t,j}$: Carcinogenic, low-dose, slope factor for animal *a* (e.g. rat) and time duration *t* (e.g. chronic) for exposure route *j* (kg·day·mg^{-1} or m^3·mg^{-1}). AF_q: Extrapolation factor for 1/q* to ED_{50}, which is a factor of 0.8.
Daily dose for animal *a* and time duration *t* per kg body weight that causes non-carcinogenic effects of 50% for exposure route *j* ($ED50_{a,t,j(non\text{-}cancer)}$)	mg·kg^{-1}·day^{-1}	$ED_{50_{a,t,j\ (non-cancer)}} = NOAEL_{a,t,j} \cdot AF_N$ (15)	For non-carcinogenic effects, the ED_{50} can also be estimated from the No-Observed Adverse Effect Level (NOAEL) by a NOAEL-to-ED_{50} extrapolation factor. $NOAEL_{a,t,j}$: Daily dose per kg body weight or concentration for animal *a* (e.g. rat) and time duration *t* (e.g. chronic) that causes No Observed Effects for exposure route *j* (mg·kg^{-1}·day^{-1} or mg·m^{-3}). AF_N: Extrapolation factor for NOAEL to ED_{50}, which is a factor of 9.
LOAEL-to-NOAEL extrapolation	mg·kg^{-1}·day^{-1}	$NOAEL_{a,t} = \frac{LOAEL_{a,t}}{AF_L}$ (16)	For some chemicals, only the Lowest Observed Adverse Effect Level (LOAEL) is available. $LOAEL_{a,t}$: Daily dose per kg body weight or concentration for animal *a* and time duration *t* that causes Lowest Observed Adverse Effect level. In these cases, the NOAEL can be derived by a LOAEL-to-NOAEL extrapolation factor. AF_L: Extrapolation factor from LOAEL to NOAEL, which is a factor of 4.

[+]Huijbregts et al. (2005b); Huijbregts et al. (2010a); Huijbregts et al. (2010b); Rosenbaum et al. (2008).
[§]Human=1.0. Dog=1.5. Rabbit=2.4. Rat=4.1. Mouse=7.3.

2.2.2. Exposure factor

The exposure factor for ecotoxicity (XF_{eco}) is calculated by Eq. 3 (Table 2). According to Huijbregts et al. (2010a), CFs for human toxicity reflect the rate at which a pollutant is able to transfer from a receiving compartment into the human population through a series of exposure pathways: air (inhalation), drinking water, above-ground leaf crops (including fruit and cereals), crops below ground (root crops), meat, dairy products, fish. For exposure via inhalation of air, the exposure factor $XF_{hum,air}$ is calculated by Eq. 9 (Table 2) and the exposure factor for a specific food item or drinking water on a specific scale (e.g. continent) $XF_{hum,i,r}$ is calculated by Eq. 10 (Table 2).

2.2.3. Effect factor

The ecotoxicological EF is estimated by Eq. 4 and Eq. 5 (Table 2). In this study, acute and chronic data were used to estimate this parameter. The US EPA ECOTOX database (US EPA, 2015) was consulted as the first option, but when data were not found, other pieces of research were consulted (Dobbins et al., 2009; Iannacone and Alvariño, 2009; Ortiz et al., 2014; Santos et al., 2010; Terasaki et al., 2009) or the ecotoxicity of chemicals was estimated by the EPI Suite™ software (US EPA, 2012). According to Huijbregts et al. (2010b) aquatic ecotoxicological CFs are specified as "interim", if EFs are based on species toxicity data covering less than three different trophic levels. This is to ensure a minimum variability of biological responses. In this study, at least three trophic levels (algae, crustaceans and fish for all compounds, and in some cases, data of bacteria, molluscs and rotifers when are available) have been considered in order to calculate ecotoxicological EF; therefore, the ecotoxicological CFs calculated may be considered as "recommended".

The human-toxicological EF reflects the change in lifetime disease probability, due to the change in lifetime intake of a pollutant. The USEtox™ model considers two separate effect factors, which are derived from non-carcinogenic and carcinogenic effects. Furthermore, for each effect type (non-carcinogenic and carcinogenic) the two exposure routes, i.e. inhalation and ingestion, are addressed separately (Huijbregts et al. 2010a). In the present study, carcinogenic and non-carcinogenic effects, and ingestion as the only route of exposure, are considered (due to the lack

of data for inhalation as a route of exposure); thus, the CFs of human toxicity calculated in this research should be taken as "interim". Equations 11 to 16 (Table 2) are used to calculate the human-toxicological EFs. The summary of the calculation is as follow: results of chronic exposure in different animals were converted to ED_{50} ($mg \cdot kg^{-1} \cdot d^{-1}$) and then it was transformed into $kg \cdot person^{-1} \cdot lifetime^{-1}$ with equations 12, 13, 14, 15 and 16 (Table 2). For each PPCP, the geometric mean of these values was calculated and finally, the effect factor was determined with equation 11 (Table 2).

2.2.4. Input data

Table 3 shows the input parameters that must be supplied by the user to the USEtox™ program in order to estimate the CFs of the 27 PPCPs. These parameters are molecular weight (MW), partition coefficient between octanol and water (K_{ow}), partition coefficient between organic carbon and water (K_{oc}), Henry law coefficient at 25ºC (K_H), vapor pressure at 25ºC (P_{vap}), solubility at 25ºC (Sol), degradation rate in air (K_{degA}), degradation rate in water (K_{degW}), bioaccumulation factor of the chemical (BAF), water ecotoxicity (as HC_{50}) and human carcinogenic and non-carcinogenic effects of compounds under study ($ED_{50ing,\ NonCancer}$ and $ED_{50ing,\ Cancer}$).

In this study, whenever possible, the experimental values of physicochemical properties (MW, K_{ow}, K_{oc}, K_H, P_{vap} and Sol) and BAF have been taken. However, when this was not possible, estimated values from EPI Suite™ were used as recommended by Huibregts et al. (2010a, 2010b). For air degradation rates, experimental values for the hydroxyl radical rate constant (K_{OH}) are available for some chemicals in EPI Suite™. To derive the K_{degA}, the K_{OH} was multiplied by the hydroxyl radical concentration [OH•]. The default [OH•] was set at $1.5 \cdot 10^6$ molecules $(radicals) \cdot cm^{-3}$ per 12h of daylight (US EPA, 2012). K_{degW}, soil (K_{degSl}) and sediment (K_{degSd}) were estimated by biodegradation half-life with EPI Suite™, and the Biowin3 model is used for USEtox™ input to convert the ultimate biodegradation probability into half-lives for all chemicals in the database. In addition, division factors of 1:2:9 are used to extrapolate biodegradation rates for water, soil and sediment compartments respectively, as is suggested in EPI Suite™ (Huijbregts et al., 2010b).

Water ecotoxicities for different species and trophic levels (bacteria, algae, crustacean, rotifer, mollusc and fish) were collected, as was explained in the effect factor section. The calculation steps of the $logHC_{50}$ (α) according to Huijbregts et al. (2010a) are: (i) gather experimental or estimated EC_{50} data for the chemical of interest; (ii) specify for every EC_{50}-value whether it is chronic or acute exposure; (iii) calculate the geometric mean chronic or acute EC_{50} for every individual species (in case of acute EC_{50}-data, derive the chronic-equivalent EC_{50} per species by dividing by a factor of 2, acute-to-chronic extrapolation factor) and (iv) take the log of the geometric mean EC_{50}s and calculate the average of the log-values (this average equals the $logHC_{50}$).

Non-carcinogenic data for rat, mouse, rabbit, dog and monkey were collected from different sources (World Health Organization database, European Agency for the Evaluation of Medicinal Products (EMEA) reports, toxicology studies of the US Food and Drugs Administration (FDA), reports of Scientific Committee on Consumer Safety of European Commission, United States Pharmacopeia monographs, material safety data sheet of Merck, Pifzer, Medsafe and La Roche and Rashmi et al., 2012). From these sources, the daily dose that causes a disease probability of 50% of population (ED_{50}) was estimated from NOAEL or the LOAEL (chronic toxicity data). Carcinogenic data (as ED_{50}) was obtained from Brambilla et al. (2012).

In this study, the steps undertaken for the ED_{50} estimation according to Huijbregts et al. (2010a) guidelines were: (i) gather experimental non-carcinogenic oral ED_{50} data, (ii) specify for every ED_{50}-value whether it is chronic, subchronic or subacute exposure; (iii) as the chronic value is needed, subchronic and subacute data have to be extrapolated to chronic ED_{50}. According to the type of ED_{50}-data found in the literature or database (non-human ED_{50}-data, NOAEL or LOAEL), the chronic-equivalent ED_{50} must be derived using equations 12 to 16 (Table 2).

The USEtox™ software calculates the remainder of the necessary data from the input parameters referred to above, supplied by the user. More information about procedure, equations, considerations, estimations and the methodology can be consulted in the main literature that supports this software (Huijbregts et al., 2005a; 2005b; 2010a; 2010b; Rosenbaum et al., 2008).

Table 3. Input parameters required for the ecotoxicological and human toxicity characterization factors calculation in USEtox^{TM} for the pharmaceuticals and personal care products under study

Compound	CAS	Physicochemical parameters						Degradation rates				Ecotoxicity	Human Toxicity•		Bioaccumulation
		MW*	K_{ow}**	K_{oc}***	K_H+	P_{vap}++	Sol.+++	K_{degA}†	K_{degW}††	K_{degSd}†††	K_{degSl}††††	α‡	$ED50_{ing, NonCancer}$••	$ED50_{ing, Cancer}$••	BAF•••
		g/mol		L kg^{-1}	Pa m^3 mol^{-1}	Pa	mg L^{-1}	s^{-1}	s^{-1}	s^{-1}	s^{-1}	log (mg L^{-1})	kg/lifetime/person	kg/lifetime/person	L kg^{-1}
Acetaminophen	103-90-2	151.17	2.88	45.09	$6.51\cdot10^{-8}$	$2.59\cdot10^{-4}$	14000	$2.65\cdot10^{-5}$	$5.30\cdot10^{-7}$	$5.89\cdot10^{-8}$	$2.65\cdot10^{-7}$	1.8800	673	NC	0.98
Alprazolam	28981-97-7	308.77	131.82	98320	$5.19\cdot10^{-5}$	$2.21\cdot10^{-6}$	13.10	$1.14\cdot10^{-5}$	$2.10\cdot10^{-7}$	$2.33\cdot10^{-8}$	$1.05\cdot10^{-7}$	-0.4360	8.11	NC	14.10
Amoxicillin	26787-78-0	365.41	7.41	108.40	$2.52\cdot10^{-16}$	$6.26\cdot10^{-15}$	4000.00	$2.08\cdot10^{-4}$	$2.10\cdot10^{-7}$	$2.33\cdot10^{-8}$	$1.05\cdot10^{-7}$	1.7800	1960	NC	1.10
Atorvastatin	134523-00-5	558.66	2290867	28570	$4.64\cdot10^{-17}$	$9.26\cdot10^{-23}$	0.0011	$3.42\cdot10^{-4}$	$1.30\cdot10^{-7}$	$1.44\cdot10^{-8}$	$6.50\cdot10^{-8}$	-0.6160	30.70	1.23	104.00
Azithromycin	83905-01-5	749.00	10471	3135.00	$4.27\cdot10^{-18}$	$3.53\cdot10^{-22}$	0.0620	$6.35\cdot10^{-4}$	$4.50\cdot10^{-8}$	$5.00\cdot10^{-9}$	$2.25\cdot10^{-8}$	0.0669	16.20	NC	12.50
Bromazepam	1812-30-2	316.16	112.20	3605.00	$4.57\cdot10^{-7}$	$2.53\cdot10^{-7}$	175.20	$8.68\cdot10^{-6}$	$1.30\cdot10^{-7}$	$1.44\cdot10^{-8}$	$6.50\cdot10^{-8}$	0.7080	103.00	NA	9.94
Cefaclor	53994-73-3	367.81	2.24	104.30	$9.15\cdot10^{-13}$	$2.96\cdot10^{-13}$	10000	$2.02\cdot10^{-4}$	$2.10\cdot10^{-7}$	$2.33\cdot10^{-8}$	$1.05\cdot10^{-7}$	3.0600	2680.00	NC	0.98
Ciprofloxacin	85721-33-1	331.35	1.91	10.00	$1.10\cdot10^{-12}$	$3.80\cdot10^{-11}$	30000	$4.70\cdot10^{-4}$	$1.30\cdot10^{-7}$	$1.44\cdot10^{-8}$	$6.50\cdot10^{-8}$	0.4450	506.00	NA	0.98
Clarithormycin	81103-11-9	747.97	1445.44	149.40	$6.77\cdot10^{-20}$	$3.10\cdot10^{-23}$	0.3420	$5.97\cdot10^{-4}$	$4.50\cdot10^{-8}$	$5.00\cdot10^{-9}$	$2.25\cdot10^{-8}$	-0.1480	344.00	NA	15.30
Enalapril	75847-73-3	376.46	1.17	348.50	$2.92\cdot10^{-10}$	$1.41\cdot10^{-10}$	16400	$1.77\cdot10^{-4}$	$5.30\cdot10^{-7}$	$5.89\cdot10^{-8}$	$2.65\cdot10^{-7}$	2.0000	353.00	NC	0.916
Ethylparaben	120-47-8	166.18	295.12	162.18	$4.86\cdot10^{-4}$	$1.24\cdot10^{-2}$	885.00	$1.89\cdot10^{-5}$	$5.30\cdot10^{-7}$	$5.89\cdot10^{-8}$	$2.65\cdot10^{-7}$	0.8930	3930.00	NC	8.15
Gabapentin	60142-96-3	171.24	0.0794	53.14	$9.42\cdot10^{-7}$	$3.91\cdot10^{-8}$	4491.00	$6.02\cdot10^{-5}$	$5.30\cdot10^{-7}$	$5.89\cdot10^{-8}$	$2.65\cdot10^{-7}$	3.5100	981.00	436.22	0.90
Iohexol	66108-95-0	821.15	0.0009	10.00	$4.17\cdot10^{-26}$	$5.41\cdot10^{-27}$	106.50	$1.04\cdot10^{-4}$	$1.30\cdot10^{-7}$	$1.44\cdot10^{-8}$	$6.50\cdot10^{-8}$	4.1000	29.70	NA	0.89
Iopamidol	60166-93-0	777.09	0.0038	10.00	$2.26\cdot10^{-27}$	$1.78\cdot10^{-28}$	140000	$8.66\cdot10^{-5}$	$1.30\cdot10^{-7}$	$1.44\cdot10^{-8}$	$6.50\cdot10^{-8}$	3.1800	68.90	NA	0.89
Irbesartan	138402-11-6	428.54	204173	1337000	$1.17\cdot10^{-9}$	$1.64\cdot10^{-13}$	0.0599	$5.58\cdot10^{-5}$	$2.10\cdot10^{-7}$	$2.33\cdot10^{-8}$	$1.05\cdot10^{-7}$	-1.3100	43.30	NC	2480
Ketorolac	74103-06-3	255.28	208.93	428.80	$8.74\cdot10^{-6}$	$1.96\cdot10^{-5}$	572.30	$3.05\cdot10^{-4}$	$5.30\cdot10^{-7}$	$5.89\cdot10^{-8}$	$2.65\cdot10^{-7}$	0.6960	12.50	NC	22.00
Levofloxacin	100986-85-4	361.38	0.4074	0.99	$1.68\cdot10^{-12}$	$1.31\cdot10^{-10}$	28260	$2.95\cdot10^{-4}$	$4.50\cdot10^{-8}$	$5.00\cdot10^{-9}$	$2.25\cdot10^{-8}$	0.9650	38.20	NC	0.90
Lorazepam	846-49-1	321.16	245.47	944.40	$1.58\cdot10^{-9}$	$4.11\cdot10^{-10}$	80.00	$1.68\cdot10^{-5}$	$1.30\cdot10^{-7}$	$1.44\cdot10^{-8}$	$6.50\cdot10^{-8}$	0.8950	67.10	NC	25.00
Methylparaben	99-76-3	152.15	91.20	86.29	$2.90\cdot10^{-3}$	$1.14\cdot10^{-1}$	2500.00	$1.66\cdot10^{-5}$	$5.30\cdot10^{-7}$	$5.89\cdot10^{-8}$	$2.65\cdot10^{-7}$	1.0600	4480.00	NC	3.88

Norfloxacin	70458-96-7	319.34	0.0933	18.68	$1.99 \cdot 10^{-12}$	$1.11 \cdot 10^{-9}$	177900	$4.82 \cdot 10^{-4}$	$1.30 \cdot 10^{-7}$	$1.44 \cdot 10^{-8}$	$6.50 \cdot 10^{-8}$	1.0200	188.00	NA	0.890
Omeprazole	073590-58-6	345.42	169.82	1455.00	$3.08 \cdot 10^{-14}$	$1.55 \cdot 10^{-9}$	82.28	$1.43 \cdot 10^{-4}$	$1.37 \cdot 10^{-8}$	$1.52 \cdot 10^{-9}$	$6.85 \cdot 10^{-9}$	-0.1690	21.70	3.49	3.46
Paroxetine	61869-08-7	329.37	8912.50	12360	$5.96 \cdot 10^{-5}$	$6.39 \cdot 10^{-6}$	35.27	$2.45 \cdot 10^{-4}$	$1.30 \cdot 10^{-7}$	$1.44 \cdot 10^{-8}$	$6.50 \cdot 10^{-8}$	-0.4580	3.93	4.36	624.00
Pregabalin	148553-50-8	159.23	0.0166	25.05	$2.19 \cdot 10^{-9}$	$2.69 \cdot 10^{-7}$	19630	$6.12 \cdot 10^{-5}$	$5.30 \cdot 10^{-7}$	$5.89 \cdot 10^{-8}$	$2.65 \cdot 10^{-7}$	3.7500	139.00	NC	0.89
Propylparaben	94-13-3	180.21	1096.48	286.60	$1.39 \cdot 10^{-2}$	$4.09 \cdot 10^{-2}$	500.00	$2.11 \cdot 10^{-5}$	$5.30 \cdot 10^{-7}$	$5.89 \cdot 10^{-8}$	$2.65 \cdot 10^{-7}$	0.4330	39.30	NC	15.60
Sertraline	79617-96-2	306.24	194984	170800	$1.36 \cdot 10^{-2}$	$1.56 \cdot 10^{-4}$	3.52	$1.47 \cdot 10^{-4}$	$1.30 \cdot 10^{-7}$	$1.44 \cdot 10^{-8}$	$6.50 \cdot 10^{-8}$	-0.4870	34.20	1.23	50800
Simvastatin	79902-63-9	418.58	47863	10940	$3.09 \cdot 10^{-7}$	$5.65 \cdot 10^{-10}$	0.0300	$3.44 \cdot 10^{-4}$	$2.10 \cdot 10^{-7}$	$2.33 \cdot 10^{-8}$	$1.05 \cdot 10^{-7}$	-0.3970	109.00	5.45	151.00
Valsartan	137862-53-4	435.53	4466.84	22630	$3.38 \cdot 10^{-11}$	$1.09 \cdot 10^{-13}$	1.41	$6.42 \cdot 10^{-5}$	$5.30 \cdot 10^{-7}$	$5.89 \cdot 10^{-8}$	$2.65 \cdot 10^{-7}$	0.2420	3.93	NA	215.00

*Molecular weight.
**Partitioning coefficient between octanol and water.
***Partitioning coefficient between organic carbon and water.
$^{+}$ Henry law coefficient at 25ºC.
$^{++}$ Vapor pressure at 25ºC.
$^{+++}$ Solubility in water at 25ºC.
† Degradation rate in air.
†† Degradation rate in water. Results of BIOWIN3 → Biodegradation rates in USEtox™: Hours →$4.7 \cdot 10^{-5}$; hours to days → $6.4 \cdot 10^{-6}$; days →$3.4 \cdot 10^{-6}$; days to weeks → $9.3 \cdot 10^{-7}$; weeks→ $5.3 \cdot 10^{-7}$; weeks to months →$2.1 \cdot 10^{-7}$; months →$1.3 \cdot 10^{-7}$; recalcitrant →$4.5 \cdot 10^{-8}$.
††† Degradation rate in sediment.
†††† Degradation rate in soil.
‡ log of HC_{50} (HC_{50}: Hazardous concentration of chemical at which 50% of the species are exposed above their EC_{50}. The EC_{50} is the water PPCP concentration at which 50% of a population displays an effect).
•According to the USEtox™ methodology the human toxicity is calculated for carcinogenic and non-carcinogenic effects and for inhalation and ingestion (exposure routes). This table only shows human toxicity for non-carcinogenic effect by ingestion, due to the lack of data of cancer effect and inhalation route. For more information see methodology and discussion section.
•• Daily dose (by ingestion) of PPCP that causes a disease (carcinogenic or non-carcinogenic) probability of 50% in a person in its lifetime.
••• Bioaccumulation factor of the chemical in fish estimated by EPI Suite™ (US EPA, 2012) .
NC No carcinogenic .
NA: Not available

2.3. Spanish toxicity impact scores (IS)

In LCA, a toxicity impact score (IS) is calculated with equations 1 and 6 as reported in Table 2. This value is the summation of the product of mass emitted per emission scenario, by the corresponding toxicity CF, taking into account all the scenarios where the pollutant is emitted (Huijbregts et al. 2010a; Rosebaum et al. 2008).

IS allows us to group into a single index the impact (ecotoxicity or human toxicity) of a compound released into the different compartments of nature. The equation and procedure for calculating IS for ecotoxicity (Eq. 1) and for human toxicity (Eq. 6) are summarized in Table 2.

The ISs are reported as comparative toxic units (CTU) that can be compared with ISs obtained from other methodologies.

In a recent study, Ortiz et al. (2013a) estimated the occurrence (mass·year^{-1}) of 88 PPCPs and metabolites in the aquatic environment in Spain. These results have been used to estimate ecotoxicological and human toxicity ISs (in CTU·year^{-1}) of the PPCPs considered. A mass balance approach was used by Ortiz et al. (2013a) in order to estimate their occurrence in aquatic environments, and the data for their removal in WWTPs was assessed by STPWIN™, a special module of EPI Suite™. STPWIN™ predicts the removal of a chemical in a typical activated sludge-based sewage treatment plant. Values are given for total removal and three processes that may contribute to removal: biodegradation, sorption to sludge, and air stripping (US EPA, 2012). The program assumes a standard system design and set of default operating conditions, and takes physico-chemical parameters from EPI Suite™, which works with a large database of experimental values, or estimates them with quantitative structure-activity relationship (QSAR) models.

EPI Suite™ has facilitated the calculation of the mass of PPCPs adsorbed in the sludge and volatilized to the air. In this way, a total ecotoxicological IS has been obtained, that includes three compartments: water, soil and air. For this case study, emissions were considered in the following environmental compartments: continental freshwater (water), continental natural soil (soil) and continental urban air (air).

3. Results and discussion

3.1. Discussion of input data

This section briefly shows the analysis of the values of the input parameters taken or estimated in order to obtain human and ecotoxicological CFs for the PPCPs under study.

3.1.1. Physico-chemical parameters

In general, the PPCPs under study present variable degrees of solubility, K_{oc} and K_{ow}. These parameters provide an estimation of the mobility of the PPCPs in water environments, soils and sediments. Atorvastatin, azithromycin, clarithromycin, irbesartan, paroxetine, simvastatin, valsartan and sertraline show the highest values of K_{ow} and K_{oc}, and low solubility; therefore, these compounds will be probably located in soils or sediments, or bioaccumulated.

Degradation rates in water, soils and sediments are of the same order of magnitude, although these are slightly higher in water than in soil and sediments, in most cases. Degradation rates in air are the highest among all the compartments, possibly due to the different photochemical effects and reactions that take place in this compartment. Despite this, all compounds present low P_{vap} (lower than 1 Pa) and K_H, which indicates that they will not be found in significant quantities in the air. The compounds with the highest values of bioaccumulation (estimated by EPI Suite™, US EPA, 2012) were: sertraline, irbesartan, paroxetine, valsartan and simvastatin.

3.1.2. Ecotoxicological effects

Usually, fish, crustaceans and algae are the main representative organisms that are considered when estimating the $logHC_{50}$ values (α) (Table 3), but in the present study, other organisms (molluscs, bacteria and rotifers) were incorporated where data was available. The $logHC_{50}$ of alprazolam, azithromycin, bromazepam, gabapentin, iohexol, iopamidol, irbesartan, ketorolac, lorazepam, pregabalin, simvastatin and valsartan were estimated only with fish, crustaceans and algae presenting acute and chronic toxicity. Sertraline, omeprazole, amoxicillin, cefaclor and levofloxacin $logHC_{50}$ were calculated from four species (the main three organisms and bacteria with acute toxicities), while acetaminophen and clarithromycin presented toxicities in fish, algae, crustaceans, rotifers and bacteria. Values for the acute and chronic toxicities caused by parabens in crustaceans, fish and bacteria were used to estimate its $logHC_{50}$. Norfloxacin toxicities present

in fish, algae, rotifers and bacteria were used for estimating its $logHC_{50}$. The remaining four compounds (paroxetine, enalapril, ciprofloxacin and atorvastatin) only had two values of toxicity (algae and crustacean).

Several levels of toxicity were found: Median lethal dose concentration; Half maximal effective concentration; Half maximal inhibitory concentration; No observed effect concentration; and Lowest observed effect concentration (for more information see complementary material). However, the PPCPs considered in this study did not have the same quantity of ecotoxicity data; so it would be important to complement this information for compounds that present high toxicity. Iohexol, pregabalin, gabapentin, iopamidol, cefaclor and enalapril were the pharmaceuticals with the highest values of $logHC_{50}$.

3.1.3. Human Health effects

It is known that chemicals may pose hazards to organisms including humans, as indicated by observable effects (e.g. in vivo and in vitro bioassays). Antibiotics is one of these cases; although the ideal antibiotic is toxic to bacteria without affecting humans/animals, the reality is more complicated, and directly toxic side effects are common for several classes of antibiotics at doses used for therapy. A few, relatively persistent antibiotics have been found in drinking-water at very low $ng \cdot L^{-1}$ levels. The greatest concern about antibiotics in the environment is their potential role in promoting resistance development in human and animal pathogens (Larsson, 2014a). Different available databases include human health effects that are generally an approximation of bioassays in some typical species used for this purpose.

In addition, there is currently a wide range of endpoints available from predictive quantitative structure–activity relationship (QSAR) models driven by many different computational software programs and data sources grouped under the term "in silico toxicology" (Valerio, 2009). These tools also are used for PPCPs that are already on the market and for estimating their human effects. In USEtox™, and therefore in this research, human toxicity includes carcinogenic and non-carcinogenic effects.

Alprazolam, atorvastatin, azithromycin, clarithromycin, irbesartan, omeprazole, paroxetine, sertraline and simvastatin are the compounds with the highest human toxicity according to the USEtox™ methodology.

3.1.3.1. Carcinogenic effects

In this study, as it can be seen in Table 3, six compounds present evidence of carcinogenic effects (atorvastatin, gabapentin, omeprazole, paroxetine, sertraline and simvastatin) in rats or mice during long term studies (chronic), fourteen have no evidence of carcinogenic effects (acetaminophen, alprazolam, amoxicillin, azithromycin, cefaclor, enalapril, ethylparaben, irbesartan, ketorolac, levofloxacin, lorazepam, methylparaben, pregabalin and propylparaben), and for seven compounds there was no available data (bromazepam, ciprofloxacin, clarithromycin, iohexol, iopamidol, paroxetine and valsartan) according to the information (ED_{50}) reported in Brambilla et al. (2012) and the database consulted and recommended by the USEtox™ users' manual.

The assessment of the carcinogenic potential of pharmaceuticals and the evaluation of their potential risk to humans is a major challenge for the scientific community, industry and regulatory agencies. The importance of reaching appropriate conclusions and balancing those conclusions with benefits, and the potential impact that those decisions may have on public health cannot be overstated (DeGeorge, 1998). Abraham and Ballinger (2012) affirm that human exposure to pharmaceuticals can cause cancer, so modern societies have assessed the carcinogenicity of new drugs since the 1960s.

Recent studies provide evidence of the carcinogenic effect of some PPCPs including estrogens, analgesic mixtures with phenacetin and antineoplastic drugs (Grosse et a l. 2009). Brambilla and Martelli (2009) made a compendium of the genotoxic and carcinogenic information of 838 marketed drugs, whose expected clinical use is for a continuous period of at least 6 months, or intermittent over an extended period of time. Of these 838 drugs, 472 (56.3%) have at least one positive test result for genotoxicity or carcinogenicity, a fairly high percentage for this type of chemical compounds. These studies serve as an experimental basis for asserting that PPCPs can

cause carcinogenic effects, so therefore this information should be considered and included in the database of USEtox™ and subsequently used in LCA studies.

The traditional approach to testing the carcinogenicity of pharmaceuticals is relatively standardized. It relies on testing the maximum tolerated dose (MTD) on usually two rodent species for 2 years. The results of these studies were viewed as either positive or negative, with only minimal attempts to evaluate the relevance of the findings for humans (DeGeorge, 1998). In this sense, Abraham and Ballinger (2012) worked on the validation and application of new techno-regulatory testing standards, specifically using genetically-engineered mouse (GEM) models in pharmaceutical carcinogenic risk assessment. This methodology or other more traditional ones, experimental or not, may be used in order to find out or predict the possible carcinogenic potential of PPCPs and to thus include carcinogenic data in studies of environmental risk/hazard assessment such as LCIA.

Data for human cancer has been found in lower quantities than for other effects; and it only remains for atorvastatin, gabapentin, omeprazole, paroxetine, sertraline, and simvastatin to have their value for $ED_{50ing,\ Cancer}$ calculated.

Despite this, there are not enough studies that provide evidence as to whether many PPCPs are carcinogenic or not, and that list the minimum doses that cause this adverse effect. In this research, there was a lack of data regarding carcinogenic effects for 30% of the PPCPs under study.

3.1.3.2. Non-carcinogenic effects

PPCPs must undergo strict controls before approving their use on animals and humans. Non-carcinogenic effects on humans or non-humans are some of those important pieces of data that must be reported for the safe use of these compounds.

In this study, for all the PPCPs, non-carcinogenic data was available as NOAEL or LOAEL, and was reported for various species (mouse, rabbit, rat, dog and monkey) and for different lengths of exposure time (sub-acute, sub-chronic and chronic). These data were converted to the chronic-equivalent ED_{50} by using Eqs. 15 and 16 (Table 2). The ingestion route was only considered due to the lack of data for other routes of exposition, such as inhalation.

Affectation of the liver, kidney, testicle, lung, eyes and central nervous system, and symptoms such as sedation, ataxia, convulsive seizures, abnormal secretion of sex hormones, decrease in blood pressure, hyperplasia of the juxtaglomerular apparatus, pallor, hematologic and pathologic alterations, benign tumors, cardiovascular malformations, embryotoxicity and teratogenicity were the main adverse effects reported in the literature consulted, and cited in the material and methods section for non-carcinogenic effects.

The effects shown in Table 4 relate to information obtained mainly from the material safety data of each compound, and from reports by the World Health Organization, EMEA and FDA.

Table 4. PPCPs non-carcinogenic effects on different species*

Compound	Non-carcinogenic effects	Specie
Acetaminophen	Sub chronic effects	Mice (males and females) and rat
Alprazolam	Embryotoxicity and teratogenic effects	Rabbit and rat
Amoxicillin and bromazepam	Reproductive effects	Rat
Atorvastatin	Effects on the liver	Dog, rat and mouse
Azithromycin		Dog and rat
Clarithromycin and bromazepam		Dog
Gabapentin and sertraline		Rat
Bromazepam	Sedation, ataxia, convulsive seizures	Dog
Clarithromycin	Cardiovascular malformation	Rat
Ethylparaben	Secretion of sex hormones	Rat
Irbesartan	Decreases in blood pressure and hyperplasia of the juxtaglomerular apparatus	Rat and monkey
Ketorolac	Hematologic and pathologic effects	Monkey
Levofloxacin	Impaired pup survival and decreased birth weight	Rat
Lorazepam	Fetotoxicity	Rabbit
Pregabalin	Adverse effects on blood forming organs and peri/postnatal developmental	Rat
Sertraline	Benign tumors	Mouse
	Effects on central nervous system	Dog
	Early embryonic development and developmental toxicity	Rat
Simvastatin	Eyes	Rat
	Eyes and central nervous system	Dog
Valsartan	Renal negative effects	Rat

*All these effects were reported by oral route of administration except for lorazepam that was intravenous

Methylparaben, ethylparaben, cefaclor, amoxicillin and gabapentin were the PPCPs with the highest values of non-cancerous human toxicity (ED_{50ing}) parameters.

According to USEtox™ methodology and software, both the human and ecotoxicity CFs were calculated with all this input data, using standard matrix algebra. This optimizes calculation efficiency (i.e. only one model run for all emission scenarios), transparency, and interpretability of results (Huijbregts et al., 2010a).

3.2. Human health CF for PPCPs under study

Table 3 shows carcinogenic and non-carcinogenic ED_{50} used by USEtox™ to calculate human health CFs for different media of release: continental urban air, continental rural air, continental freshwater, continental seawater, continental natural soil and continental agricultural soil. Both carcinogenic and non-carcinogenic CFs have been added, assuming equal weighting between cancerous and non-cancerous effects in those compounds where both effects were present. These aggregated results of the characterization factors per emission compartment (Huijbregts et al., 2010a), expressed as cases·$kg_{emitted}^{-1}$, are shown in Table 5 for the 27 PPCPs investigated.

Table 5. Human health characterization factor for PPCPs under study

Compound	Aggregated Human health characterization factor ($CTU_h \cdot kg_{emitted}^{-1}$ = Cases·$kg_{emitted}^{-1}$)[a] for:					
	ECUair*	ECRair**	ECFW***	ECSW+	ECNS++	ECAS+++
Acetaminophen	$5.6 \cdot 10^{-9}$	$6.00 \cdot 10^{-9}$	$2.90 \cdot 10^{-8}$	$5.40 \cdot 10^{-12}$	$3.40 \cdot 10^{-9}$	$6.10 \cdot 10^{-9}$
Alprazolam	$1.39 \cdot 10^{-6}$	$1.50 \cdot 10^{-6}$	$2.12 \cdot 10^{-6}$	$1.41 \cdot 10^{-8}$	$6.31 \cdot 10^{-10}$	$1.80 \cdot 10^{-9}$
Amoxicillin	$1.75 \cdot 10^{-8}$	$1.80 \cdot 10^{-8}$	$2.11 \cdot 10^{-8}$	$4.84 \cdot 10^{-12}$	$2.74 \cdot 10^{-9}$	$4.50 \cdot 10^{-9}$
Atorvastatin	$5.10 \cdot 10^{-5}$	$5.28 \cdot 10^{-5}$	$4.72 \cdot 10^{-5}$	$9.47 \cdot 10^{-7}$	$6.10 \cdot 10^{-8}$	$2.82 \cdot 10^{-6}$
Azithromycin	$4.60 \cdot 10^{-6}$	$4.72 \cdot 10^{-6}$	$6.11 \cdot 10^{-6}$	$2.10 \cdot 10^{-8}$	$1.76 \cdot 10^{-7}$	$9.44 \cdot 10^{-7}$
Bromazepam	$1.99 \cdot 10^{-7}$	$2.06 \cdot 10^{-7}$	$5.60 \cdot 10^{-7}$	$1.25 \cdot 10^{-9}$	$5.08 \cdot 10^{-9}$	$9.60 \cdot 10^{-9}$
Cefaclor	$1.24 \cdot 10^{-8}$	$1.28 \cdot 10^{-8}$	$1.54 \cdot 10^{-8}$	$3.17 \cdot 10^{-12}$	$2.06 \cdot 10^{-9}$	$3.02 \cdot 10^{-9}$
Ciprofloxacin	$1.11 \cdot 10^{-7}$	$1.15 \cdot 10^{-7}$	$1.13 \cdot 10^{-7}$	$2.51 \cdot 10^{-11}$	$4.46 \cdot 10^{-8}$	$6.17 \cdot 10^{-8}$
Clarithormycin	$2.92 \cdot 10^{-7}$	$3.01 \cdot 10^{-7}$	$3.14 \cdot 10^{-7}$	$1.21 \cdot 10^{-9}$	$8.60 \cdot 10^{-8}$	$1.95 \cdot 10^{-7}$
Enalapril	$6.58 \cdot 10^{-9}$	$6.92 \cdot 10^{-9}$	$5.55 \cdot 10^{-8}$	$9.64 \cdot 10^{-12}$	$1.20 \cdot 10^{-9}$	$1.98 \cdot 10^{-9}$
Ethylparaben	$1.14 \cdot 10^{-9}$	$1.21 \cdot 10^{-9}$	$5.33 \cdot 10^{-9}$	$7.73 \cdot 10^{-12}$	$2.32 \cdot 10^{-10}$	$7.27 \cdot 10^{-10}$
Gabapentin	$5.86 \cdot 10^{-9}$	$6.57 \cdot 10^{-9}$	$6.53 \cdot 10^{-8}$	$1.11 \cdot 10^{-11}$	$6.83 \cdot 10^{-9}$	$1.01 \cdot 10^{-8}$
Iohexol	$1.93 \cdot 10^{-6}$	$2.00 \cdot 10^{-6}$	$1.93 \cdot 10^{-6}$	$3.89 \cdot 10^{-10}$	$7.59 \cdot 10^{-7}$	$8.81 \cdot 10^{-7}$
Iopamidol	$8.32 \cdot 10^{-7}$	$8.59 \cdot 10^{-7}$	$8.30 \cdot 10^{-7}$	$1.68 \cdot 10^{-10}$	$3.27 \cdot 10^{-7}$	$3.79 \cdot 10^{-7}$
Irbesartan	$7.28 \cdot 10^{-7}$	$7.49 \cdot 10^{-7}$	$9.36 \cdot 10^{-7}$	$2.57 \cdot 10^{-7}$	$9.90 \cdot 10^{-11}$	$1.77 \cdot 10^{-9}$
Ketorolac	$4.62 \cdot 10^{-8}$	$3.61 \cdot 10^{-8}$	$1.87 \cdot 10^{-6}$	$6.56 \cdot 10^{-9}$	$3.33 \cdot 10^{-8}$	$8.94 \cdot 10^{-8}$
Levofloxacin	$2.17 \cdot 10^{-6}$	$2.26 \cdot 10^{-6}$	$2.51 \cdot 10^{-6}$	$6.45 \cdot 10^{-10}$	$1.20 \cdot 10^{-6}$	$1.41 \cdot 10^{-6}$
Lorazepam	$5.42 \cdot 10^{-7}$	$5.52 \cdot 10^{-7}$	$1.02 \cdot 10^{-6}$	$4.81 \cdot 10^{-9}$	$3.30 \cdot 10^{-8}$	$6.14 \cdot 10^{-8}$
Methylparaben	$1.04 \cdot 10^{-9}$	$1.09 \cdot 10^{-9}$	$4.51 \cdot 10^{-9}$	$3.27 \cdot 10^{-12}$	$3.36 \cdot 10^{-10}$	$8.13 \cdot 10^{-10}$
Norfloxacin	$1.20 \cdot 10^{-7}$	$1.25 \cdot 10^{-7}$	$3.05 \cdot 10^{-7}$	$6.17 \cdot 10^{-11}$	$1.09 \cdot 10^{-7}$	$1.28 \cdot 10^{-7}$
Omeprazole	$3.61 \cdot 10^{-5}$	$3.71 \cdot 10^{-5}$	$4.25 \cdot 10^{-5}$	$5.39 \cdot 10^{-8}$	$6.38 \cdot 10^{-6}$	$1.09 \cdot 10^{-5}$
Paroxetine	$2.92 \cdot 10^{-6}$	$1.09 \cdot 10^{-6}$	$1.46 \cdot 10^{-4}$	$3.83 \cdot 10^{-6}$	$4.06 \cdot 10^{-7}$	$9.01 \cdot 10^{-7}$
Pregabalin	$1.35 \cdot 10^{-8}$	$1.54 \cdot 10^{-8}$	$1.42 \cdot 10^{-7}$	$2.40 \cdot 10^{-11}$	$2.34 \cdot 10^{-8}$	$3.44 \cdot 10^{-8}$
Propylparaben	$1.03 \cdot 10^{-7}$	$1.09 \cdot 10^{-7}$	$5.62 \cdot 10^{-7}$	$1.50 \cdot 10^{-9}$	$1.58 \cdot 10^{-8}$	$7.36 \cdot 10^{-8}$
Sertraline	$6.70 \cdot 10^{-5}$	$1.18 \cdot 10^{-5}$	$4.77 \cdot 10^{-3}$	$4.85 \cdot 10^{-4}$	$1.62 \cdot 10^{-6}$	$2.03 \cdot 10^{-6}$
Simvastatin	$4.32 \cdot 10^{-6}$	$4.31 \cdot 10^{-6}$	$1.55 \cdot 10^{-5}$	$2.48 \cdot 10^{-7}$	$3.01 \cdot 10^{-8}$	$5.20 \cdot 10^{-7}$
Valsartan	$3.86 \cdot 10^{-6}$	$3.85 \cdot 10^{-6}$	$1.18 \cdot 10^{-5}$	$2.01 \cdot 10^{-10}$	$4.62 \cdot 10^{-9}$	$2.56 \cdot 10^{-8}$

[a]Total, for cancerous and non-cancerous effects, for those compounds that exhibit both effects.

*Emission into continental urban air.
**Emission into continental rural air.
***Emission into continental freshwater.
+Emission into continental seawater.
++Emission into continental natural soil.
+++Emission into continental agricultural soil.

Emission into the continental freshwater compartment showed the highest CFs of human health for most compounds, ranging from, 10^{-9} to 10^{-3} cases·$kg_{emitted}^{-1}$ (or $CTU_h \cdot kg^{-1}$) followed by the air compartment (both urban and rural, having values in the same order: 10^{-9} to 10^{-5} $CTU_h \cdot kg^{-1}$), the soil compartment (agricultural and natural) in the order of 10^{-11} to 10^{-5} $CTU_h \cdot kg^{-1}$ and finally, continental seawater in the order of 10^{-12} to 10^{-4} $CTU_h \cdot kg^{-1}$. These results indicate the relative order of importance of different PPCP emissions, and to what grade of magnitude they can affect human health, with the emission of drugs into continental freshwater being the most important compartment.

PPCPs listed in Table 5 can be compared with each other in each emission compartment. In this case, CF could be used as an index for prioritizing substances under the same emission conditions. Omeprazole, atorvastatin, sertraline, levofloxacin, azithromycin and simvastatin are the compounds that are highlighted as having the highest CFs, under this assumption. Omeprazole, atorvastatin and sertraline have the highest values of CFs for emissions into the air (continental and rural); valsartan, simvastation and atorvastatin have the highest CFs for emissions into freshwater; and paroxetine, simvastatin and irbesartan for emissions into seawater. Emissions of levofloxacin, sertraline and omeprazole into natural soil generated the highest CFs; and levofloxacin, sertraline and atorvastatin into agricultural soil. Nevertheless, in nature or in industrial processes, the quantities emitted in each compartment and for each compound are different and variable, implying that the amount emitted should be known in order to generate a human hazard ranking score under real conditions.

3.3. Ecotoxicological CF for PPCPs under study

At the moment, ecotoxicological effects (from bioassays or estimated by software) are always taken into account when evaluating the effects of PPCPs in the environment. Specifically, for LCIA, many different impact categories exist with which to measure the impact of contaminant substances in nature. This is the case of the USEtox™ model, which calculates the freshwater ecotoxicological CFs when the compound under study is released into different environmental compartments (air, water and soil). Table 6 shows the values of the CFs obtained by the USEtox™ model for the PPCPs considered.

Table 6. Freshwater ecotoxicological characterization factor for PPCPs under study.

Compound	Freshwater ecotoxicological characterization factor ($CTU_e \cdot kg^{-1} = PAF \cdot m^3 \cdot day \cdot kg^{-1}$) for:					
	ECUair*	**ECRair****	**ECFW*****	**ECSW^{+}**	**ECNS^{++}**	**ECAS^{+++}**
Acetaminophen	5.07	3.84	$1.25 \cdot 10^{2}$	$4.09 \cdot 10^{-9}$	$1.47 \cdot 10^{1}$	$1.47 \cdot 10^{1}$
Alprazolam	$5.39 \cdot 10^{2}$	$2.67 \cdot 10^{2}$	$2.01 \cdot 10^{4}$	$3.94 \cdot 10^{-4}$	5.99	5.99
Amoxicillin	$4.37 \cdot 10^{1}$	$4.04 \cdot 10^{1}$	$3.33 \cdot 10^{2}$	$2.94 \cdot 10^{-16}$	$4.32 \cdot 10^{1}$	$4.32 \cdot 10^{1}$
Atorvastatin	$1.76 \cdot 10^{3}$	$1.10 \cdot 10^{3}$	$4.53 \cdot 10^{4}$	$1.62 \cdot 10^{-15}$	$5.85 \cdot 10^{1}$	$5.85 \cdot 10^{1}$
Azithromycin	$2.19 \cdot 10^{3}$	$1.66 \cdot 10^{3}$	$3.68 \cdot 10^{4}$	$5.59 \cdot 10^{-16}$	$1.06 \cdot 10^{3}$	$1.06 \cdot 10^{3}$
Bromazepam	$1.70 \cdot 10^{2}$	$1.02 \cdot 10^{2}$	$5.00 \cdot 10^{3}$	$2.12 \cdot 10^{-6}$	$4.53 \cdot 10^{1}$	$4.53 \cdot 10^{1}$
Cefaclor	2.27	2.10	$1.71 \cdot 10^{1}$	$5.53 \cdot 10^{-14}$	2.28	2.28
Ciprofloxacin	$3.05 \cdot 10^{3}$	$3.04 \cdot 10^{3}$	$9.84 \cdot 10^{3}$	$1.52 \cdot 10^{-10}$	$3.88 \cdot 10^{3}$	$3.88 \cdot 10^{3}$
Clarithormycin	$1.52 \cdot 10^{4}$	$1.49 \cdot 10^{4}$	$6.46 \cdot 10^{4}$	$7.95 \cdot 10^{-17}$	$1.77 \cdot 10^{4}$	$1.77 \cdot 10^{4}$
Enalapril	2.01	$8.31 \cdot 10^{-1}$	$9.40 \cdot 10^{1}$	$2.92 \cdot 10^{-12}$	2.04	2.04
Ethylparaben	$3.85 \cdot 10^{1}$	$2.42 \cdot 10^{1}$	$1.21 \cdot 10^{3}$	$1.87 \cdot 10^{-4}$	$5.23 \cdot 10^{1}$	$5.23 \cdot 10^{1}$
Gabapentin	$7.94 \cdot 10^{-2}$	$4.87 \cdot 10^{-2}$	2.94	$7.22 \cdot 10^{-10}$	$3.08 \cdot 10^{-1}$	$3.08 \cdot 10^{-1}$
Iohexol	$6.97 \cdot 10^{-1}$	$6.96 \cdot 10^{-1}$	2.17	$9.73 \cdot 10^{-28}$	$8.54 \cdot 10^{-1}$	$8.54 \cdot 10^{-1}$
Iopamidol	5.85	5.84	$1.82 \cdot 10^{1}$	$4.50 \cdot 10^{-28}$	7.17	7.17
Irbesartan	$6.39 \cdot 10^{2}$	$3.94 \cdot 10^{2}$	$1.68 \cdot 10^{4}$	$6.56 \cdot 10^{-9}$	1.78	1.78
Ketorolac	$3.48 \cdot 10^{1}$	6.24	$1.89 \cdot 10^{3}$	$7.50 \cdot 10^{-7}$	$3.37 \cdot 10^{1}$	$3.37 \cdot 10^{1}$
Levofloxacin	$1.67 \cdot 10^{3}$	$1.68 \cdot 10^{3}$	$4.99 \cdot 10^{3}$	$2.83 \cdot 10^{-10}$	$2.38 \cdot 10^{3}$	$2.38 \cdot 10^{3}$
Lorazepam	$2.12 \cdot 10^{2}$	$1.66 \cdot 10^{2}$	$3.42 \cdot 10^{3}$	$1.20 \cdot 10^{-8}$	$1.11 \cdot 10^{2}$	$1.11 \cdot 10^{2}$
Methylparaben	$3.24 \cdot 10^{1}$	$2.34 \cdot 10^{1}$	$8.27 \cdot 10^{2}$	$1.11 \cdot 10^{-3}$	$6.02 \cdot 10^{1}$	$6.02 \cdot 10^{1}$
Norfloxacin	$3.68 \cdot 10^{2}$	$3.59 \cdot 10^{2}$	$2.64 \cdot 10^{3}$	$3.27 \cdot 10^{-11}$	$9.42 \cdot 10^{2}$	$9.42 \cdot 10^{2}$
Omeprazole	$1.29 \cdot 10^{4}$	$1.21 \cdot 10^{4}$	$8.84 \cdot 10^{4}$	$8.25 \cdot 10^{-11}$	$1.33 \cdot 10^{4}$	$1.33 \cdot 10^{4}$
Paroxetine	$1.10 \cdot 10^{3}$	$1.59 \cdot 10^{2}$	$6.25 \cdot 10^{4}$	$4.24 \cdot 10^{-4}$	$1.74 \cdot 10^{2}$	$1.74 \cdot 10^{2}$
Pregabalin	$5.36 \cdot 10^{-2}$	$3.90 \cdot 10^{-2}$	1.67	$1.37 \cdot 10^{-12}$	$2.76 \cdot 10^{-1}$	$2.76 \cdot 10^{-1}$
Propylparaben	$8.11 \cdot 10^{1}$	$4.22 \cdot 10^{1}$	$3.44 \cdot 10^{3}$	$9.06 \cdot 10^{-3}$	$8.88 \cdot 10^{1}$	$8.88 \cdot 10^{1}$
Sertraline	$2.43 \cdot 10^{2}$	$2.75 \cdot 10^{1}$	$1.80 \cdot 10^{4}$	$1.50 \cdot 10^{-2}$	6.11	6.11
Simvastatin	$1.39 \cdot 10^{3}$	$8.08 \cdot 10^{2}$	$4.08 \cdot 10^{4}$	$6.79 \cdot 10^{-6}$	$7.92 \cdot 10^{1}$	$7.92 \cdot 10^{1}$
Valsartan	$1.67 \cdot 10^{2}$	$1.03 \cdot 10^{2}$	$4.37 \cdot 10^{3}$	$3.96 \cdot 10^{-11}$	1.71	1.71

*Emission into continental urban air.
**Emission into continental rural air.
***Emission into continental freshwater.
$^{+}$Emission into continental seawater.
$^{++}$Emission into continental natural soil.
$^{+++}$Emission into continental agricultural soil
.

Emissions into continental urban and rural air present CFs values of between 10^{-2} and 10^{4} PAF·m^3·day·kg^1 (or CTU_e·kg^{-1}) for the PPCPs under study. Continental freshwater has CFs values of between 1 and 10^4 CTU_e·kg^{-1}; continental seawater of between 10^{-28} and 10^{-3} CTU_e·kg^{-1} and continental natural soil and continental agricultural soil in the same order, between 10^{-1} and 10^4 CTU_e·kg^{-1}. The highest CFs values were those from continental freshwater, due to the direct contact between the source of emission and the compartment affected. The lowest CFs values are those with continental seawater as the emission source, probably due to the difficulty in the inter-compartmental transfer (continental seawater to continental freshwater); moreover, the USEtox™ default concentration values of dissolved (colloidal) organic carbon, and the concentration of suspended matter for freshwater, are much higher than those values for seawater (five and three times higher, respectively). Furthermore, the mixed depth of continental freshwater is 2.5 m, while for seawater it is 100 m (continental) or 200 m (global) (Fantke et al. 2017). Therefore, these parameters could influence the differences between the fresh and seawater compartments; seawater presents lower bioavailability of the compounds than freshwater.

It can be observed, when comparing the results of the compounds studied for each emission compartment, that omeprazole, clarithromycin and ciprofloxacin have the highest values of CFs for emissions into the air (continental and rural) and soil (natural and agricultural). Omeprazole, paroxetine and clarithromycin have the highest CFs values for emissions into freshwater; and sertraline, methylparaben and propylparaben for emissions into seawater.

In this study, it was found that freshwater ecotoxicological CFs are much higher than human health CFs; this behavior is similar to that observed in the compounds in the USEtox™ database and in the Alfonsín et al. (2014) results. According to Daughton (2001), aquatic life, in particular, has the highest potential for perpetual exposure to PPCPs since these highly bioactive chemicals can be continually introduced into the environment (e.g. by way of sewage treatment facilities), therefore, it is highly probably that the effect of PPCPs on the aquatic environment could be much higher than the human impact. Besides, generally speaking, the concentration levels that affect aquatic species are much lower than those that affect humans.

Very few LCA studies include the CFs of PPCPs in their LCIA stages. Alfonsín et al. (2014) included PPCPs in a LCA for the completely autotrophic nitrogen removal from a nitrite pilot plant, and they found that the impact associated with the technology varied when CFs were applied. The most significant variation was observed in the human toxicity impact category calculated with USEtox™, where PPCPs represented more than 50% of the global impact after updating CFs, whereas they showed a negligible effect in the default scenario. Muñoz et al. (2008) applied a LCIA to a Spanish wastewater treatment plant with emerging pollutants, and their results showed that PPCPs are very important contributors to toxicity in this wastewater, with ciprofloxacin, fluoxetine and nicotine being the main compounds of concern. Lorenzo-Toja et al. (2016) evaluated two Spanish WWTPs including the presence of PPCPs in water and sludge lines. They found that the presence of PPCPs influenced the freshwater ecotoxicity potential, and the removal of these compounds generated benefits, compared with the non-treatment scenario. Thus, if the toxicity and ecotoxicity of PPCPs are excluded from LCA studies, the potential impact of many of these compounds on the human health and ecosystems could be critically underestimated.

3.4. Spanish impact score of PPCPs

The growing public awareness of the importance of protecting both ecosystems and human health from the risks associated to chemical exposure has given rise to the development of an increasingly important body of regulations in the last several years, especially in developed countries. In this context, risk assessment (and hence the elaboration of priority lists of chemical substances) provides the necessary scientific basis for more regulations (Guillen et al. 2012). Therefore, in this study a toxicity impact score for a group of PPCPs commonly used worldwide has been carried out using the CFs available in the database of USEtox™, the USEtox™ CFs available in literature (Alfonsín et al., 2014), and the new CFs calculated in this research. The mass of the PPCPs under study emitted into the air, freshwater and soil, in Spain in a year was calculated following the methodology indicated in Ortiz et al.(2013a), and this information was used in conjunction with the CFs to obtain the human and ecotoxicological Impact Score in $CTU \cdot year^{-1}$.

The IS results are shown in Table 7 and in Figures 1 and 2. The compounds with the highest toxicity impact score also concern compounds presented in other rankings made by different methodologies. This is the case of Ortiz et al. (2013b), who did a ranking of concern considering occurrence, persistence, bioaccumulation and toxicity as environmental and toxicological indexes, finding that hormones, antidepressants, antibiotics, blood lipid regulators and personal care products presented the highest levels of risk (as happens with CF and IS values). Kumar and Xagoraraki (2010) developed a comprehensive ranking system for prioritizing the monitoring of PPCPs and endocrine-disrupting chemicals using 4 criteria: occurrence, treatment in drinking water treatment plants, ecological effects, and health effects. Their ranking highlighted some compounds that coincide with this study: 17β-Estradiol, estrone, carbamazepine, azithromycin and fluoxetine, despite the fact that both studies applied different methodologies.

Helwig et al. (2016) carried out an environmental risk assessment that included hospital consumption of pharmaceuticals, with a newly available dataset on pharmaceuticals used in Scottish hospitals. They found nine compounds with a risk quotient greater than 1, among then, four antimicrobials. Their results differ from ours since the antibiotics in this study were not found to be in the highest level of the impact score ranking. Cooper et al. (2008) drew up a preliminary risk assessment database for common pharmaceuticals and put them into a web-accessible database named "Pharmaceuticals in the Environment, Information for Assessing Risk" (PEIAR) to help others evaluate the potential risks of pharmaceutical contaminants in the environment. Information from PEIAR was used to prioritize compounds that may threaten the environment, with a focus on marine and estuarine environments. They found that anti-infectives (antibiotics) might pose the greatest overall risk, based upon their results using a combination of factors that measure environmental transport, fate, and aquatic toxicity. In our study, most antibiotics were found to be at an intermediate level in the ranking. These differences may be due to the varied methodologies, the pattern of consumption of the geographical regions and the compounds under studied.

Sanderson et al. (2004b) ranked 2986 different pharmaceutical compounds in 51 classes in relation to the hazards they pose toward algae, daphnids, and fish using the EPIWIN program.

They found a high mean hazard quotient (HQ) for all three-model species combined for cardiovascular, sedatives, hormones and gastrointestinal PPCPs. Despite the large difference in the amount of compounds evaluated in their study comparing to the present research, similarly, gastrointestinal drugs (e.g. omeprazole) and hormones showed a high toxicity impact score. Muñoz et al. (2008) estimated characterization factors for 98 frequently detected pollutants (approximately half of them were PPCPs), using two characterization models, EDIP97 and USES-LCA, and developed a LCIA-based ranking of the potential impacts of priority and emerging pollutants in urban wastewater. They found that PPCPs were very important contributors to the toxicity in WWTPs, with ciprofloxacin, fluoxetine and nicotine (not considered in our study) being the main PPCPs of concern. In the present study, these two first compounds also appear as sixth and thirteenth in the ranking of ecotoxicological potential impact calculated from USEtox^{TM} CFs.

Hence, the IS of PPCPs highlights those compounds that may be of special interest in environmental impact studies such as LCA.

It is important to highlight that, generally, all these methodologies and their rankings are based on the individual effect of each compounds, and the effect of the mixture has rarely been compared. In LCA studies, the contribution of each compound to each impact category is considered (e.g. global warming, ozone depletion, toxicity, acidification, energy and water use, etc.), but mixtures and complex interactions in the environment are not well characterized, especially in human and ecosystems. Toxicologists consider that compounds which affect the same organ can cause an additive effect; LCA do not work with target organisms, their impact categories are much broader, so it is more difficult for this methodology to manage the possible synergistic or antagonistic effects of mixtures (UNEP, 2003). In this sense, some researches were conducted in order to obtain CFs for evaluating the potential impacts of complex mixtures on ecosystems, such as the studies carried out by Bamard et al. (2011) who developed a method to calculated CFs for hydrocarbon mixtures, and Li et al. (2015), who improved health impact estimates of 16 polyclyclic aromatic hydrocarbons (PAH) with the USEtox^{TM} method. They explored the importance of emission profiles for the PAH mixture and illustrated how these

improvements affect the LCIA case study; but for the majority of existing compounds which can reach the environment, be mixed and interact with it, much still remains to be studied.

Table 7. Spanish toxicity impact score of PPCPs based on human health and ecotoxicity characterization factors.

Compound	Human health characterization factor (CTU*$_h$·kg^{-1}) and mass emitted in the different compartments (kg·year^{-1})						Human toxicity impact score (CTU$_h^+$·year^{-1})	Ecotoxicity characterization factor (CTU*$_e$·kg^{-1}) and mass emitted in the different compartments (kg·year^{-1})						Ecotoxicity impact score (CTU$_e^+$·year^{-1})
	ECUair[a]	M_{Air}**	ECFW[b]	M_{water}**	ECNS[c]	M_{Soil}**		ECUair[a]	M_{Air}**	ECFW[b]	M_{water}**	ECNS[c]	M_{Soil}**	
17α-Ethinylestradiol	$6.79\cdot10^{-2}$	na	$2.45\cdot10^{-2}$	0.29	$3.02\cdot10^{-6}$	0.66	$7.11\cdot10^{-3}$	$3.02\cdot10^{4}$	na	$1.69\cdot10^{6}$	0.29	$2.56\cdot10^{5}$	0.66	$6.59\cdot10^{5}$
17β-estradiol	$7.76\cdot10^{-4}$	na	$2.18\cdot10^{-3}$	69.12	$3.02\cdot10^{-6}$	54.86	$1.51\cdot10^{-1}$	$3.30\cdot10^{6}$	na	$1.84\cdot10^{8}$	69.12	2.56	54.86	$1.27\cdot10^{10}$
Acetaminophen	$5.6\cdot10^{-9}$	na	2.90·10-8	23267	$3.40\cdot10^{-9}$	453155	$2.22\cdot10^{-3}$	5.07	na	$1.25\cdot10^{2}$	23267	$1.47\cdot10^{1}$	453155	$9.57\cdot10^{6}$
Alprazolam	$1.39\cdot10^{-6}$	na	$2.12\cdot10^{-6}$	60.21	$6.31\cdot10^{-10}$	1.69	$1.28\cdot10^{-4}$	$5.39\cdot10^{2}$	na	$2.01\cdot10^{4}$	60.21	5.99	1.69	$1.21\cdot10^{6}$
Amoxicillin	$1.75\cdot10^{-8}$	na	$2.11\cdot10^{-8}$	15257	$2.74\cdot10^{-9}$	101325	$5.99\cdot10^{-4}$	$4.37\cdot10^{1}$	na	$3.33\cdot10^{2}$	15257	$4.32\cdot10^{1}$	101325	$9.45\cdot10^{6}$
Atorvastatin	$5.10\cdot10^{-5}$	na	$4.72\cdot10^{-5}$	715.39	$6.10\cdot10^{-8}$	1145.81	$3.38\cdot10^{-2}$	$1.76\cdot10^{3}$	na	$4.53\cdot10^{4}$	715.39	$5.85\cdot10^{1}$	1145.81	$3.24\cdot10^{7}$
Azithromycin	$4.60\cdot10^{-6}$	na	$6.11\cdot10^{-6}$	1933.32	$1.76\cdot10^{-7}$	958.03	$1.20\cdot10^{-2}$	$2.16\cdot10^{3}$	na	$3.68\cdot10^{4}$	1933.32	$1.06\cdot10^{3}$	958.03	$7.22\cdot10^{7}$
Bromazepam	$1.99\cdot10^{-7}$	na	$5.60\cdot10^{-7}$	100.13	$5.08\cdot10^{-9}$	2.72	$5.61\cdot10^{-5}$	$1.70\cdot10^{2}$	na	$5.00\cdot10^{3}$	100.13	$4.53\cdot10^{1}$	2.72	$5.01\cdot10^{5}$
Carbamazepine	$2.08\cdot10^{-6}$	na	$7.68\cdot10^{-6}$	2595.31	$1.12\cdot10^{-7}$	1204.28	$2.01\cdot10^{-2}$	$1.65\cdot10^{1}$	na	$8.54\cdot10^{2}$	2595.31	$1.25\cdot10^{1}$	1204.28	$2.23\cdot10^{6}$
Cefaclor	$1.24\cdot10^{-8}$	na	$1.54\cdot10^{-8}$	119.60	$2.06\cdot10^{-9}$	2.62	$1.85\cdot10^{-6}$	2.27	na	$1.71\cdot10^{1}$	119.60	2.28	2.62	$2.05\cdot10^{3}$
Ciprofloxacin	$1.11\cdot10^{-7}$	na	$1.13\cdot10^{-7}$	2402.03	$4.46\cdot10^{-8}$	12957	$8.50\cdot10^{-4}$	$3.05\cdot10^{3}$	na	$9.84\cdot10^{3}$	2402.03	$3.88\cdot10^{3}$	12957	$7.39\cdot10^{7}$
Clarithormycin	$2.92\cdot10^{-7}$	na	$3.14\cdot10^{-7}$	5820.23	$8.60\cdot10^{-8}$	1669.22	$1.97\cdot10^{-3}$	$1.52\cdot10^{4}$	na	$6.46\cdot10^{4}$	5820.23	$1.77\cdot10^{4}$	1669.22	$4.05\cdot10^{8}$
Clofibrate	$2.07\cdot10^{-7}$	$1.11\cdot10^{-2}$	$3.67\cdot10^{-7}$	2.45	$2.58\cdot10^{-8}$	0.56	$9.16\cdot10^{-7}$	na	$1.11\cdot10^{-2}$	na	2.45	na	0.56	na
Cyclophosphamide	$2.45\cdot10^{-6}$	na	$7.33\cdot10^{-6}$	9.78	$1.03\cdot10^{-6}$	119.86	$1.95\cdot10^{-4}$	na	na	na	9.78	na	119.86	na
Diclofenac	$3.08\cdot10^{-7}$	na	$1.22\cdot10^{-6}$	3963.10	$4.84\cdot10^{-8}$	6613.79	$5.16\cdot10^{-3}$	$5.03\cdot10^{1}$	na	$2.67\cdot10^{3}$	3963.10	$1.05\cdot10^{2}$	6613.79	$1.13\cdot10^{7}$
Enalapril	$6.58\cdot10^{-9}$	na	$5.55\cdot10^{-8}$	725.20	$1.20\cdot10^{-9}$	1188.09	$4.17\cdot10^{-5}$	2.01	na	$9.40\cdot10^{1}$	725.20	2.04	1188.09	$7.06\cdot10^{4}$
Erythromycin	na	na	na	910.75	na	116.94	na	$3.22\cdot10^{3}$	na	$2.49\cdot10^{4}$	910.75	$3.15\cdot10^{3}$	116.94	$2.30\cdot10^{7}$
Estrone	$2.64\cdot10^{-4}$	na	$3.17\cdot10^{-4}$	28.22	$5.37\cdot10^{-7}$	153.00	$9.03\cdot10^{-3}$	$4.39\cdot10^{1}$	na	$2.14\cdot10^{4}$	28.22	$1.93\cdot10^{1}$	153.00	$6.07\cdot10^{5}$
Ethylparaben	$1.14\cdot10^{-9}$	na	$5.33\cdot10^{-9}$	na	$2.32\cdot10^{-10}$	na	na	$3.85\cdot10^{1}$	na	$1.21\cdot10^{3}$	na	$5.23\cdot10^{1}$	na	na
Fluoxetine	$2.49\cdot10^{-5}$	na	$2.6\cdot10^{-5}$	324.51	na	125.92	$8.44\cdot10^{-3}$	$3.82\cdot10^{2}$	na	$4.64\cdot10^{4}$	324.51	$7.32\cdot10^{1}$	125.92	$1.51\cdot10^{7}$
Gabapentin	$5.86\cdot10^{-9}$	na	$6.53\cdot10^{-8}$	1943.87	$6.83\cdot10^{-9}$	47406	$4.51\cdot10^{-4}$	$7.94\cdot10^{-2}$	na	2.94	1943.87	$3.08\cdot10^{-1}$	47406	$2.03\cdot10^{4}$
Galaxolide	$6.95\cdot10^{-7}$	na	$5.00\cdot10^{-7}$	69221	$4.69\cdot10^{-9}$	102389	$3.51\cdot10^{-2}$	$2.19\cdot10^{1}$	na	$1.01\cdot10^{4}$	69221	$1.72\cdot10^{1}$	102389	$7.01\cdot10^{8}$
Ibuprofen	$4.16\cdot10^{-7}$	6.74	$3.71\cdot10^{-7}$	4849.50	$1.74\cdot10^{-8}$	87853	$3.33\cdot10^{-3}$	3.25	6.74	$2.09\cdot10^{2}$	4849.50	3.65	87853	$1.33\cdot10^{6}$
Iohexol	$1.93\cdot10^{-6}$	na	$1.93\cdot10^{-6}$	5127.22	$7.59\cdot10^{-7}$	4691.52	$1.34\cdot10^{-2}$	$7.00\cdot10^{-1}$	na	2.17	5127.22	$8.54\cdot10^{-1}$	4691.52	$1.51\cdot10^{4}$

Iopamidol	$8.32\cdot10^{-7}$	na	$8.30\cdot10^{-7}$	11416	$3.27\cdot10^{-7}$	1296.93	$9.90\cdot10^{-3}$	5.90	na	$1.82\cdot10^{1}$	11416	7.17	1296.93	$2.17\cdot10^{5}$
Iopromide	$2.29\cdot10^{-7}$	na	$1.86\cdot10^{-7}$	14752	$7.29\cdot10^{-8}$	6202.81	$3.20\cdot10^{-3}$	5.57	na	$1.74\cdot10^{1}$	14752	6.82	6202.81	$2.99\cdot10^{5}$
Irbesartan	$7.28\cdot10^{-7}$	na	$9.36\cdot10^{-7}$	3810.87	$9.90\cdot10^{-11}$	23076	$3.57\cdot10^{-3}$	$6.39\cdot10^{2}$	na	$1.68\cdot10^{4}$	3810.87	1.78	23076	$6.42\cdot10^{7}$
Ketorolac	$4.62\cdot10^{-8}$	na	$1.87\cdot10^{-6}$	217.64	$3.33\cdot10^{-8}$	6.94	$4.06\cdot10^{-4}$	$3.48\cdot10^{1}$	na	$1.89\cdot10^{3}$	217.64	$3.37\cdot10^{1}$	6.94	$4.12\cdot10^{5}$
Levofloxacin	$2.17\cdot10^{-6}$	na	$2.51\cdot10^{-6}$	4041.49	$1.20\cdot10^{-6}$	87.97	$1.03\cdot10^{-2}$	$1.67\cdot10^{3}$	na	$4.99\cdot10^{3}$	4041.49	$2.38\cdot10^{3}$	87.97	$2.04\cdot10^{7}$
Lorazepam	$5.42\cdot10^{-7}$	na	$1.02\cdot10^{-6}$	304.99	$3.30\cdot10^{-8}$	10.25	$3.11\cdot10^{-4}$	$2.12\cdot10^{2}$	na	$3.42\cdot10^{3}$	304.99	$1.11\cdot10^{2}$	10.25	$1.05\cdot10^{6}$
Methylparaben	$1.04\cdot10^{-9}$	na	$4.51\cdot10^{-9}$	2148.67	$3.36\cdot10^{-10}$	56.43	$9.70\cdot10^{-6}$	$3.24\cdot10^{1}$	na	$8.27\cdot10^{2}$	2148.67	$6.02\cdot10^{1}$	56.43	$1.78\cdot10^{6}$
Naproxen	$1.42\cdot10^{-7}$	na	$2.95\cdot10^{-7}$	4196.75	$6.61\cdot10^{-9}$	12592	$1.32\cdot10^{-3}$	3.94	na	$2.18\cdot10^{2}$	4196.75	4.86	12592	$9.76\cdot10^{5}$
Norfloxacin	$1.20\cdot10^{-7}$	na	$3.05\cdot10^{-7}$	1118.69	$1.09\cdot10^{-7}$	2334.02	$5.94\cdot10^{-4}$	$3.68\cdot10^{2}$	na	$2.64\cdot10^{3}$	1118.69	$9.42\cdot10^{2}$	2334.02	$5.15\cdot10^{6}$
Omeprazole	$3.61\cdot10^{-5}$	na	$4.25\cdot10^{-5}$	12992	$6.38\cdot10^{-6}$	1388.34	$5.61\cdot10^{-1}$	$1.29\cdot10^{4}$	na	$1.63\cdot10^{1}$	12992	$3.92\cdot10^{2}$	1388.34	$7.55\cdot10^{5}$
Paroxetine	$2.92\cdot10^{-6}$	na	$1.46\cdot10^{-4}$	58.60	$4.06\cdot10^{-7}$	22.66	$8.54\cdot10^{-3}$	$1.10\cdot10^{3}$	na	$6.25\cdot10^{4}$	58.60	$1.74\cdot10^{2}$	22.66	$3.66\cdot10^{6}$
Pregabalin	$1.35\cdot10^{-8}$	na	$1.42\cdot10^{-7}$	4175.19	$2.34\cdot10^{-8}$	90.88	$5.95\cdot10^{-4}$	$5.36\cdot10^{-2}$	na	1.67	4175.19	$2.76\cdot10^{-1}$	90.88	$7.00\cdot10^{3}$
Propylparaben	$1.03\cdot10^{-7}$	na	$5.62\cdot10^{-7}$	688.81	$1.58\cdot10^{-8}$	51.53	$3.88\cdot10^{-4}$	$8.11\cdot10^{1}$	na	$3.44\cdot10^{3}$	688.81	$8.88\cdot10^{1}$	51.53	$2.37\cdot10^{6}$
Roxythromycin	na	na	na	34.24	na	4.38	na	$9.84\cdot10^{1}$	na	$2.18\cdot10^{3}$	34.24	$2.21\cdot10^{1}$	4.38	$7.47\cdot10^{4}$
Salicylic acid	na	na	na	859.07	na	7984.66	na	$1.35\cdot10^{1}$	na	$1.61\cdot10^{2}$	859.07	$2.82\cdot10^{1}$	7984.66	$3.63\cdot10^{5}$
Sertraline	$6.70\cdot10^{-5}$	na	$4.77\cdot10^{-3}$	488.95	$1.62\cdot10^{-6}$	99.09	2.33	$2.43\cdot10^{2}$	na	$1.80\cdot10^{4}$	488.95	6.11	99.09	$8.82\cdot10^{6}$
Simvastatin	$4.32\cdot10^{-6}$	na	$7.55\cdot10^{-5}$	1267.82	$3.01\cdot10^{-8}$	2647.25	$1.97\cdot10^{-2}$	$1.39\cdot10^{3}$	na	$4.08\cdot10^{4}$	1267.82	$7.92\cdot10^{1}$	2647.25	$5.20\cdot10^{7}$
Sulphametoxazole	$3.24\cdot10^{-8}$	na	$1.58\cdot10^{-7}$	2084.07	$1.03\cdot10^{-8}$	2315.58	$3.53\cdot10^{-4}$	$6.07\cdot10^{1}$	na	$2.99\cdot10^{3}$	2084.07	$1.95\cdot10^{2}$	2315.58	$6.68\cdot10^{6}$
Tamoxifen	na	na	na	9.78	na	119.86	na	$2.82\cdot10^{2}$	na	$1.99\cdot10^{4}$	9.78	3.08	119.86	$1.95\cdot10^{5}$
Testosterone	na	na	na	0.14	na	0.02	na	$2.37\cdot10^{2}$	na	$1.30\cdot10^{4}$	0.14	$1.17\cdot10^{2}$	0.02	$1.82\cdot10^{3}$
Tonalide	$1.04\cdot10^{-6}$	$9.43\cdot10^{1}$	$2.77\cdot10^{-5}$	11075	$1.82\cdot10^{-7}$	35161	$3.13\cdot10^{-1}$	$3.00\cdot10^{1}$	$9.43\cdot10^{1}$	$1.20\cdot10^{4}$	11075	$4.26\cdot10^{1}$	35161	$1.34\cdot10^{8}$
Triclosan	$1.11\cdot10^{-7}$	na	$2.21\cdot10^{-7}$	na	$5.01\cdot10^{-10}$	na	na	$2.58\cdot10^{3}$	na	$1.06\cdot10^{5}$	na	$1.61\cdot10^{1}$	na	na
Trimethoprim	$9.16\cdot10^{-8}$	na	$5.66\cdot10^{-7}$	44.57	$2.29\cdot10^{-8}$	5.69	$2.54\cdot10^{-5}$	9.11	na	$4.74\cdot10^{2}$	44.57	$1.92\cdot10^{1}$	5.69	$2.12\cdot10^{4}$
Valproic acid	na	8.52	na	229.80	na	5645.91	na	2.14	8.52	$1.21\cdot10^{2}$	229.80	$1.53\cdot10^{1}$	5645.91	$1.14\cdot10^{5}$
Valsartan	$3.86\cdot10^{-6}$	na	$1.18\cdot10^{-5}$	20351	$4.62\cdot10^{-9}$	4810.05	$2.40\cdot10^{-1}$	$1.67\cdot10^{2}$	na	$4.37\cdot10^{3}$	20351	1.71	4810.05	$8.89\cdot10^{7}$

*Comparative toxic units. **Ortiz et al. (2013a). [a]Emission into continental urban air. [b] Emission into continental freshwater. [c] Emission in to continental natural soil. Compounds of this study are shaded

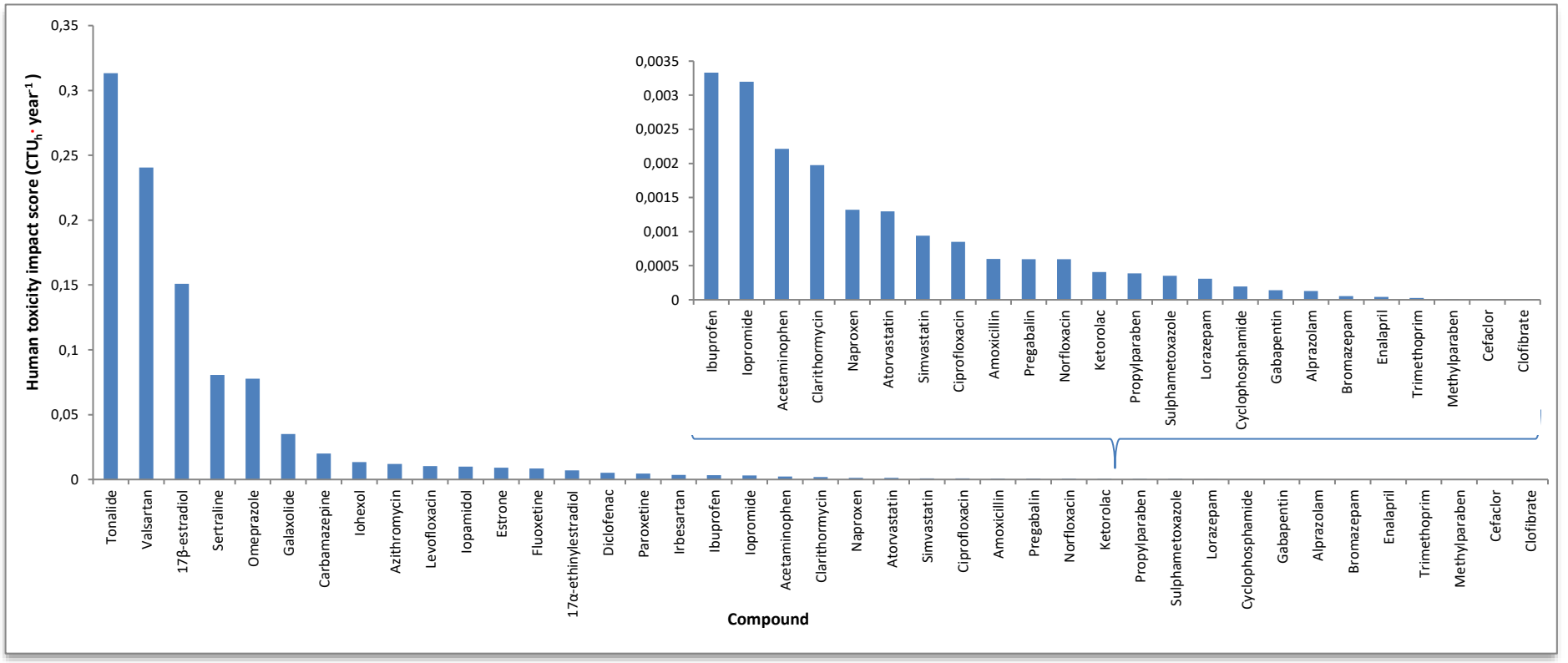

Figure 1. Spanish human toxicity impact score (IS_{hum}) for the selected PPCPs.

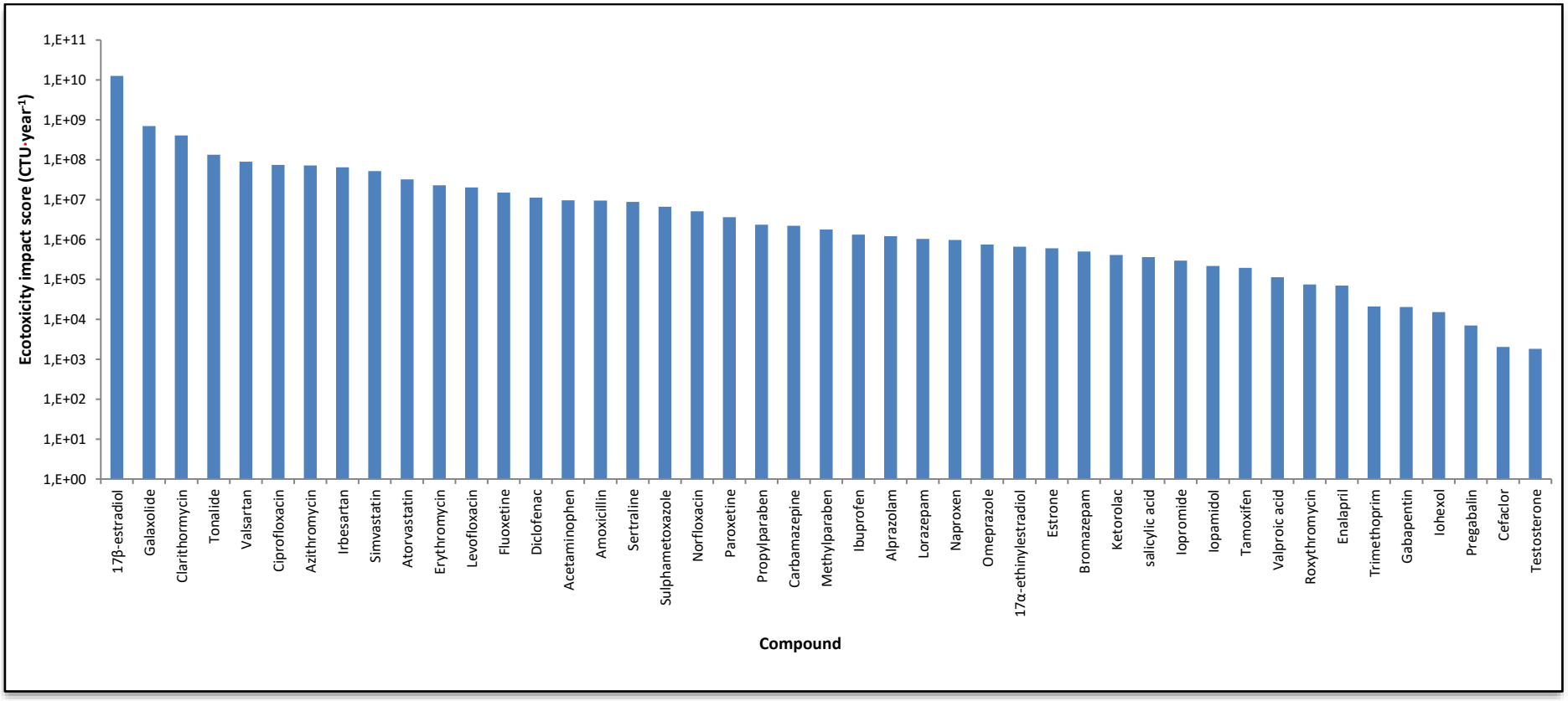

Figure 2. Spanish ecotoxicity impact score (IS_{eco}) for the selected PPCPs

Conclusion

PPCPs are a large group of compounds which are present in all compartments of nature. It is impossible to analyze all the interactions and effects of these compounds on the environment; therefore, the use of LCA studies and risk/hazard assessments are very useful tools for predicting their ecotoxicological and human impacts/effects. In order to implement these methodologies, an estimation of CFs is needed, using routines such as USEtox™. With this in mind, 27 CFs have been calculated for PPCPs widely used at present. A Spanish ranking toxicity impact score (IS) was done for ecotoxicological and human toxicity for 49 PPCPs as a case study, using these 27 new CFs found and 22 others existing in literature, in combination with data regarding the occurrence of these compounds in the Spanish environment.

Angiotensin receptor blocker (valsartan, irbesartan), blood lipid regulators (simvastatin atorvastatin), H_2 blocker (omeprazole) and antidepressant (sertraline) were the pharmaceuticals with the highest human health CFs in the different compartments of emission. Omeprazole, antibiotics (clarithromycin, ciprofloxacin) antidepressant (paroxetine, sertraline) and parabens had the highest ecotoxicological CFs.

This study has established that emissions into continental freshwater originate the highest CFs, for both human and ecological impacts. Ecotoxicological CFs were much higher than human toxicity CFs, since the human tolerance of PPCPs is higher than for environmental biota.

In the case of this study, the toxicity impact scores derived from the USEtox™ CFs place fragrances, hormones, antibiotics, antidepressants, angiotensin receptor blockers and blood lipid regulators at the top of the ranking, similar to other rankings generated with other methodologies. The CFs of PPCPs estimated in this work offer the possibility of incorporation into new LCIA of LCA studies, or to formulate a ranking impact score list.

Although this study focused on PPCPs, it is important to highlight the fact that other emerging micropollutants such as pesticides, alkylphenols, perflourinated compounds and various industrial organic chemicals are highly polluting, so it is recommended that CF estimation should continue for all these types of compounds, in order to thus include them in LCA studies.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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