Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals

Emily E. Burns,[†] Laura J. Cater,[‡] Jason Snape,[§] Jane Thomas-Oates,[†] Alistair B.A. Boxall*[‡]

[†]Chemistry Department, University of York, Heslington, YO10 5DD, United Kingdom

[‡]Environment Department, University of York, Heslington, YO10 5DD, United Kingdom

[§]AstraZeneca UK, Global Safety, Health and Environment, Macclesfield, SK10 4TG, United Kingdom

*Address correspondence to alistair.boxall@york.ac.uk

Emily E. Burns: +44 [0]1904324078, emily.burns@york.ac.uk

Laura J. Carter: +44 [0]1904324226, laura.carter@york.ac.uk

Jason Snape: +44 [0] 7884735218, jason.snape@astrazeneca.com

Jane Thomas-Oates: +44 [0] 1904324459, jane.thomas-oates@york.ac.uk

Alistair B.A. Boxall: +44 [0] 1904324791, alistair.boxall@york.ac.uk

Abstract

Pharmaceuticals are ubiquitous in the natural environment with concentrations expected to rise as human population increases. Environmental risk assessments are available for a small portion of pharmaceuticals in use, raising concerns over the potential risks posed by other drugs that have little or no data. With >1900 active pharmaceutical ingredients in use, it would be a major task to test all of the compounds with little or no data. Desk-based prioritization studies provide a potential solution by identifying those substances that are likely to pose the greatest risk to the environment and which therefore need to be considered a priority for further study. The aim of this review was to (1) employ different prioritization methodologies used for pharmaceuticals in the environment and the results generated and (2) propose a new holistic risk-based prioritization framework for drugs in the environment. Suggested models to underpin this framework are discussed in terms of validity and applicability. The availability of data required to run the models was assessed and data gaps identified for future research needs. The implementation of this framework may harmonize pharmaceutical prioritization efforts and indicate that in the future, experimental resources might focused on molecules, endpoints and environmental compartments that are biologically relevant.

Keywords: Active pharmaceutical ingredient, Prioritization, Environmental risk assessment, Exposure modelling, Effects prediction

Introduction

Pharmaceuticals are an invaluable commodity to society; their use enables greater quality and longevity of life. Extensive patient and veterinary use, incomplete metabolism, continuous use by society, and lack of rapid biodegradability of many active pharmaceutical ingredients (APIs) resulted in their ubiquitous presence in various environmental media (Redshaw et al. 2013; Gaw and Brooks 2016; Bergheim et al. 2014), and detection in non-target organisms (Miller et al. 2015; Tanoue et al. 2015; Cuthbert et al. 2014). Pharmaceuticals can reach the environment *via* multiple point source and diffuse pathways including incomplete removal in conventional wastewater treatment and subsequent release into surface waters (Luo et al. 2014); release of untreated wastewater directly or through combined sewer overflows (CSOs) (Mennigen et al. 2011; Phillips et al. 2012); migration in landfill leachate (Masoner et al. 2016); agricultural use and sludge spreading (Mohapatra et al. 2016); domestic septic tank discharge (Yang et al. 2016); and release of manufacturing effluent (Cardoso et al. 2014; Larsson 2014).

Environmental monitoring studies detected 631 pharmaceuticals in 71 countries (aus der Beek et al. 2016), with these monitoring campaigns reporting concentrations in the aquatic environment typically at low µg/L to sub-ng/L levels (Batt et al. 2017; Singer et al. 2016). Despite the low concentrations, this widespread occurrence of pharmaceuticals in the environment has led to concerns over their potential impacts due to their known biological activity in various species including fish, amphibians, and humans which indicates that non-target organisms are affected (Ankley et al. 2007; Mennigen et al. 2011; Brodin et al. 2017). Environmental effects of pharmaceuticals have been documented in wildlife (Oaks et al. 2004; Scholz and Klüver 2009; Weatherly and Gosse 2017) and potential effects suspected in human populations; however further research is required to demonstrate this (Wang et al. 2016). An increasing, ageing population, rising welfare standards and projected elevation in global populations within a progressively urbanized environment (United Nations, 2014), is expected to result in increased use of pharmaceutical , which

might amplify existing concentrations of compounds in environmental media and, potentially, associated risks for some specific drugs for which there is a low margin of safety (MOS), or site-specific risks where high population densities and low dilution occurs. Recent projections suggest that pharmaceutical usage in the UK alone might double by 2052 (Royal Commission on Environmental Pollution, 2011). On the other hand, (1) improved preventative health measures, (2) development of green or biologically-based pharmaceuticals, or (3) increased oral absorption might reduce environmental input loads (Straub 2016), while improved wastewater treatment (Itzel et al, 2017) or increased access to sanitation might also mitigate environmental and non-therapeutic human exposure in future.

An environmental risk assessment (ERA) is required as part of the marketing authorization process for new APIs in the European Union and United States. In the European Union, the European Medicines Agency (EMA) has implemented an ERA process for human medicinal products registered after 2006. Detailed criticism of this process is outside the scope of this review; however, many limitations were identified (BIO Intelligence Service 2013; Pereira et al. 2017). Specifically, trigger values to assess environmental compartments beyond the aquatic assessment may not be sufficient to catch risks in the current ERA process. EMA based ERAs were only conducted for a small proportion of the APIs currently granted market authorization (Datapharm Communications Limited 2017). An analysis of the availability of European Public Assessment Reports (EPARs) from the EMA (2017) for the top 350 pharmaceuticals in use in the UK, demonstrates that ERA data were available for only 71 of these molecules (Supplementary Material). High volume use pharmaceuticals such as paracetamol, carbamazepine, or amoxicillin, all commonly cited in the literature as high priority compounds possess no publicly available EMA ERA. Other regional ERA initiatives exist such as Sweden's Wikipharma (MistraPharma, 2018). These assessments may not be directly comparable, but if pooled into a new central database might be a more effective tool for identifying which ERA data are currently available and where significant data gaps exist for specific APIs or specific mechanisms of action (BIO Intelligence Service, 2013).

The difference between number of pharmaceuticals currently authorized for market use and those with environmental data is therefore large (Figure 1). Potentially, those substances with little or no environmental data may pose risks. To conduct full ERAs on all pre-2006 authorized pharmaceuticals would be a substantial and likely unnecessary task, as the majority of currently assessed pharmaceuticals demonstrate a good MOS with studies focused in Europe predicting that approximately 5-10% of drugs in use might pose any appreciable risk to the environment (Roos et al. 2012; Küster and Adler 2014). Therefore it would be valuable to identify those pharmaceuticals most likely to pose the greatest risk then assess these through targeted experimental testing and environmental monitoring. Desk-based prioritization approaches which screen pharmaceuticals based upon either hazard, exposure, or risk might help as they may be utilized to focus monitoring campaigns, effects testing, or decide which pharmaceuticals most urgently require a tailored ERA (Boxall et al. 2012). The use of such approaches might help ensure that APIs of potential concern are identified and tested while minimizing unnecessary organism testing and not compromising testing of novel APIs by saturating environmental testing capacity in contract research organizations.

A variety of prioritization approaches were suggested, which employ different methodologies (Dong et al. 2013; Kumar and Xagoraraki 2010; Diamond et al. 2011; Besse et al 2012; Fick et al. 2010; Ortiz de García et al. 2013, Guo et al. 2016). Many of these approaches are limited in scope in terms of both number of compounds included and environmental exposure routes considered. The reason for this might be due to lack of suitable models currently available to explore environmental exposure beyond freshwater aquatic compartments. Currently, prioritization approaches are generally employed to inform monitoring campaigns or select compounds to undertake effects research. The number of pharmaceuticals currently missing an ERA and those for which there are data might be limited in terms of endpoints/environmental compartments considered, indicating risks may be missed. This presents another opportunity for pharmaceutical prioritization, to inform the ERA process.

The aim of this critical review was to develop an optimal prioritization framework that might be applied to various understudied exposure scenarios and regions of the world, to serve as a guide to researchers, industry, and regulators, whilst highlighting which investigations specifically are needed to address knowledge gaps prior to implementation of the framework. The development of the optimal prioritization framework was achieved through the following objectives: to i) identify the variability of prioritized pharmaceuticals geographically, thereby helping to determine the scale at which the optimal prioritization needs to be undertaken, ii) collate previous pharmaceutical prioritization results to identify which approach was most balanced, iii) based upon this approach, evaluate the strengths and weaknesses and identify opportunities for improvement, and iv) develop a framework based upon the selected prioritization approach and evaluate the models which might underpin the approach in terms of validity and suitability for pharmaceuticals.

To address these goals, a systematic literature search of the Web of Science™ and Scopus® databases as well as the Google Scholar search engine was conducted, using combinations of the keywords 'pharmaceutical' with either 'prioritization', 'ranking' or 'priority'. Additional targeted searching was included where appropriate from identified literature references. Prioritization exercises and risk assessments that either identified a pharmaceutical of concern or several priority compounds were included. A total of 73 papers were identified, several of which included multiple priority lists (total 76) either representing different environmental compartments or prioritization approaches. References are reported in the Supplemental Material. To limit the scope, only human pharmaceutical usage is considered. Pharmaceutical mixtures, while gaining significant attention in terms of pharmaceutical risk assessment, are beyond the scope of the framework currently. Finally, as this is a review, an optimal prioritization framework is presented; further research required to ultimately implement this framework is outlined.

Previous prioritization approaches

Geographical spread

In total, 76 prioritization exercises were identified covering 24 countries (Figure 2). Multiple prioritization exercises were performed in the USA, France, Switzerland and Sweden. In each of these countries, prioritization exercises used a variety of approaches including risk, hazard or exposure (see General approaches section) and were both generic and country-specific (e.g. *via* local usage data). The most common approach for countries in which a single prioritization was undertaken is risk-based such as combined exposure and effects. Regional differences in priority compounds suggests that risks are regionally specific, likely driven by the existence of national marketing authorization approaches, pharmaceutical costs, prescribing practices, disease pressures, wastewater treatment and connectivity, and climatic or hydrological conditions, all of which affect exposure and therefore potential risk posed by particular compounds (Figure 2). This is an important consideration and suggests that a prioritization result from one geographical region may not be suitable for another location. While the majority of pharmaceutical prioritizations focused in Europe and USA, and to a lesser extent Asia, the remainder of the world is scarcely covered (Figure 2). These understudied areas might be harboring hot spots of pharmaceutical exposure and risk, due for example to environmental inputs from pharmaceutical manufacturing and formulation sites with inadequate effluent treatment (Larsson 2014), large urban populations such as India, Brazil or Nigeria or the fact that many of these regions have limited or no sewage treatment connectivity.

General Approaches

Different prioritization approaches used globally may be characterized into three general categories: exposure-based; hazard-based and risk-based. These approaches are discussed in more detail below.

Exposure-based methods

Exposure-based methods prioritize pharmaceuticals solely based upon predictions or measurements of compound concentrations in the environment. In general, this type of approach is utilized to develop monitoring campaigns by selecting pharmaceuticals most likely to be present, thereby focusing on costly monitoring efforts (Kim et al. 2006; Riva et al. 2015; Götz et al. 2010). The greater the pharmaceutical usage, the higher the load that is expected to reach the environment and therefore the greater the priority score (Riva et al. 2015). To prioritize based upon predicted exposure, simple predicted environmental concentrations (PECs) are calculated using approaches such as that defined by the EMA (2006), Equation 1.

$$PEC = \frac{Mass * F_{excreta} * (1\text{-}WWTP_{removal})}{WW_{inhabitants} * Environmental\ dilution} \quad [1]$$

Pharmaceutical consumption (Mass) per capita (µg/person·day) is estimated based upon sales or prescription data. The $F_{excretra}$ term is patient excretion, derived from peer-reviewed pharmacokinetic studies of the compound. . Wastewater treatment plant (WWTP) removal is either predicted utilizing quantitative structure activity relationships (QSARs), for example the STPWIN program (which predicts removal of a chemical in a typical conventional activated sludge WWTP), part of the USEPA's EPISUITE software package which estimates the environmental fate of a molecule using physico-chemical properties (US Environmental Protection Agency 2015) or based upon measured values previously reported in the literature. WWTP removal may be assumed to be zero to reflect the worst case exposure scenario (Le Corre et al. 2012). The numerator (i.e. the predicted pharmaceutical load) is diluted based upon mean amount of wastewater generated per person served by the WWTP (WW_{inhab}); the EMA (2006) suggests a default value of 200 L/per person·day, although Henze and Comeau (2008) suggest 50 to 400 L/per person·day reflects the range in actual water usage practices throughout the world. The EMA (2006) default environmental dilution factor is 10, which a global study of dilution factors of WWTP effluent indicating suitability for assessing risk (Keller et al. 2014).

Exposure-based prioritizations may also be based upon measured environmental concentrations (MECs). Exposure-based prioritizations offer a means of overcoming limited ecotoxicological knowledge of pharmaceuticals by placing a greater focus on what is continually entering and present in the environment (Götz et al. 2010; Castiglioni et al. 2006).

Hazard-based methods

A small number of pharmaceutical prioritizations identify priority compounds based upon their hazard properties. Hazard-based approaches are unbiased by environmental occurrence and therefore indicate compounds that display the potential to be harmful based upon potency and/ or their mechanism(s) of action such as synthetic hormones or anti-cancer drugs. These might be missed in some risk-based methods (Christen et al. 2010), or exposure-based methods which intentionally focus on high-use drugs, compounds of known environmental presence, or which lack exposure data. Hazard-based methods might also be useful for informing pharmaceutical substitution policies as part of a risk mitigation measure (Larsson 2014). Generally, hazard-based methods identify and score pharmaceuticals based upon their persistence, bioaccumulation, and toxicity (PBT) (Fàbrega et al. 2013; Ortiz de García et al. 2013; Wennmalm and Gunnarsson 2005) or simply their persistence and bioaccumulation (P&B) (Howard and Muir 2011). These data are usually obtained from systems such as the United States USEPA's PBT Profiler or EPISuite software programs: BIOWIN, BCFBAF and ECOSAR (US Environmental Protection Agency 2015; Environmental Health Analysis Center 2016).

Hazard-based prioritization might also involve 'read-across' from readily available pharmacokinetic data (Lalone et al. 2014). This leveraging of parameters derived during drug development processes enables a consistent comparison across all pharmaceuticals instead of biasing the prioritization towards data rich or poor compounds. The absorption, distribution, metabolism and excretion (ADME) of substances has been correlated with how a pharmaceutical might behave in an organism and therefore the likelihood of causing an adverse effect in the

environment (Berninger et al. 2016; Lalone et al. 2014). A simpler 'read-across' approach assumes that the plasma concentration of a drug that produces a therapeutic response in a human, might potentially induce an effect in a fish at similar plasma concentrations (Huggett et al. 2003). The lower the environmental concentration required to reach this concentration in a fish, the higher the priority (Fick et al. 2010; Roos et al. 2012). These simpler 'read-across' hazard-based methods not based upon ADME parameters, rely on predicting internal organism concentrations based upon the bioconcentration factor (BCF) of a compound. While these approaches attempt to overcome heavy dependence on predicted PBT data to select priority compounds, their validity as indicators of hazard has yet to be extensively assessed and validated.

Risk-based methods

The majority of prioritization methods and exercises reported in the literature are risk-based, where a measure of risk resulting from the ratio of exposure to effect is ranked by decreasing severity (Kools et al. 2008). By placing effects or hazards in the context of environmental occurrence, resources are focused not just on detectable or hazardous pharmaceuticals, but those present at a concentration likely to result in an appreciable risk. Previous critical assessments of prioritization methods concluded that risk-based approaches are most appropriate for prioritizing pharmaceuticals (Roos et al. 2012; Caldwell et al. 2014).

The most common approach to risk-based prioritization is to calculate a risk-quotient (RQ), Equation 2. The PEC may be calculated according to Eqn. 1, while the predicted no-effect concentration (PNEC) may be extrapolated from the most sensitive ecotoxicological endpoint by adjustment with a safety factor, depending upon the source, coverage and nature of the ecotoxicity data such as measured or predicted, endpoint reported, acute or chronic to help ensure risks are not missed (Guo et al. 2016). These safety factors are based upon assessment factors, which are applied to derive a PNEC for an ERA based on the quantity of ecotoxicity data available, outlined by regulatory bodies such as the EMA (2006) and US Food and Drug Administration (1998). Similarly to

PBT hazard-based methods, ecotoxicity data employed in many risk-based prioritization studies are often derived from QSAR models such as ECOSAR (Dong et al. 2013), again placing a heavy reliance on predictive rather than experimental methods.

$$RQ = \frac{PEC}{PNEC} \quad [2]$$

Other risk-based methods focused on assessment of risks to predators or humans posed by secondary poisoning *via* exposure from food or water. In the case of human unintended exposure, the acceptable daily intake (ADI) is typically used to derive the PNEC (Cunningham et al. 2009; Murray et al. 2010; Leung et al. 2013). Other approaches 'read-across' from pharmacokinetic data to make ecotoxicological predictions (Huggett et al. 2003; Kostich and Lazorchak 2008). Some risk-based studies included risks to mammals and humans in addition to the aquatic ecotoxicological endpoints frequently considered such as fish, invertebrate, and algae, but rely heavily on predicted data (Guo et al. 2016) or complex weighting schemes to deliver rankings (Dong et al. 2013; Guo et al. 2016; Kumar and Xagoraraki 2010).

Similar to exposure-based prioritizations, risk-based prioritizations rely on either MECs (Li et al. 2014; Morais et al. 2014), PECs (Perazzolo et al. 2010), or a mixture of the two (Roos et al. 2012). These PECs and MECs are generally applied to entire countries or regions (Guo et al. 2016). Higher-tier spatial PEC modelling approaches might also be used. These models digitize the river network within a GIS framework to generate spatially refined PECs, such as P*h*ATE (US) and GREAT-ER (EU) models (Cunningham et al. 2009; Feijtel et al. 1997). Spatial PECs are achieved by allocating WWTPs, their characteristics (population served and WWTP technology), and discharges spatially into the river network, while accounting for mixing with pharmaceuticals transported from upstream, to make exposure predictions for large-scale river basins (Alder et al. 2010). Oldenkamp et al. (2013) refined this concept further by creating a smaller-scale screening tool for Europe capable of deriving potential pharmaceutical environmental hotspots. The model generates emissions aggregated into 100 km x 100 km grids and also includes environmental fate considerations such as hydrolysis,

biodegradation, photolysis, partitioning to sediment, and releases to soils, based on the SimpleBox model (Hollander et al. 2007).

Prioritization results and current limitations

Which pharmaceutical classes are most commonly prioritized?

In total, 332 pharmaceuticals were identified as a priority in the 76 prioritization exercises. There were 197 compounds identified only once, while 76 pharmaceuticals were selected as priority compounds by three or more exercises. In Table 1, the 76 pharmaceuticals prioritized 3 or more times are categorized by prioritization approach, then by therapeutic class. A marked difference may be seen in the dominant therapeutic classes selected based upon type of prioritization approach employed (Table 1), a similar conclusion to that reached by Roos et al. (2012).

Our findings support the findings that potent low-dose pharmaceuticals or those with generally higher limits of detections, or both, such as hormones, are completely overlooked by purely environmental exposure-based methods.

The top three therapeutic classes flagged by risk-based approaches are antibiotics (16) followed by hormones (10) and analgesics (9). When exposure-based prioritization systems were evaluated, antibiotics (10) comprised the largest therapeutic class followed by analgesics (5) and lipid-lowering agents (4). Hormones were not selected in any of the exposure-based exercises despite their prevalence in hazard- and risk-based prioritization methods. This is expected because hormones are potent and administered in small doses, which, despite prevalent usage, results in low environmental inputs in terms of mass. Therefore, these compounds are less likely to be detected in the environment than their higher mass use counterparts such as antibiotics and analgesics. On the other hand, antibiotics and analgesics are prevalent in exposure-based priority lists, similar to risk-based priorities, indicating that their associated risks may be related to high exposures in mass terms.

Hazard-based methods identified hormones (9) followed by antidepressants (6), cardio-vascular agents (5) and antibiotics (5) as pharmaceutical classes of highest priority. Analgesics were less of a priority according to these approaches, despite their prevalence in risk-based and exposure-based prioritization outcomes, again indicating that the perceived risks of analgesics are more likely a result of high exposure than potency. Antidepressants were the fourth most highly selected therapeutic class in risk-based studies and second in hazard-based investigations, but again overlooked almost entirely by exposure-based approaches.

This analysis indicates that prioritizations relying solely on hazard- or exposure-based approaches might be misleading, as key therapeutic classes of known environmental risk, whether they be hormones or analgesics, were under-represented in comparison to risk-based methods. Data are currently not available to determine the accuracy of risk-based approaches which are also flawed as these are reliant on combinations of PECs and MECs for exposure, and predicted or empirical data for effects. Research efforts need to focus on increasing the certainty in exposure and effects approaches to be employed in a reliable prioritization approach, for example validation of exposure models through targeted environmental monitoring or validation of ecotoxicity QSARs and 'read-across' theories for a range of pharmaceuticals with differing physico-chemical characteristics and modes of action. Despite this, the balance between exposure and hazard with a risk-based approach is likely the most effective approach for prioritization (Roos et al. 2012; Caldwell et al. 2014).

What drives priority compound selection?

The most common top priority pharmaceuticals were diclofenac and ethinylestradiol (EE2), designated as priority compounds in 36% of reviewed priority lists or 26 and 25 times respectively (Figure 3). This is predictable considering the substantial focus on these two compounds in the literature, documented environmental effects, and their inclusion on the Water Framework Directive (WFD) watch list (Negrao de Carvalho et al. 2015). Risk-based methods dominate priority compound

selection (Figure 3) due to the greater number of studies using this approach (78%), while hazard- and exposure-based make up 12 and 9% of prioritizations, respectively. Of the entire list of identified pharmaceutical priorities (n=332), which represents roughly 17% of drugs in use, only 17 compounds were selected by all three method types. Forty-six were selected by both hazard- and risk-based methods or by both exposure- and risk-based methods. Risk-based methods identified 96% of the pharmaceuticals in Figure 3, while hazard- and exposure-based methods identified 49 and 45% respectively. Clemastine and etonogestrel were identified exclusively by hazard-based methods. Whilst identifying those drugs that are selected most often indicates that these might constitute the highest risk pharmaceuticals, the driving factor behind these selections is uncertain. It seems to be equally driven by hazard and exposure, which is a similar conclusion to that drawn when results were grouped by therapeutic class.

Limitations and opportunities with current methodologies

Prioritization methodologies have differing goals, whether it is deciding on which pharmaceuticals to conduct standard or non-standard effects testing, environmental monitoring, selecting legacy compounds for a targeted ERA, or underpinning risk management options. Many different variations of the three main prioritization approaches were undertaken suggesting that consensus on a suitable method has yet to be reached. Based upon collated previous prioritization results, exposure- and hazard-based approaches likely overlook pharmaceuticals that may pose a potential risk. It was therefore concluded that the use of risk-based approaches for prioritization is preferable. While several risk-based methods are available, these employ different approaches. Some used experimental monitoring data while others utilized exposure predictions. Some use toxicity ‘read-across’ approaches while others employ QSARs developed for general chemicals. Table 2 highlights the strengths, limitations, threats and opportunities of different approaches that were employed previously for risk-based prioritization of pharmaceuticals.

In terms of exposure (Table 2), it is evident that relying upon monitoring data limits the number of compounds than might be considered to those already present in the environment or a small fraction of drugs in use. Prioritization based upon MECs may be skewed by methodological limitations including: limited number of detections, analytical detection limits, compounds considered, or the risks being overstated by using maximal MECs (Vazquez-Roig et al. 2012; Pereira et al. 2016). Therefore prioritizations dependent upon MECs may not be sufficiently comprehensive to provide meaningful results to risk assessors (Caldwell et al. 2014). Conversely, a simple PEC (based on the EMA (2006) approach) permits inclusion of a larger range of compounds in a prioritization, however PECs are complicated by a lack of, or variability in, parameters required to calculate them. Access to regionally defined usage data is important, but sometimes difficult to obtain or does not capture all relevant usage pathways. Over-the-counter (OTC) pharmaceutical usage might be missed by prescription-based usage, while sales data might overlook generic formulations. The public availability of prescription, hospital, and OTC pharmaceutical sales data is uncommon and generally only available at the national or regional scale, which may not be representative of localized conditions. In most countries/regions, pharmaceutical consumption datasets are only available through expensive market research. To overcome this, calculations of per capita drug usage might be estimated similar to an approach used recently in a prioritization in Kazakhstan where usage estimates were based upon the number of products available for each active ingredient utilized in the country (Aubakirova et al. 2017). This accuracy of this method is unknown, as it has yet to be validated against monitoring data.

Another difficulty encountered is the diversity in patient metabolism estimations, compounded with the variability in WWTP removal efficiency along with potential of conjugated metabolites such as glucuronide or sulfato-conjugates to reform the active parent compound due to cleavage of the conjugate during water treatment processes (Burns et al. 2017). Environmental dilution exhibits substantial spatial and temporal variability, which is another significant source of uncertainty. The impact of local dilution variability on simple PECs was investigated by Verlicchi

(2014) and estimated to produce an uncertainty of up to 695%. Environmental fate is generally overlooked which includes dissipation processes such as biodegradation and partitioning to sludge and sediment, both of which affect exposure estimates and potentially prioritization rankings (Booker et al. 2014; Huber et al. 2016). Further, simple PECs are limited to single source systems such as a single WWTP on a river with no upstream contribution, which is not a frequent scenario. Higher-tier spatial models provide an opportunity to move past these limited simple PECs by incorporating multiple pharmaceutical sources and upstream contributions along with in-stream fate to generate spatially relevant PECs. Inclusion of all these factors to derive localized concentrations may be necessary to manage risk at the local/regional level (Gardner et al. 2013), as prioritization results were found to be influenced by localized conditions as well as by the scale at which the exercise is undertaken (e.g. European Union, country, or locally) (Oldenkamp et al. 2016).

In terms of the PNEC (Table 2), experimental ecotoxicity data for pharmaceuticals is limited and to compensate for this, models are extensively utilized which may be inappropriate for all or for specific groups of pharmaceuticals and/or have yet to be validated for drugs specifically. ECOSAR was commonly cited as the source of modelled ecotoxicity data despite many compounds falling outside its applicability domain (Dong et al. 2013; Guo et al. 2016; Ortiz de García et al. 2013). In addition, the relevance to pharmaceuticals is questionable as ECOSAR was originally validated using a small set of industrial chemicals with simple molecular structures dissimilar to those of drugs and mainly acting *via* a non-specific narcosis mode of action (Sangion and Gramatica 2016; Sanderson et al. 2004). Further, non-specific narcosis and apical acute toxicity endpoints such as endpoints related to growth, reproduction and mortality used for ERAs, are likely to occur at concentrations higher than those arising through chronic exposure as these conditions do not reflect low level continuous exposure. Chronic experimental data derived for ERAs, while more suitable for risk assessment than acute data, still focuses on apical endpoints and therefore might also be missing key effects related to the intended mode of action (MoA) of the pharmaceutical (Ankley et al. 2007; Brausch et al. 2012). Therefore a prioritization approach which captures MoA-based concerns concomitant with

apical endpoints, need to be incorporated into a prioritization framework aimed at informing risk assessment monitoring and testing strategies to ensure these potential risks are not overlooked.

Although the results of the reviewed prioritizations are useful; there are several general scope limitations that potentially diminish confidence in the findings. Certain prioritization approaches remove pharmaceuticals that lack relevant experimental data (Stuer-Lauridsen et al. 2000; Jones et al. 2002; Besse et al. 2008), thus a criticism of prioritization is that it continually prioritizes pharmaceuticals that have already been examined; the phenomenon is termed the 'Matthew Effect' (Daughton 2014). Suitable models, which are validated and may be applied across physico-chemically diverse range of pharmaceuticals are required to overcome this limitation. All prioritizations reviewed considered a single pharmaceutical source to the environment, WWTP discharge. Many compounds are manufactured in countries such as India or China, where investigations showed manufacturing effluent reached concentrations of 237 mg/L in production heavy regions, leading to localized pharmaceutical hot spots (Cardoso et al. 2014; Lübbert et al. 2017; Larsson 2014). Moreover, while less manufacturing is done in Europe and North America, increased pharmaceutical loads in surface water due to manufacturing were documented at concentrations 30-500-fold higher than those in unaffected areas (Phillips et al. 2010), highligting the fact that this is a global consideration. Not considering these sources may thus markedly underestimate risks and therefore identification of priority compounds (Larsson 2014).

The main focus of the reviewed prioritizations was on a single environmental compartment, surface water. The reason for limiting the scope to surface water might be a current lack of validated exposure models suitable for predicting concentrations in other relevant environmental compartments such as sediments, biosolids, soils and porewater. Only three prioritizations included or focused on the sediment compartment (Al-Khazrajy and Boxall 2016; Olsen et al. 2013; Casado-Martinez et al. 2017). Another exposure pathway overlooked in the vast majority of reviewed approaches is the application of biosolids (Guo et al. 2016) and reclaimed irrigation waters (Lees et

al. 2016) to agricultural fields. Agricultural soil exposure is derived from sludge concentrations of pharmaceuticals in WWTPs, which is the result of sorption characterized by the sludge/water partition coefficient (K_d) (Berthod et al. 2017). Most sorption models are driven by hydrophobicity (i.e. logKow > 4), however many pharmaceuticals are ionizable at environmentally relevant pH values and Pan et al. (2009) demonstrated that sorption is also affected by ionic state. Therefore models that estimate sorption and do not consider the ionic state of a compound may be unreliable; an example is the commonly used STPWIN model (US Environmental Protection Agency 2015), as estimates of pharmaceuticals in both WWTP sludge and the aquatic environment may be over/underestimated (Dong et al. 2013; Sanderson et al. 2004). Models that do include ionic state considerations (e.g. SimpleTreat 4.0) are thus preferred.

The absence of ecotoxicity data or validated ecotoxicity models available, is another factor which may have contributed to the scope of reviewed prioritizations encapsulating only the water column. There is evidence that drugs were detected in invertebrate organisms in benthos and soil (Grabicova et al. 2015; Heye et al. 2016; Karlsson et al. 2016; Kinney et al. 2008); therefore, risks to these compartments needs to be considered. In addition, potential risks to predators and humans have, with a few exceptions (Murray-Smith et al. 2012; Guo et al. 2016), been overlooked, despite recent findings to suggest that these risks may be present (Wang et al. 2016; Mottaleb et al. 2016; Franklin et al. 2016; Malchi et al. 2014; Oaks et al. 2004). Therefore, several opportunities to improve prioritization exist, such as including understudied environmental pathways and compartments, diet and food chain assessments for predators, pharmaceutical sources beyond the WWTP, and inclusion of MoA-based concerns concomitant with apical ecotoxicological effects data. The following section brings together the strengths of existing methods and attempt to overcome current limitations in scope to develop an optimal prioritization framework which may be used in the future for pharmaceutical prioritization.

Proposed prioritization framework

The proposed prioritization methodology uses a tiered, risk-based approach. The method is holistic in that it: (1) considers all relevant environmental compartments; (2) assesses specific risks to plants, invertebrates, vertebrates and mammals (human and non-human) as well as incorporating food chain interactions; and (3) considers endpoints related to MoA, in addition to apical acute and chronic ecotoxicological endpoints of a pharmaceutical. It is based upon models capable of leveraging existing data to overcome bias towards data-rich or -poor pharmaceuticals when generating risk ranks. The framework also accounts for differences in pathways of exposure for different regions as well as variations in the drivers of exposure such as differences in water chemistry which affect compound uptake and equilibrium partitioning. The framework will be underpinned by thorough model validation and defined applicability domains to yield greater confidence in results whilst highlighting current weaknesses and knowledge gaps. In the future, the overall approach needs to be validated against both lab and field data to demonstrate it is a reliable tool in pharmaceutical prioritization.

Navigating the Framework

The starting point and progression through the framework is dependent upon the question being asked, which generally falls into one of 4 main categories: i) Identifying highest risk pharmaceuticals from the approximately 1900 APIs in use to determine which are in greatest need of targeted relevant effects testing or ERAs, ii) developing a catchment-scale or national monitoring campaign to determine the status of predicted risks in the real world, iii) identifying compounds posing a risk at regional or local scales, for effects research based upon predicted effects data, or iv) identifying risk mitigation measures that aim to minimize the mass of an API reaching the environment, for example risk-benefit analysis, WWTP upgrades, reductions of incorrect disposal, increased pharmaceutical bioavailability, or incorporation into legislation such as the WFD.

The acquisition of relevant pharmaceutical consumption data is critical to progressing through the exposure component of the framework regardless of the research question (Figure 4). Despite the shortcomings of PECs and difficulties in obtaining accurate consumption data, these should still be favored for prioritization over a MEC, to ensure a wider range of pharmaceuticals is considered and potent drugs with high analytical limits of detection are not overlooked. Effluents from pharmaceutical manufacturing facilities need to be treated using a tailored approach, as many compounds are produced through batch production producing transient pharmaceutical hot spots, in contrast to low level continuous therapeutic use. Manufacturing PECs require knowledge of industrial manufacturing schedules, batch production and a mass balance of pharmaceutical recovery and losses (Murray-Smith et al. 2012) paired with localized effluent and environmental dilution. In the case of hospitals treating and releasing their own effluent, these sources also need to be accounted for. In addition to the sources, interactions between environmental compartments also need to be considered, including re-partitioning between pore water and sediment/soil as well as between these solid phases and surface water.

A limitation with the framework is pharmaceutical sources currently not considered because their impacts are expected to be minimal or localized, such as septic systems, CSOs, animal husbandry, aquiculture and landfills. There are currently no apparent models available to incorporate these pathways; however, as such models become available these need to be incorporated into the framework. Further, spatial and temporal variations in pharmaceutical usage and environmental conditions might impact the accuracy of exposure predictions. Higher-tier spatial exposure models are most desirable to accommodate spatial variability; however, these are currently only available for certain regions. When not available, the scale at which a prioritization is conducted dictates whether EMA (2006) suggested defaults (Supplementary Material) for parameters such as environmental dilution are most suitable (e.g. national scale) or whether the inclusion of site-specific parameters would be useful (e.g. local scale) (Burns et al. 2017). There is a limited, but growing knowledge of temporal fluctuations of pharmaceutical concentrations in the

environment (Burns et al. 2018). Currently, there are no apparent models or initiatives to include this temporal variability in exposure predictions, which is a limitation of both prioritization and risk assessment initiatives. To compensate for enhanced environmental pharmaceutical loading from sources not currently considered, as well as spatial and temporal variability, a series of exposure scenarios may be calculated similar to Perazzolo et al. (2010). This includes using different combinations of WWTP removal estimations (no removal, lowest estimated and highest estimated removal) and environmental dilution such as no dilution, factor of 10 dilution and site-specific dilution.

Prioritizations were also developed to include PECs for major active metabolites (Lienert et al. 2007; Besse et al. 2008; Guo et al. 2016). Evidence showed that the majority of metabolites are less potent than parent compound (Obach 2013), although exceptions do exist (Besse and Garric 2010; Celiz et al. 2009). In addition, glucuronide or sulfated metabolites may revert back to parent drug during water treatment (Jelic et al. 2011), therefore the fraction of these metabolites excreted needs to be added to the active pharmaceutical excretion estimate. For a worst case approach, when the excretion or potency of an active metabolite is unknown, a total residue approach (e.g. no metabolism), similar to that used for ERA, may be employed to account for potentially risky metabolites with limited data which might then be assessed in greater detail at a later stage. In addition, the current framework focuses on assessing risks of pharmaceuticals singly, which might be underestimating risks posed by pharmaceutical mixtures, as mixture toxicity was reported in lab-based studies (Vasquez et al. 2014). Initially, it is important to master single compound approaches prior to introducing further potential error by working with mixtures toxicity models. As the mixture toxicity models develop and exposure models presented herein validated, mixture toxicity may be incorporated into the framework.

A prioritization needs to begin by considering as many pharmaceuticals as possible, enabling investigation of the large proportion of compounds currently in the ‘unknown’ region presented in

Figure 1. It is suggested to begin with the aquatic compartment (Figure 5), subsequently assess the sediment compartment as $PEC_{surfacewater}$ is required to calculate $PEC_{sediment}$ (Figure 4). Both the A (apical ecotoxicity endpoints) and B (MoA-based concerns) methods need to be used for both aquatic and sediment compartments. For the terrestrial assessment (Figure 5), the mass of pharmaceutical sorbed to sludge in the WWTP (PEC_{sludge}) along with $PEC_{effluent}$ to represent irrigation with reclaimed wastewater both contribute to the PEC_{soil} estimate (Figure 4). The food chain assessments, terrestrial (Figure 5) or aquatic (Figure 6), need to be triggered for all pharmaceuticals assessed in the relevant environmental compartment (aquatic or soil). This is due to the lack of experimental biomagnification and bioaccumulation factors and therefore understanding of how pharmaceuticals may accumulate through the food chain. If risks are identified, further refinements to exposure may be made, for example estimating drug metabolism in wildlife or employing more complex ecosystem modelling approaches. For human assessment, $PEC_{surfacewater}$ is employed in this assessment to reflect the worst case scenario or direct exposure such as wildlife swimming or drinking. In addition to $PEC_{surfacewater}$, human assessment also needs to include all compounds which undergo a food chain assessment in the either aquatic or soil compartment (Figure 6). This approach may also be utilized by water managers when the mere presence, despite limited risks, of certain compounds requires action to reduce (e.g. X-ray contrast media). In these cases, the $PEC_{surfacewater}$ might be compared directly to the established safety/exposure value (Figure 6).

These sequential assessments lead to risk score (PEC/PNEC) lists for each considered environmental compartment (Figure 5 and 6) as well as two risk score (RS) lists in cases where an A and B scenario are presented, Figure 5. A RS of 1 or greater indicates that PEC is equivalent to or higher than PNEC, thus a risk may be present. It is suggested that as part of a conservative approach, any compound with a RS greater than 0.1 needs to be ranked as a priority, with the largest RS ranking as the highest priority. The parameters needed to apply each of the models presented in each of the assessment scenarios is listed in the dotted box with a number (Figures 4 to 6). The availability of these parameters and reliability of the models/experimental data that are used to

derive them is crucial to the success of the prioritization and a frequently cited limitation (Guo et al. 2016; Bouissou-Schurtz et al. 2014). The current knowledge surrounding these parameters and models is detailed in Supplementary Material, Table S2.

Why a new prioritization framework is needed

Results demonstrated that over 75 human pharmaceutical prioritizations have been undertaken globally (Figure 2). However the multitude of suggested approaches indicate that credibility for any particular approach is low, especially when prioritizations are repeated in the same region. Different sets of priority compounds are expected based upon the region and scale of assessment (Figure 2), due to differences in populations, prescribing practices and hydrology. Therefore deriving some level of standardization, such as this framework, might be important for harmonization of research and regulatory goals across the world, as prioritization results obtained using the same methodology may be comparable. Moreover, our approach goes beyond the aquatic compartment to prioritize risks in sediment, soil and exposure *via* the food chain to provide a compressive assessment of all relevant environmental compartments. These considerations are especially important when put in a global context. For example, biosolids containing pharmaceuticals were noted as a significant pathway by which drugs enter and accumulate in terrestrial environment (Kinney et al. 2006b). In addition, compounds might persist in soils and build up to detectable concentrations after repeated applications of reclaimed wastewater (Chefetz et al. 2008; Kinney et al. 2006a). The use of both treated and untreated reclaimed wastewater and biosolids in agriculture is a widely adopted practice in countries suffering from water shortages such as Mexico, Israel, Australia and Southern Europe. (Asano et al. 2007; Pedrero et al. 2010; Dalkmann et al. 2012; Lees et al. 2016) Further, crops are grown on agricultural soils and cattle producing meat and milk are grazing on grasslands that have been amended with sludge-based biosolids and/or reclaimed wastewater, which poses a potential risk of indirect human exposure via these products (Mohapatra

et al. 2016; Paz et al. 2016; Kinney et al. 2006a), which was previously demonstrated (Mottaleb et al. 2016; Franklin et al. 2016; Malchi et al. 2014).

The expansion beyond exposure to aquatic compartments is important, however this needs to be paired with intelligent approaches of effect estimation capable of capturing pharmaceutical potency across diverse range of pharmaceuticals in use, even when available parameters are limited to certain physico-chemical properties (e.g. LogP and pKa) and those derived during drug development (e.g. Cmax and ADME parameters). This intelligent effect estimation is achieved through a combination of apical and MoA-related endpoints in aquatic, benthic and terrestrial species belonging to multiple trophic levels. Further, the prioritization of risks from food chain exposures in predators as well as humans was only apparently reported in a single prioritization (Guo et al. 2016). Our framework builds upon this and reflects realistic dietary habits consisting of multiple prey sources and/or vegetation.

While many aspects of the framework are similar to previous prioritization approaches, a major departure concerns consideration of MoA-based issues. Due to their larger assessment factor, acute PNECs based upon experimental data were demonstrated as consistently lower than chronic PNECs (except when a chronic MoA of concern is present) and therefore protective (Vestel et al. 2016). The application of this approach might only continue to replicate prioritization of acute endpoints, while the more environmentally relevant chronic concerns may go unaddressed. Predicted acute data in previous prioritizations are almost entirely derived from unsuitable models (e.g. ECOSAR) and have little relevance to real world exposures (Hulzebos and Posthumus 2003; de Haas et al. 2011). Instead, development of new chronic QSARs may be more useful for identifying pharmaceuticals without a concerning MoA, while other approaches are required to identify pharmaceuticals with MoA concerns.

The MoA considerations involve predicting internal concentrations and relating them to therapeutic effect levels in humans such as using the fish plasma model (FPM) (Huggett et al. 2003).

Endocrine disruption which might be related to human side effects/unintended uses were recently observed in fish at concentrations lower than the therapeutic level (Niemuth and Klaper 2016). In addition, the decline of vultures (*Gyps bengalensis*) in Pakistan was linked to the organism exhibiting a known side effect of diclofenac (renal failure) (Oaks et al. 2004). Data suggest the therapeutic concentration alone may not be sufficiently protective to encompass the concentrations at which side effects occur. Therefore application of a safety factor originally suggested to encompass cross-species sensitivity might also be appropriate to account for potential side effects or effects pertaining to the unintended or unauthorized use of a pharmaceutical (Huggett et al. 2003; Niemuth and Klaper 2016).

Teleost fish possess approximately 80% of drug targets through ortholog conservation, while certain invertebrate species conserve 50-60% of drug targets (Vebruggen et al. 2018). Exposure of *Daphnia magna* to pharmaceuticals with highly conserved drug targets resulted in predictable molecular effects, while exposure to compounds with non-conserved drug targets did not exert an effect, implying that 'read-across' approaches might also be important for invertebrates (Furuhagen et al. 2014). Therefore, expanding past fish to also predict internal invertebrate concentrations may be useful. While less appropriate than for teleost fish, comparison with therapeutic concentrations with a safety factor applied may be a useful starting point for flagging compounds which might pose a potential risk to invertebrates. Complex bioinformatic approaches may then be utilized to further prioritize identified pharmaceuticals based upon the extent of evolutionary conservation of relevant receptors. The FPM still requires further experimental work but is a promising tool (Margiotta-Casaluci et al. 2014; Patel et al. 2016), while development of an invertebrate internal concentration (IIC) model which considers invertebrate specific uptake (e.g. invertebrate BCFs) may serve as an important step to ensuring potential risks are not missed. The goal of using FPM and potentially IIC is to identify the majority of MoA-based concerns (Figure 5), from where targeted and more complex predictive approaches beyond the scope of the prioritization framework might be used to inform effects testing.

In summary, our proposed approach builds upon many of the ideas presented in previous prioritization exercises and brings them together in a coherent and comprehensive framework. The framework does resemble a risk assessment, which is intentional as the aim of the optimal prioritization framework is to underpin the ERA process. The goal of a prioritization undertaken using this framework will be to identify which pharmaceuticals are of greatest risk and as it is holistic, in which environmental compartments/food chains these risks are most likely to emerge. After prioritization, the most at-risk species in the relevant environmental compartment or food chain might be identified, for example using bioinformatic approaches where % of evolutionary conservation of drug targets within the species of interest may be a precursor to testing effects (Verbruggen et al. 2018) or more complex ecosystems models employed to better characterize risks predicted exposure in food chains. In this way, effect studies might be directed towards the most sensitive species and most pertinent endpoints to examine, resulting in a reduction in number of test animals required. If evolutionary conservation of a drug target is identified in a species, the evaluation can enter the experimental stage. Targeted chronic effects testing is then undertaken and environmental exposure may be demonstrated through monitoring. As the effect endpoints are most likely non-standard or molecular, approaches such as the adverse outcome pathway (AOP) framework (Ankley et al. 2010) might be employed to help put this mechanistic toxicological data in context and fed into the risk assessment process. In this manner, pharmaceutical prioritization might serve as the basis to inform further risk assessment, such that confidence in prioritization outcomes is important. It is recognized that simplicity is advantageous, but difficulties arise when using unsuitable QSARs for one size fits all fate and effects estimation. Extensive use of these QSARs leads to similar compounds being identified as priority pharmaceuticals continuously (Figure 3), which is not beneficial when attempting to identify knowledge gaps. Our framework tackles these biases by promoting more intelligent assessment approaches and clearly identifying where research is needed to implement this optimum framework. The following section describes data availability and state of models required to implement our framework.

Data availability and quality

Each of the experimental parameters required to parameterize the exposure and effect models mentioned in Figures 4 to 6 were evaluated for availability in Table 3. For brevity, a high-level overview of each parameter is presented while specifics such as OECD tests, default values and QSARs may be found in the Supplementary Material, Table S2. The intention of Table 3 is to detail relative availability of data required for our prioritization and highlight where research is needed most to achieve parameterization of the optimum framework. In addition to the optimum framework, further development and validation of the tools and models in Table 3 might also be useful for incorporating environmental considerations earlier in the pharmaceutical development process itself.

The experimental sources in Table 3 relate to environmental measurements or data from the peer-reviewed literature. Tailoring the parameters listed as defaults is recommended for localized prioritization or those outside of the region they were developed for (e.g. EU). Wastewater generation practices vary globally by 50-400 L/per person·day (Henze and Comeau 2008), while environmental dilution of 10 may not be sufficiently protective in some regions or overly conservative in others (Gardner et al. 2013; Verlicchi et al. 2014).

It is immediately clear from the status of parameters in Table 3, that models are lacking that adequately predict the behavior of ionizable compounds. A red designation in Table 3 indicates a research gap that needs to be filled in order to effectively implement the prioritization. The 'Intelligent assessment of Pharmaceuticals in the Environment (iPiE)' column was included in Table 3 to demonstrate the type of data and estimated coverage held by industry which is currently being developed into an online database as part of a large European initiative. It is anticipated that this database will become available to the research community in the future. The database may be used as a data source or to reduce the 'Matthew Effect' where previously studied compounds are subject to similar tests repeatedly. The iPiE database contains high quality data and thus might reduce

reliance on unsuitable experimental data or QSARs. Prioritization is an exercise in efficiency, and a database such as this might vastly improve the efficiency of the process.

Conclusions

The overall reliability of the models required to progress through the proposed prioritization framework (Figures 4 to 6) was evaluated based upon the status of parameters from the previous section and experimental validation from the literature. Detailed results may be found in Supplementary Material, Table S2, while a summary of results is presented in Table 4. The largest knowledge gaps and therefore greatest research needs are easily identifiable by the red colors and pertain largely to terrestrial species and invertebrates both aquatic and terrestrial. This summary may be used as a guide to direct further development of predictive models that are a) suitable and validated for pharmaceuticals and b) have applicability domains encompassing the majority of compounds. As these knowledge gaps are filled, the optimal prioritization framework might emerge and be suitable for assessing risks to relevant environmental compartments globally so that a greater focus may be placed upon risk mitigation where is it most needed.

The majority of pharmaceuticals do not have an ERA and current risk assessment approaches do not address all relevant environmental compartments and exposure scenarios. There is therefore a real need for a prioritization methodology to identify those molecules that have not been tested which are of a potential concern in the environment as well as potentially identifying where risk mitigation measures may be required. Many prioritization approaches were proposed in the literature. The majority of these use a risk-based approach, which in many cases is the combination of limited or inappropriate hazard- and effect-based methods not suited for all pharmaceuticals or exposure scenarios. The methods have tended to focus on aquatic exposure scenario and on the few regions of the world with a developed wastewater and drinking water treatment infrastructure and low levels of grey water reuse. This review has brought together the most promising components

from several approaches and presented them as part of a holistic framework for prioritizing risks posed by pharmaceuticals to multiple environmental compartments. Much research is still required to confidently administer the prioritization framework, including both model development and validation; nevertheless it could form an important part of the risk assessment process to ensure risks to environment are not missed.

Acknowledgements

The present work was funded by the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 608014 (CAPACITIE) and partly supported by the EU/EFPIA Innovative Medicines Initiative Joint Undertaking (iPiE Grant 115635).

References

Alder, A.C., C. Schaffner, M. Majewsky, J. Klasmeier, K. Fenner. 2010 Fate of β-blocker human pharmaceuticals in surface water: Comparison of measured and simulated concentrations in the Glatt Valley Watershed, Switzerland. *Water Res.* 44: 936–948.

Al-Khazrajy, O.S.A., and A.B.A. Boxall. 2016. Risk-based prioritization of pharmaceuticals in the natural environment in Iraq. *Environ. Sci. Pollut. Res.* 23: 15712–15726.

Ankley, G.T., B.W. Brooks, D.B. Huggett, and J.P. Sumpter. 2007. Repeating history: Pharmaceuticals in the environment. *Environ. Sci. Technol.* 41: 8211–8217.

Ankley G.T., Bennett, R.S., Erickson, R.J., Hoff, D.J., Hornung, M.W., Johnson, R.D., Mount, D. R., Russom, C.L., Schmeider, P.K., Serrano, J. A., Tietge, J.E., Villeneuve, D.L. 2010. Adverse outcome pathways: A conceptual framework to support ecotoxicology research and risk assessment. *Environ. Toxicol. Chem.* 29: 730–741.

Asano, T., A.D. Levine, H. Leverenz, R. Tsuchihashi, and G. Tchobanoglous. 2007. *Water Reuse: Issues, Technologies, and Applications*. New York: McGraw-Hill.

Aubakirova, B., R. Beisenova, and A.B. Boxall. 2017. Prioritization of pharmaceuticals based on risks to aquatic environments in Kazakhstan. *Integr. Environ. Assess. Manage.* 5: 832–839.

aus der Beek, T., F.-A. Weber, A. Bergmann, S. Hickmann, I. Ebert, A. Hein, and A. Küster. 2016. Pharmaceuticals in the environment-global occurrences and perspectives. *Environ. Toxicol. Chem.* 35: 823–835.

Batt, A.L., E.T. Furlong, H.E. Mash, S.T. Glassmeyer, and D.W. Kolpin. 2017. The importance of quality control in validating concentrations of contaminants of emerging concern in source and treated drinking water samples. *Sci. Total Environ.* 579: 1618–1628.

Bergheim, M., R. Gminski, A.B. Spangenberg, C. Malgorzata, D. Ebiak, D.A. Bü, V. Mersch-Sundermann, K. Kü, and R. Gier. 2014. Recalcitrant pharmaceuticals in the aquatic environment: A comparative screening study of their occurrence, formation of photo-transformation products and their *in vitro* toxicity. *Environ. Chem.* 11: 431–444.

Berninger, J.P., C.A. Lalone, D.L. Villeneuve, and G.T. Ankley. 2016. Prioritization of pharmaceuticals for potential environmental hazard through leveraging a large-scale mammalian pharmacological dataset. *Environ. Toxicol. Chem.* 35: 1007–1020.

Berthod, L., D.C. Whitley, G. Roberts, A. Sharpe, R. Greenwood, and G.A. Mills. 2017. Quantitative structure-property relationships for predicting sorption of pharmaceuticals to sewage sludge during waste water treatment processes. *Sci. Total Environ.* 579: 1512–1520.

Besse, J.-P., and J. Garric. 2010. Environmental risk assessment and prioritisation strategies for human pharmaceuticals, review and discussion. In *Pharmaceuticals in the Environment: Current Knowledge and Need Assessment to Reduce Presence and Impact*, ed. B. Roig. London: IWA Publishing. pp.137–168.

Besse, J.P., C. Kausch-Barreto, and J. Garric. 2008. Exposure assessment of pharmaceuticals and their metabolites in the aquatic environment: Application to the French situation and preliminary prioritisation. *Human Ecol. Risk Assess.* 14: 665–695.

Besse, J.P., J.F. Latour, and J. Garric. 2012. Anticancer drugs in surface waters. What can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs? *Environ. Int.* 39: 73–86.

BIO Intelligence Service, 2013. Study on the environmental risks of medicinal products, Final Report prepared for Executive Agency for Health and Consumers.

Booker, V., C. Halsall, N. Llewellyn, A. Johnson, and R. Williams. 2014. Prioritising anticancer drugs for environmental monitoring and risk assessment purposes. *Sci. Total Environ* 473–474: 159–170.

Bouissou-Schurtz, C., P. Houeto, M. Guerbet, M. Bachelot, C. Casellas, A.C. Mauclaire, P. Panetier, C. Delval, and D. Masset. 2014. Ecological risk assessment of the presence of pharmaceutical residues in a French national water survey. *Reg. Toxicol. Pharmacol.* 69: 296–303.

Boxall, A.B.A., M.A. Rudd, B.W. Brooks, D.J. Caldwell, K. Choi, S. Hickmann, E. Innes, T. Verslycke, G.T. Ankley, K.F. Beazley, S.E. Belanger, J.P. Berninger, P. Carriquiriborde, A. Coors, P.C. DeLeo, S.D. Dyer, J.F. Ericson, F. Gagné, J.P. Giesy, T. Gouin, L. Hallstrom, M.V. Karlsson, D.G.J. Larsson, J.M. Lazorchak, F. Mastrocco, A. McLaughlin, M.E. McMaster, R.D. Meyerhoff, R. Moore, J.L. Parrott, J.R. Snape, R. Murray-Smith, M.R. Servos, P.K. Sibley, J.O. Straub, N.D. Szabo, E. Topp, G.R. Tetreault, V.L. Trudeau, and G. Van Der Kraak. 2012. Pharmaceuticals and personal care products in the environment: What are the big questions? *Environ. Health Persp.* 120: 1221–1229.

Brausch, J.M., K.A. Connors, B.W. Brooks, and G.M Rand. 2012. Human pharmaceuticals in the aquatic environment: A review of recent toxicological studies and considerations for toxicity testing. *Rev. Environ. Contam. Toxicol.* 218: 1–99.

Brodin T, J. Nordling, A. Lagesson, J. Klaminder, G. Hellström, B. Christensen, and J. Fick. 2017. Environmental relevant levels of a benzodiazepine (oxazepam) alters important behavioural traits in a common planktivorous fish, (*Rutilus rutilus*). *J Toxicol Environ Health A* 80: 963-970.

Burns, E.E., J. Thomas-Oates, D.W. Kolpin, E.T. Furlong, and A.B.A. Boxall. 2017. Are exposure predictions, used for the prioritization of pharmaceuticals in the environment, fit for purpose? *Environ. Toxicol. Chem*. 36, 2823–2832.

Burns, E.E., L.J. Carter, D.W. Kolpin, J. Thomas-Oates, and A.B.A. Boxall. 2018. Temporal and spatial variation in pharmaceuitcal concentrations in an urban river system. *Water Res.* 137: 72–85.

Caldwell, D.J., F. Mastrocco, L. Margiotta-Casaluci, and B.W. Brooks. 2014. An integrated approach for prioritizing pharmaceuticals found in the environment for risk assessment, monitoring and advanced research. *Chemosphere* 115: 4–12.

Cardoso, O., J.-M. Porcher, and W. Sanchez. 2014. Factory-discharged pharmaceuticals could be a relevant source of aquatic environment contamination: Review of evidence and need for knowledge. *Chemosphere* 115: 20–30.

Casado-Martinez, M., M. Wildi, B. Ferrari, and I. Werner. 2017. Prioritization of substances for national ambient monitoring of sediment in Switzerland. *Environ. Sci. Pollut. Res*. 25: 3127-3138.

Castiglioni, S., R. Bagnati, R. Fanelli, F. Pomati, D. Calamari, and E. Zuccato. 2006. Removal of pharmaceuticals in sewage treatment plants in Italy. *Environ. Sci. Technol.* 40: 357–363.

Celiz, M.D., J. Tso, and D.S. Aga. 2009. Pharmaceutical metabolites in the environment: Analytical challenges and ecological risks. *Environ. Toxicol. Chem.* 28: 2473–2484.

Chefetz, B., T. Mualem, and J. Ben-Ari. 2008. Sorption and mobility of pharmaceutical compounds in soil irrigated with reclaimed wastewater. *Chemosphere* 73: 1335–1343.

Christen, V., S. Hickmann, B. Rechenberg, and K. Fent. 2010. Highly active human pharmaceuticals in aquatic systems: A concept for their identification based on their mode of action. *Aquat. Toxicol.* 96: 167–181.

Cunningham, V.L., S.P. Binks, and M.J. Olson. 2009. Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment. *Reg. Toxicol. Pharmacol.* 53: 39–45.

Cuthbert, R.J., M.A. Taggart, V. Prakash, S.S. Chakraborty, P. Deori, T. Galligan, M. Kulkarni, S. Ranade, M. Saini, A.K. Sharma, et al. 2014. Avian scavengers and the threat from veterinary pharmaceuticals. *Phil. Trans. R. Soc. B. Biol. Sci.* 369: 20130574.

Dalkmann, P., M. Broszat, C. Siebe, E. Willaschek, T. Sakinc, J. Huebner, W. Amelung, E. Grohmann, and J. Siemens. 2012. Accumulation of pharmaceuticals, *Enterococcus*, and resistance genes in soils irrigated with wastewater for zero to 100 Years in Central Mexico. *PLoS ONE* 7: e45397.

Datapharm Communications Limited. 2017. The Electronic Medicines Compendium (eMC). *Medicines*. https://www.medicines.org.uk/emc/browse-documents. Accessed: 2017-08-21

Daughton, C.G. 2014. The Matthew Effect and widely prescribed pharmaceuticals lacking environmental monitoring: Case study of an exposure-assessment vulnerability. *Sci. Total Environ.* 466–467: 315–325.

de Haas, E.M., T. Eikelboom, and T. Bouwman. 2011. Internal and external validation of the long-term QSARs for neutral organics to fish from ECOSAR. *SAR QSAR Environ. Res.* 22: 545–559.

Diamond, J.M., H.A. Latimer, K.R. Munkittrick, K.W. Thornton, S.M. Bartell, and K.A. Kidd. 2011. Prioritizing contaminants of emerging concern for ecological screening assessments. *Environ. Toxicol. Chem.* 30: 2385–2394.

Dong, Z., D.B. Senn, R.E. Moran, and J.P. Shine. 2013. Prioritizing environmental risk of prescription pharmaceuticals. *Reg. Toxicol. Pharmacol.* 65: 60–67.

Environmental Health Analysis Centre under contract to the Office of Chemical Safety and Pollution Prevention. 2016. PBT Profiler, A Component of OPPT'S P2 Framework: Assessing Chemicals in the Absence of Data. U.S. Environmental Protection Agency. http://www.pbtprofiler.net/ (accessed November 3, 2017).

European Medicines Agency (EMA). 2006. Pre-Authorisation evaluation of medicines for human use: Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CHMP/SWP/4447/00. Committee for Medicinal Products for Human Use, London, UK. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003978.pdf (accessed November 3, 2017).

European Medicines Agency (EMA). 2017. Human medicines: European Public Assessment Reports. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125 (accessed August 21, 2017).

Fàbrega, F., M. Marquès, A. Ginebreda, M. Kuzmanovic, D. Barceló, M. Schuhmacher, J.L. Domingo, and M. Nadal. 2013. Integrated risk index of chemical aquatic pollution (IRICAP): Case studies in Iberian rivers. *J. Hazard. Mater.* 263: 187–196.

Feijtel, T., G. Boeije, M. Matthies, A. Young, G. Morris, C. Gandolfi, B. Hansen, K. Fox, M.Holt, V. Koch, R. Schroder, et al. Development of a geography-referenced regional exposure assessment tool for European rivers – Great-ER: Contribution to GREAT-ER #1. 1997. *Chemosphere* 34: 2351–2373

Fick, J., R.H. Lindberg, M. Tysklind, and D.G.J. Larsson. 2010. Predicted critical environmental concentrations for 500 pharmaceuticals. *Reg. Toxicol. Pharmacol.* 58: 516–523.

Franklin, A.M., C.F. Williams, D.M. Andrews, E.E. Woodward, and J.E. Watson. 2016. Uptake of three antibiotics and an antiepileptic drug by wheat crops spray irrigated with wastewater treatment plant effluent. *J. Environ. Qual.* 45: 546.

Furuhagen, S., A. Fuchs, E. Lundström Belleza, M. Breitholtz, and E. Gorokhova. 2014. Are pharmaceuticals with evolutionary conserved molecular drug targets more potent to cause toxic effects in non-target organisms? *PloS One* 9: e105028.

Gardner, M., V. Jones, S. Comber, M.D. Scrimshaw, T. Coello-Garcia, E. Cartmell, J. Lester, and B. Ellor. 2013. Performance of UK wastewater treatment works with respect to trace contaminants. *Sci. Total Environ.* 456–457: 359–369.

Gaw, S., and B.W. Brooks. 2016. Changing tides: Adaptive monitoring, assessment, and management of pharmaceutical hazards in the environment through time. *Environ. Toxicol. Chem.* 35: 1037–1042.

Götz, C.W., C. Stamm, K. Fenner, H. Singer, M. Schärer, and J. Hollender. 2010. Targeting aquatic microcontaminants for monitoring: Exposure categorization and application to the Swiss situation. *Environ. Sci. Pollut. Res.* 17: 341–354.

Grabicova, K., R. Grabic, M. Blaha, V. Kumar, D. Cerveny, G. Fedorova, and T. Randak. 2015. Presence of pharmaceuticals in benthic fauna living in a small stream affected by effluent from a municipal sewage treatment plant. *Water Res.* 72: 145–153.

Guo, J., C.J. Sinclair, K. Selby, and A.B.A. Boxall. 2016. Toxicological and ecotoxicological risk-based prioritization of pharmaceuticals in the natural environment. *Environ. Toxicol. Chem.* 35: 1550–1559.

Henze, M., and Y. Comeau. 2008. *Biological Wastewater Treatment Principles, Modelling and Design*. Ed. Mogens Henze, M.C.M van Loosdrecht, G.A. Ekama, and D. Brdjanovic. London: IWA Publishing.

Heye, K., D. Becker, C. Lütke Eversloh, V. Durmaz, T.A. Ternes, M. Oetken, and J. Oehlmann. 2016. Effects of carbamazepine and two of its metabolites on the non-biting midge *Chironomus Riparius* in a sediment full life cycle toxicity test. *Water Res.* 98: 19–27.

Hollander, A., F. Sauter, H. den Hollander, M. Huijbregts, A. Ragas, and D. van de Meent. 2007. Spatial variance in multimedia mass balance models: Comparison of LOTOS–EUROS and SimpleBox for PCB-153. *Chemosphere* 68: 1318–1326.

Howard, P.H., and D.C.G. Muir. 2011. Identifying new persistent and bioaccumulative organics among chemicals in commerce II: Pharmaceuticals. *Environ. Sci. Technol.* 45: 6938–6946.

Huber, S., M. Remberger, L. Kaj, M. Schlabach, H.Ó. Jörundsdóttir, J. Vester, M. Arnórsson, I. Mortensen, R. Schwartson, and M. Dam. 2016. A first screening and risk assessment of pharmaceuticals and additives in personal care products in waste water, sludge, recipient water and sediment from Faroe Islands, Iceland and Greenland. *Sci. Total Environ.* 562: 13–25.

Huggett, D.B., J.C. Cook, J.F. Ericson, and R.T. Williams. 2003. A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. *Human Ecol. Risk Assess.* 9: 1789–1799.

Hulzebos, E.M., and R. Posthumus. 2003. (Q)SARs: Gatekeepers against risk of chemicals? *SAR QSAR Environ. Res.* 14: 285–316.

Itzel, F., L. Gehrmann, H. Bielak, P. Ebersbach, A. Boergers, H. Herbst, C. Maus, A. Simon, E. Dopp, M. Hammers-Wirtz, T. Schmidt and J. Tuerk. 2017. Investigation of full-scale ozonation at a municipal wastewater treatment plant using a toxicity-based evaluation concept. *J Toxicol Environ Health A* 80: 1242-1258.

Jelic, A., M. Gros, A. Ginebreda, R. Cespedes-Sánchez, F. Ventura, M. Petrovic, and D. Barcelo. 2011. Occurrence, partition and removal of pharmaceuticals in sewage water and sludge during wastewater treatment. *Water Res.* 45: 1165–1176.

Ji, K., E.J. Han, S. Back, J. Park, J. Ryu, and K. Choi. 2016. Prioritizing human pharmaceuticals for ecological risks in the freshwater environment of Korea. *Environ. Toxicol. Chem.* 35: 1028–1036.

Jones, O.A.H., N. Voulvoulis, and J.N. Lester. 2002. Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. *Water Res.* 36: 5013–5022.

Karlsson, M. V., S. Marshall, T. Gouin, and A.B.A. Boxall. 2016. Routes of uptake of diclofenac, fluoxetine, and triclosan into sediment-dwelling worms. *Environ. Toxicol. Chem.* 35: 836–842.

Keller V.D.J., R.J. Williams, C. Lofthouse, and A.C. Johnson. 2014. Worldwide estimation of river concentrations of any chemical originating from sewage-treatment plants using dilution factors. *Environ. Toxicol. Chem.* 33: 447–452.

Kim, M.H., J. Park, Y.H. Kim, and K. Choi. 2006. Prioritising human use antibiotics for environmental health management and estimating their environmental concentrations in Korean waterway. *Korean J. Environ. Health Sci.* 32: 462–468.

Kinney, C.A., E.T. Furlong, S.L. Werner, and J.D. Cahill. 2006a. Presence and distribution of wastewater-derived pharmaceuticals in soil irrigated with reclaimed water. *Environ. Toxicol. Chem.* 25: 317–326.

Kinney, C.A., E.T. Furlong, S.D. Zaugg, M.R. Burkhardt, S.L. Werner, J.D. Cahill, and G.R. Jorgensen. 2006b. Survey of organic wastewater contaminants in biosolids destined for land application. *Environ. Sci. Technol.* 40: 7207–7215.

Kinney, C.A, E.T. Furlong, K.D. W, M.R. Burkhardt, Z.S. D, S.L. Werner, B.J. P, and B.M. J. 2008. Bioaccumulation of pharmaceutical and other anthropogenic waste indicators in earthworms from agricultural soil amended with biosolid or swine manure. *Environ. Sci. Technol.* 42: 1863–1870.

Kools, S.A.E., J.F. Moltmann, and T. Knacker. 2008. Estimating the use of veterinary medicines in the European Union. *Reg. Toxicol. Pharmacol.* 50: 59–65.

Kostich, M.S., and J.M. Lazorchak. 2008. Risks to aquatic organisms posed by human pharmaceutical use. *Sci. Total Environ.* 389: 329–339.

Kumar, A., and I. Xagoraraki. 2010. Pharmaceuticals, personal care products and endocrine-disrupting chemicals in U.S. surface and finished drinking waters: A proposed ranking system. *Sci. Total Environ.* 408: 5972–5989.

Küster, A., and N. Adler. 2014. Pharmaceuticals in the environment: Scientific evidence of risks and its regulation. *Phil. Trans. R. Soc. B. Biol. Sci.* 369: 20130587.

Lalone, C.A., J.P. Berninger, D.L. Villeneuve, and G.T. Ankley. 2014. Leveraging existing data for prioritization of the ecological risks of human and veterinary pharmaceuticals to aquatic organisms. *Phil. Trans. R. Soc. B. Biol. Sci.* 369: 20140022.

Larsson, D.G.J. 2014. Pollution from drug manufacturing: Review and perspectives. *Phil. Trans. R. Soc. B. Biol. Sci.* 369: 20130571.

Le Corre, K.S., C. Ort, D. Kateley, B. Allen, B.I. Escher, and J. Keller. 2012. Consumption-based approach for assessing the contribution of hospitals towards the load of pharmaceutical residues in municipal wastewater. *Environ. Int.* 45: 99–111.

Lees, K., M. Fitzsimons, J. Snape, A. Tappin, and S. Comber. 2016. Pharmaceuticals in soils of lower income countries: Physico-chemical fate and risks from wastewater irrigation. *Environ. Int.* 94: 712–723.

Leung, H.W., L. Jin, S. Wei, M.M.P. Tsui, B. Zhou, L. Jiao, P.C. Cheung, Y.K. Chun, M.B. Murphy, and P.K.S. Lam. 2013. Pharmaceuticals in tap water: Human health risk assessment and proposed monitoring framework in China. *Environ. Health Persp* 7: 839–846.

Li, Z., M. Li, X. Liu, Y. Ma, and M. Wu. 2014. Identification of priority organic compounds in groundwater recharge of China. *Sci. Total Environ.* 493: 481–486.

Lienert, J., K. Güdel, and B.I. Escher. 2007. Screening method for ecotoxicological hazard assessment of 42 pharmaceuticals considering human metabolism and excretory routes. *Environ. Sci. Technol.* 12: 4471–4478.

Lübbert, C., C. Baars, A. Dayakar, N. Lippmann, A.C. Rodloff, M. Kinzig, and F. Sörgel. 2017. Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. *Infection* 45: 479–491.

Luo, Y., W. Guo, H.H. Ngo, L.D. Nghiem, F.I. Hai, J. Zhang, S. Liang, and X.C. Wang. 2014. A review on the occurrence of micropollutants in the aquatic environment and their fate and removal during wastewater treatment. *Sci. Total Environ.* 473–474: 619–641.

Malchi, T., Y. Maor, G. Tadmor, M. Shenker, and B. Chefetz. 2014. Irrigation of root vegetables with treated wastewater: Evaluating uptake of pharmaceuticals and the associated human health risks. *Environ. Sci. Technol.* 48: 9325–33.

Margiotta-Casaluci, L., S.F. Owen, R.I. Cumming, A. de Polo, M.J. Winter, G.H. Panter, M. Rand-Weaver, and J.P. Sumpter. 2014. Quantitative cross-species extrapolation between humans and fish: The case of the anti-depressant fluoxetine. *PLoS One* 10: e110467.

Masoner, J.R., D.W. Kolpin, E.T. Furlong, I.M. Cozzarelli, and J.L. Gray. 2016. Landfill leachate as a mirror of today's disposable society: Pharmaceuticals and other contaminants of emerging concern in final leachate from landfills in the conterminous United States. *Environ. Toxicol. Chem.* 4: 906–918.

Mennigen, J., P. Stroud, J. Zamora, T. Moon, V. Trudeau. 2011. Pharmaceuticals as Neuroendocrine Disruptors: Lessons Learned from Fish on Prozac. *J Toxicol Environ Health B* 14: 387-412.

Miller, T.H., G.L. McEneff, R.J. Brown, S.F. Owen, N.R. Bury, and L.P. Barron. 2015. Pharmaceuticals in the freshwater invertebrate, *Gammarus Pulex*, determined using pulverised liquid extraction, solid phase extraction and liquid chromatography–tandem mass spectrometry. *Sci. Total Environ.* 511: 153–160.

MistraPharma, 2018. WikiPharma Database. http://www.wikipharma.org/welcome.asp (accessed January 4, 2018).

Mohapatra, D.P., M. Cledón, S.K. Brar, and R.Y. Surampalli. 2016. Application of wastewater and biosolids in soil: Occurrence and fate of emerging contaminants. *Water Air Soil Pollut.* 227: 77.

Morais, S.A., C. Delerue-Matos, and X. Gabarrell. 2014. An uncertainty and sensitivity analysis applied to the prioritisation of pharmaceuticals as surface water contaminants from wastewater treatment plant direct emissions. *Sci. Total Environ.* 490: 342–350.

Mottaleb, M.A., C. Stowe, D.R. Johnson, M.J. Meziani, and M.A. Mottaleb. 2016. Pharmaceuticals in grocery market fish fillets by gas chromatography–mass spectrometry. *Food Chem.* 190: 529–536.

Murray, K.E., S.M. Thomas, and A.A. Bodour. 2010. Prioritizing research for trace pollutants and emerging contaminants in the freshwater environment. *Environ. Pollut.* 12: 3462–3471.

Murray-Smith, R.J., V.T. Coombe, M.H. Grönlund, F. Waern, and J.A. Baird. 2012. Managing emissions of active pharmaceutical ingredients from manufacturing facilities: An environmental quality standard approach. *Integr. Environ. Assess. Manage.* 8: 320–330.

Negrao de Carvalho, R., L. Ceriani, A. Ippolito, and T. Lettieri. 2015. JRC Technical Report: Development of the first watch list under the environmental quality standards directive. EUR 27142. *Publications Office of the European Union*. https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/development-first-watch-list-under-environmental-quality-standards-directive (accessed November 3, 2017).

Niemuth, N.J., and R.D. Klaper. 2016. On the unexpected reproductive impacts of metformin: A need for support and new directions for the evaluation of the impacts of pharmaceuticals in the environment. *Chemosphere.* 165: 570–574.

Oaks, J.L., M. Gilbert, M.Z. Virani, R.T. Watson, C.U. Meteyer, B.A. Rideout, H.L. Shivaprasad, S. Ahmed, M.J.I. Chaudhry, M. Arshad, S. Mahmood, A. Ali and A.A. Khan. 2004. Diclofenac residues as the cause of vulture population decline in Pakistan. *Nature* 427: 630–633.

Obach, R.S. 2013. Pharmacologically active drug metabolites: Impact on drug discovery and pharmacotherapy. *Pharmacol. Rev.* 65: 578–640.

Oldenkamp, R., M.A.J. Huijbregts, A. Hollander, A. Versporten, H. Goossens, and A.M.J. Ragas. 2013. Spatially explicit prioritization of human antibiotics and antineoplastics in Europe. *Environ. Int.* 51: 13–26.

Oldenkamp, R., M.A.J. Huijbregts, and A.M.J. Ragas. 2016. The influence of uncertainty and location-specific conditions on the environmental prioritisation of human pharmaceuticals in Europe. *Environ. Int.* 91: 301–311.

Olsen, L., J.F. Valder, J.M. Carter, and J.S. Zogorski. 2013. Prioritization of constituents for national- and region-scale ambient monitoring of water and sediment in the United States. Scientific Investigations Report 2012-5218. United States Geological Survey. https://pubs.er.usgs.gov/publication/sir20125218 (accessed November 3, 2017).

Ortiz de García, S., G.P. Pinto, P.A. García-Encina, and R.I. Mata. 2013. Ranking of concern, based on environmental indexes, for pharmaceutical and personal care products: An application to the Spanish case. *J. Environ. Manage.* 129: 384–397.

Pan, B., P. Ning, and B. Xing. 2009. Part V—Sorption of pharmaceuticals and personal care products. *Environ. Sci. Pollut. Res.* 16: 106–116.

Patel, A., G.H. Panter, H.T. Trollope, Y.C. Glennon, S.F. Owen, J.P. Sumpter, and M. Rand-Weaver. 2016. Testing the "read-across hypothesis" by investigating the effects of ibuprofen on fish. *Chemosphere* 163: 592–600.

Paz, A., G. Tadmor, T. Malchi, J. Blotevogel, T. Borch, T. Polubesova, and B. Chefetz. 2016. Fate of carbamazepine, its metabolites, and lamotrigine in soils irrigated with reclaimed wastewater: Sorption, leaching and plant uptake. *Chemosphere* 160: 22–29.

Pedrero, F., I. Kalavrouziotis, J.J. Alarcón, P. Koukoulakis, and T. Asano. 2010. Use of treated municipal wastewater in irrigated agriculture—Review of some practices in Spain and Greece. *Agric. Water Manage.* 97: 1233–1241.

Perazzolo, C., B. Morasch, T. Kohn, A. Magnet, D. Thonney, and N. Chèvre. 2010. Occurrence and fate of micropollutants in the Vidy Bay of Lake Geneva, Switzerland. Part I: Priority list for environmental risk assessment of pharmaceuticals. *Environ. Toxicol. Chem.* 29: 1649–1657.

Pereira, A.M.P.T., L.J.G. Silva, C.M. Lino, L.M. Meisel, and A. Pena. 2016. Assessing environmental risk of pharmaceuticals in Portugal: An approach for the selection of the Portuguese monitoring stations in line with Directive 2013/39/EU. *Chemosphere* 144: 2507–2515.

Phillips, P.J., S.G. Smith, D.W. Kolpin, S.D. Zaugg, H.T. Buxton, E.T. Furlong, K. Esposito, and B. Stinson. 2010. Pharmaceutical formulation facilities as sources of opioids and other pharmaceuticals to wastewater treatment plant effluents. *Environ. Sci. Technol.* 44: 4910–4916.

Phillips, P.J., A.T. Chalmers, J.L Gray, D.W. Kolpin, W.T. Foreman, and G.R. Wall. 2012. Combined sewer overflows: An environmental source of hormones and wastewater micropollutants. *Environ. Sci. Technol.* 46: 5336–5343.

Redshaw, C. H., W. Stahl-Timmins, L. Fleming, I. Davidson, and Depledge M. 2013. Potential Changes in disease patterns and pharmaceutical use in response to climate change. *J Toxicol Environ Health B* 16: 285-320.

Riva, F., E. Zuccato, and S. Castiglioni. 2015. Prioritization and analysis of pharmaceuticals for human use contaminating the aquatic ecosystem in Italy. *J. Pharm. Biomed. Anal.* 106: 71–78.

Roos, V., L. Gunnarsson, J. Fick, D.G.J. Larsson, and C. Rudén. 2012. Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection. *Sci. Total Environ.* 421–422: 102–110.

Royal Commission on Environmental Pollution. 2011. Demographic Change and the Environment (Twenty-ninth Report) London UK. http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/228980/8001.pdf (accessed Feb 21, 2018).

Sanderson, H., D.J. Johnson, T. Reitsma, R.A. Brain, C.J. Wilson, and K.R. Solomon. 2004. Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Reg. Toxicol. Pharmacol.* 39: 158–183.

Sangion, A., and P. Gramatica. 2016. Hazard of pharmaceuticals for aquatic environment: Prioritization by structural approaches and prediction of ecotoxicity. *Environ. Int.* 95: 131–143.

Scholz, S., and N. Klüver. 2009. Effects of endocrine disrupters on sexual, gonadal development in fish. *Sex. Dev.* 3: 136–51.

Singer, H.P., A.E. Wössner, C.S. Mcardell, and K. Fenner. 2016. Rapid screening for exposure to "non-target" pharmaceuticals from wastewater effluents by combining HRMS-based suspect screening and exposure modelling. *Environ. Sci. Technol.* 50: 6698–6707.

Straub, J.A. 2016. Reduction in the environmental exposure of pharmaceuticals through diagnostics, Personalised Healthcare and other approaches. A mini review and discussion paper. *Sustain. Chem Pharm.* 3: 1–7.

Stuer-Lauridsen, F., M. Birkved, L.P. Hansen, H.C. Lützhøft, and B. Halling-Sørensen. 2000. Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. *Chemosphere* 40: 783–93.

Tanoue, R., K. Nomiyama, H. Nakamura, J.-W. Kim, T. Isobe, R. Shinohara, T. Kunisue, and S. Tanabe. 2015. Uptake and tissue distribution of pharmaceuticals and personal care products in wild fish from treated-wastewater impacted Streams. *Environ. Sci. Technol.* 49: 11649–11658.

United Nations, Department of Economic and Social Affairs: Population Division. 2014. World Urbanization Prospects: The 2014 Revision, Highlights (*ST/ESA/SER.A/352)*. New York. https://esa.un.org/unpd/wup/publications/files/wup2014-highlights.Pdf (accessed November 3, 2017).

US Environmental Protection Agency. 2015. Estimation Programs Interface Suite™ for Microsoft® Windows. United States Environmental Protection Agency, Washington, DC, USA. https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface (accessed November 3, 2017).

United States Food and Drug Administration. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. CMC 6. Revision 1. https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf (accessed November 3, 2017).

Vasquez M., Lambrianides, A., Schneider M., Kümmerer, K. Fatta-Kassinos, D. 2014. Environmental side effects of pharmaceutical cocktails: What we know and what we should know. *J. Hazard. Mater.* 279:169–189.

Vazquez-Roig, P., V. Andreu, C. Blasco, and Y. Picó. 2012. Risk assessment on the presence of pharmaceuticals in sediments, soils and waters of the Pego–Oliva Marshlands (Valencia, eastern Spain). *Sci. Total Environ.* 440: 24–32.

Verbruggen, B., Gunnarsson, L., Kristiansson, E., Österlund, T., Owen, S.F., Snape, J.R. and C.R. Tyler. 2018. ECOdrug: A database connecting drugs and conservation of their targets across species. *Nucl Acid Res*. 46: D930-D936.

Verlicchi, P., M. Al Aukidy, A. Jelic, M. Petrović, and D. Barceló. 2014. Comparison of measured and predicted concentrations of selected pharmaceuticals in wastewater and surface water: A case study of a catchment area in the Po valley (Italy). *Sci. Total Environ.* 470–471: 844–854.

Vestel, J., D.J. Caldwell, L. Constantine, V.J. D'Aco, T. Davidson, D.G. Dolan, S.P. Millard, R. Murray-Smith, N.J. Parke, J.J. Ryan, J.O. Straub, and P. Wilson. 2016. Use of acute and chronic ecotoxicity data in environmental risk assessment of pharmaceuticals. *Environ. Toxicol. Chem.* 35: 1201–1212.

Wang, H., N. Wang, B. Wang, H. Fang, C. Fu, C. Tang, F. Jiang, Y. Zhou, G. He, Q. Zhao, Y. Chen, and Q. Jiang. 2016. Antibiotics detected in urines and adipogenesis in school children. *Environ. Int.* 89: 204–211.

Weatherly, L. M. and Gosse, J.A. 2017. Triclosan exposure, transformation and human health effects. *J Toxicol Environ Health B* 20: 447-469.

Wennmalm, A., and B. Gunnarsson. 2005. Public health care management of water pollution with pharmaceuticals: Environmental classification and analysis of pharmaceutical residues in sewage water. *Ther. Innovat. Reg. Sci.* 39: 291–297.

Yang, Y.-Y., G.S. Toor, P.C. Wilson, and C.F. Williams. 2016. Septic systems as hot-spots of pollutants in the environment: Fate and mass balance of micropollutants in septic drain fields. *Sci. Total Environ.* 566: 1535–1544.

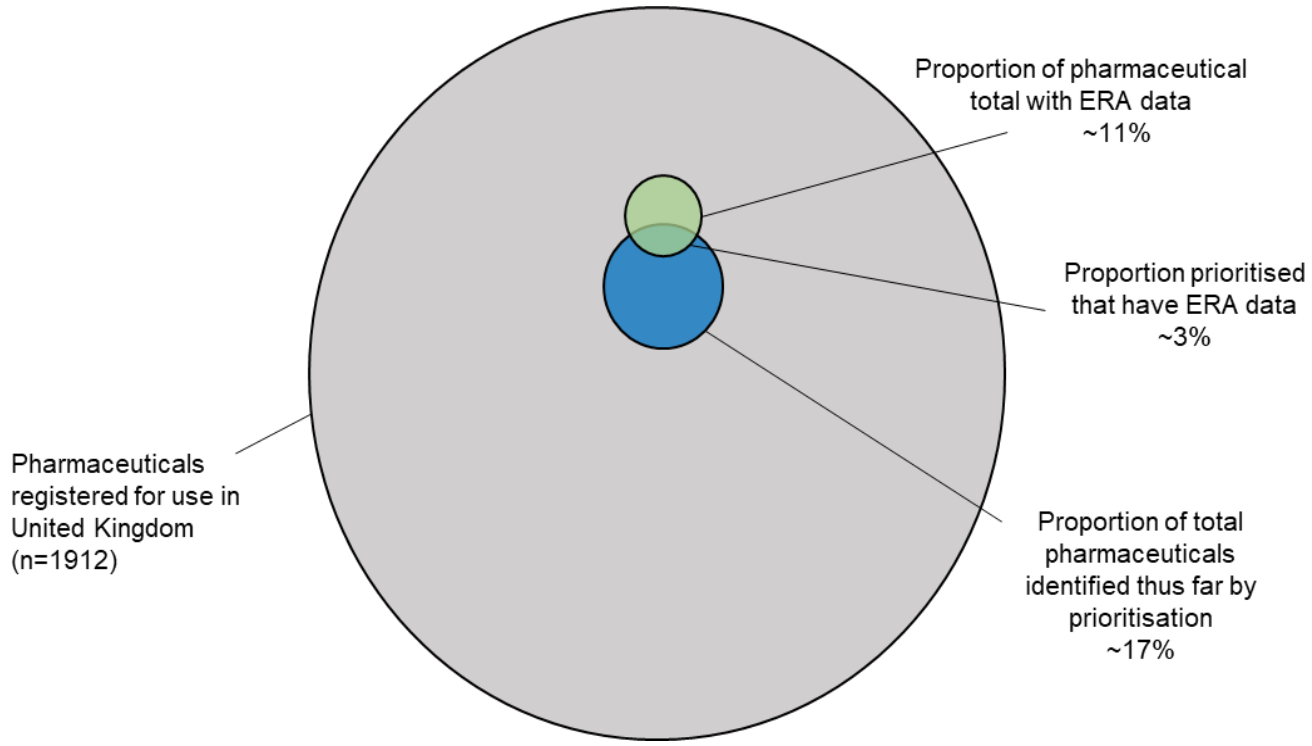

Figure 1. A qualitative representation of the estimated active pharmaceutical ingredients (APIs) registered for market use in the UK (eMC, 2017) (grey, n=1912), proportion of pharmaceuticals identified thus far by prioritisation exercises (blue, n=332), roughly the portion of total UK registered APIs that have EMA ERA data (green) and the overlap between APIs prioritised thus far and also assessed within the EMA ERA framework (blue and green).

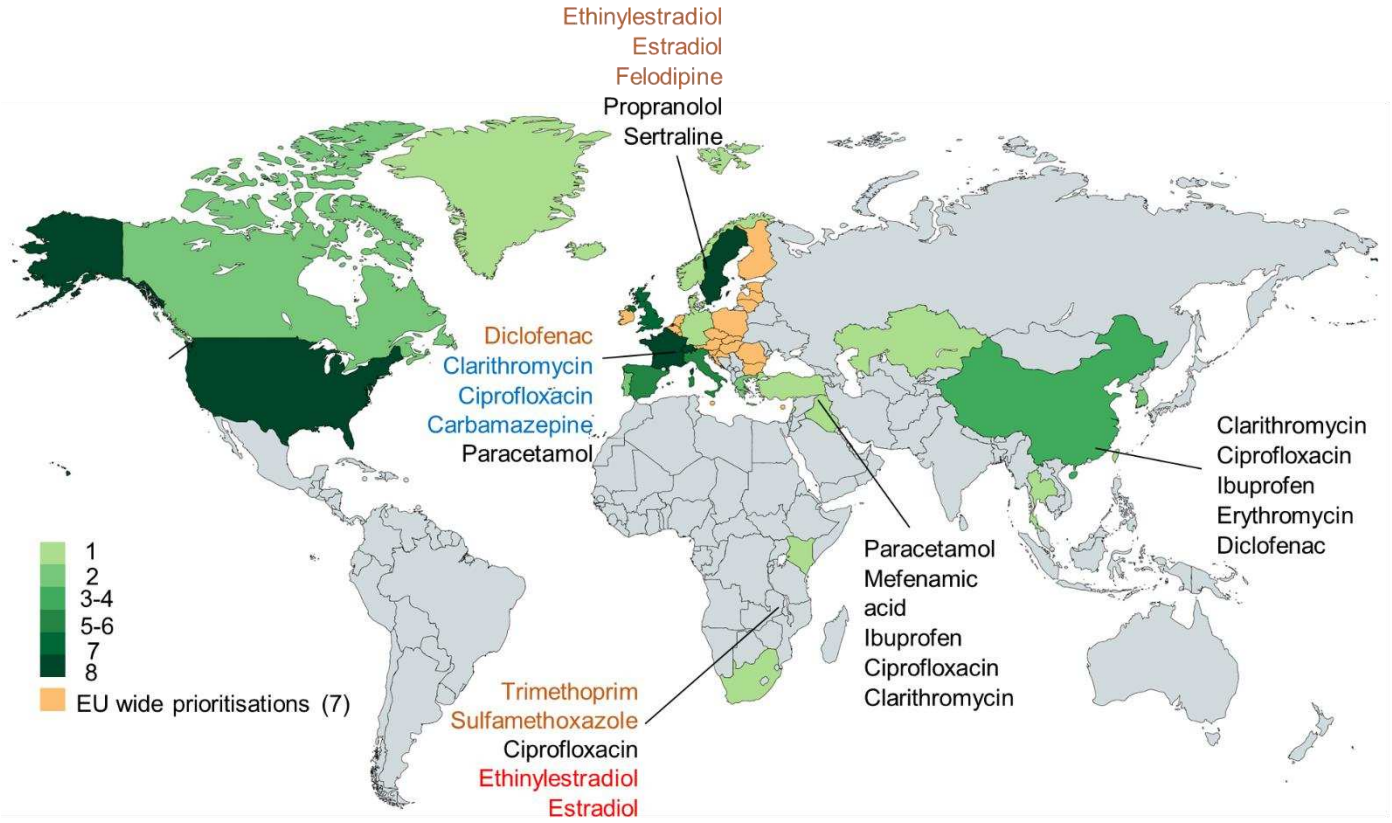

Figure 2. Areas of the world where priority pharmaceuticals have been identified by either risk-, hazard- or exposure-based approaches. Colouring corresponds to the number of prioritisations undertaken within that region (i.e. 1 to 8). The top 5 priorities selected for each region are based on the number of times a pharmaceutical appears on applicable priority lists. The font colour indicates the type of prioritisation that identified these compound: black: entirely or vast majority risk-based, red: entirely hazard based, green: entirely exposure based, blue: at least 50% risk-based while remainder are exposure-based and orange: at least 50% risk-based while remainder are hazard-based.

Table 1. Pharmaceuticals classified 3 or more times (n=76) sorted initially by prioritisation approach that identified each of the 76 compounds, then by therapeutic class within each approach.

Category	Therapeutic Class	Pharmaceutical
Risk	Antibiotics (16)	Amoxicillin, Ampicillin, Azithromycin, Cephalexin, Ciprofloxacin, Clarithromycin, Clindamycin, Clotrimazole, Erythromycin, Levofloxacin, Lincomycin, Metronidazole, Ofloxacin, Oxytetracyline, Sulfamethoxazole, Trimethoprim
	Hormones (including synthetic) (10)	Equilenin, Estradiol, Estriol, Estrone, Ethinylestradiol, Levonorgestrel, Medoxyprogesterone, Mestranol, Noreistherone, Testosterone
	Analgesic (8)	Acetylsalicylic acid, Dextropropoxyphene, Diclofenac, Ibuprofen, Mefenamic acid, Naproxen, Paracetamol, Tramadol, Ketoprofen
	Antidepressant (6)	Amitriptyline, Citalopram, Fluoxetine, Norfluoxetine, Paroxetine, Sertraline
	Lipid-lowering agent (5)	Atorvastatin, Bezafibrate, Clofibrate, Gemfibrozil, Simvastatin
	Cardiovascular agent (4)	Felodipine, Fenofibrate, Losartan, Valsartan
	Anti-cancer (4)	Cyclophosphosphamide, Ifosfamine, Tamoxifen
	Beta-blocker (3)	Atenolol, Metoprolol, Propranolol
	Antidiabetic (2)	Metformin, Glyburide
	Contrast agent (2)	Iopamidol, Iopromide
	Diuretic (2)	Furosemide, Hydrochlorothiazide
	Anaesthetic (1)	Lidocaine
	Antiarrhythmic (1)	Amiodarone
	Antibacterial (1)	Triclosan
	Antifungal (1)	Ketoconazole
	Antihistamine (1)	Loratadine
	Anti-convulsant (1)	Carbamazepine
	Antineoplastic (1)	Mitotane
	Antiretroviral (1)	Ritonavir
	Benzodiazepine (1)	Oxazepam

	H2 Blocker (1)	Ranitidine
	Proton pump inhibitor (1)	Omeprazole
Exposure	Antibiotic (10)	Amoxicillin, Azithromycin, Ciprofloxacin, Clarithromycin, Erythromycin, Levofloxacin, Lincomycin, Ofloxacin, Sulfamethoxazole, Trimethoprim
	Analgesic (5)	Diclofenac, Ibuprofen, Naproxen, Paracetamol, Ketoprofen
	Lipid-lowering agent (4)	Atorvastatin, Bezafibrate, Gemfibrozil, Simvastatin
	Anti-cancer (3)	Cyclophosphosphamide, Ifosfamine, Tamoxifen
	Cardiovascular agent (3)	Irbesartan, Losartan, Valsartan
	Diuretic (2)	Furosemide, Hydrochlorothiazide
	Antidiabetic (2)	Metformin, Glyburide
	Antidepressant (1)	Paroxetine
	Beta-blocker (1)	Atenolol
	Anti-convulsant (1)	Carbamazepine
	H2 Blocker (1)	Ranitidine
Hazard	Hormones (including synthetic) (9)	Equilenin, Estradiol, Estriol, Estrone, Ethinylestradiol, Etonogestrel, Levonorgestrel, Medoxyprogesterone, Testosterone
	Antidepressant (6)	Amitriptyline, Citalopram Fluoxetine, Norfluoxetine, Paroxetine, Sertraline
	Lipid-lowering agent (5)	Atorvastatin, Bezafibrate, Clofibrate, Gemfibrozil, Simvastatin
	Antibiotic (5)	Amoxicillin, Ciprofloxacin, Clotrimazole, Erythromycin, Sulfamethoxazole
	Cardiovascular agent (3)	Felodipine, Fenofibrate, Irbesartan
	Analgesic (2)	Diclofenac, Ibuprofen
	Antihistamine (2)	Clemastine, Loratadine
	Contrast agent (2)	Iopamidol, Iopromide
	Anticancer (1)	Tamoxifen
	Antineoplastic (1)	Mitotane
	Beta-blocker (1)	Propranolol

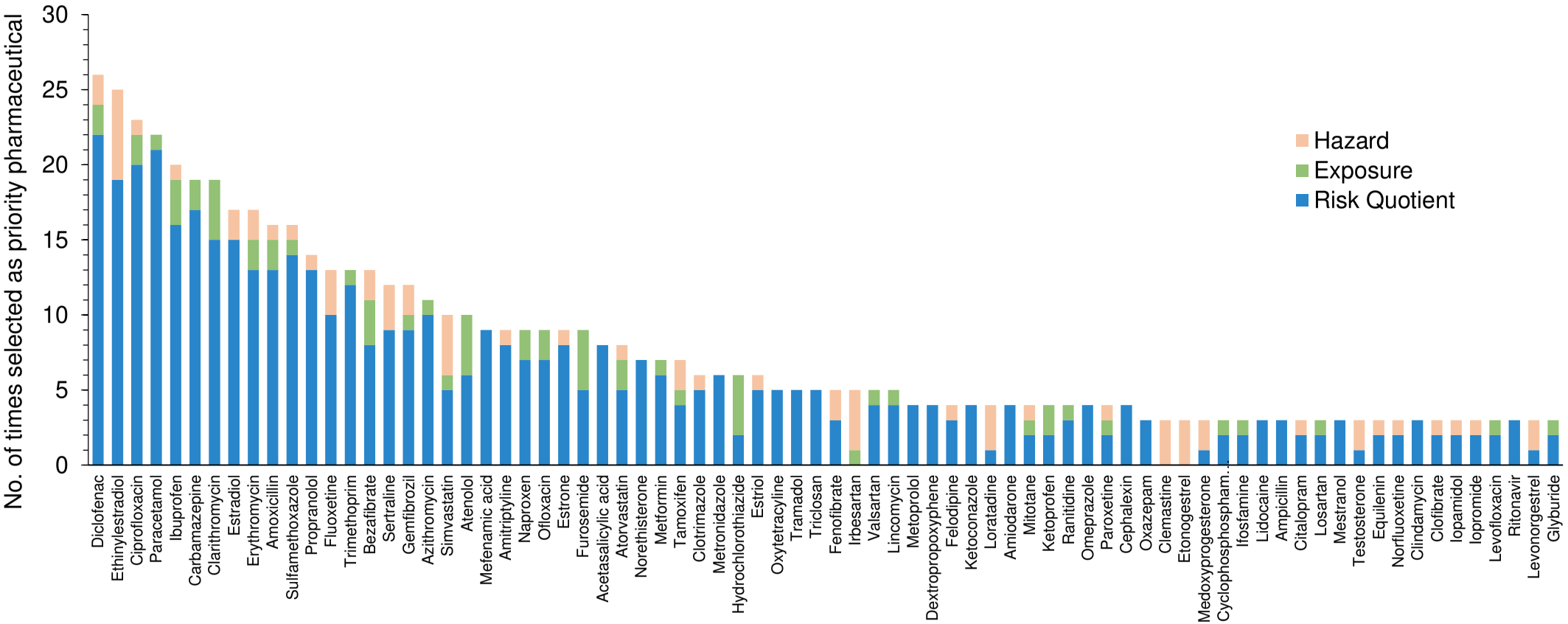

Figure 3. Pharmaceuticals identified as priorities three or more times (n=76) from on the 76 approaches reviewed in the literature.

Table 2. Strengths and limitations of major parameters in current risk-based prioritisation approaches and the opportunities and threats for developing a new or improved approach.

	Parameter	Strengths	Limitations	Opportunities	Threats
Exposure	Simple PEC	• Cost effective • Tailored to be local or regional • Applied to all APIs for which consumption data available • Simple algorithms and EMA defaults available. • Provide basis for local/regional monitoring campaigns	• No over-the-counter usage • No hospital usage • Prescription data only available for select regions • Single environmental pathway (WWTP) • Not representative of local wastewater usage/environmental dilution. • Variability in patient metabolism	• Alternative methods to derive usage • Incorporate other major sources (e.g. manufacturing effluent) • Approach that can assess the 87% of APIs in use that without ERA data • Development/validation of exposure models for understudied compartments such as soil, sediment and porewater.	• First tier may unknowingly eliminate compounds (e.g. assessment trigger values) • Unsuitable exposure models (e.g. ionisable)
	Higher tier spatial PEC	• Multiple pharmaceutical sources • Incorporate mixing with pharmaceuticals transported from upstream • Identify local concentration hot spots • Incorporate hydrological characteristics/long term flow trends	• Only developed for specific regions/watersheds • Access limited • Similar pharmaceutical consumption, WWTP removal and metabolisms issues to simple PEC	• Development of open-access platforms to make predictions • Open-access tools to develop spatial models for currently unstudied areas • Incorporate sludge and soil sorption models which can account for ionisable compounds • Expand past surface water to include sediment and vulnerable soils (e.g. agriculture) • Probabilistic risk assessment	
	MEC	• Confidence in results • All environmental pathways considered (when representative sampling used) • Localised	• Limited number of APIs/compounds • Costly • Maximal MECs • Limits of detection • Unrepresentative sampling • Limited to pharmaceuticals already detected/already of concern	• Lower cost monitoring approaches • Improved limits of detection • Use to confirm risky predictions	• Poorly representative sampling

Table 2 (continued). Strengths and limitations of major parameters in current risk-based prioritisation approaches and the opportunities and threats for developing a new or improved approach.

P	Experimental	• Regulatory relevance	• Limited availability	• Create comprehensive database of industry held data to prevent 'Matthew	• Missing specific MoA concerns

	(chronic/acute)	• Confidence in results	• Limited relevance of acute data • Chronic ECOSAR not yet validated for APIs and likely not robust • Considers only apical endpoints (mortality, reproduction, growth)	Effect'	• Experimentally filling data gaps defeats purpose of desk-based prioritation.
	ECOSAR	• Rapid, can be applied to all APIs.	• Heavy reliance on predicted data, 'Matthew Effect' • Large arbitrary safety factors	• Improve chronic QSAR	• 'Matthew effect' • Missing specific MoA concerns
	FPM	• Readily available pharmacokinetic parameters • QSAR to predict BCF based on octanol-water partition coefficient (Kow) • Can be applied to vast majority of APIs • Covers mode of action (MoA) concerns	• BCFs not experimentally available for most APIs • Applicability of BCF QSAR • Only relevant for fish • Experimental validation limited, but growing	• Expand to invertebrates (water column, benthos and soil) • Reduce animal testing by prioritising legacy APIs and focusing efforts towards those most likely to have an adverse impact • Use internal concentrations to develop predator exposure models	• Unsuitable uptake models (e.g. ionisables) • Miss specific MoA concerns pertaining to an API's side effect/off label use
	ADI	• Can calculate for all APIs which have mammalian toxicity studies	• Based on arbitrary uncertainty factors to ensure conservative risk assessment • Focuses on water exposure (surface and drinking)	• Include a diet component (fish, meat, water, crops)	• Diet (fish, meat, water, crops)

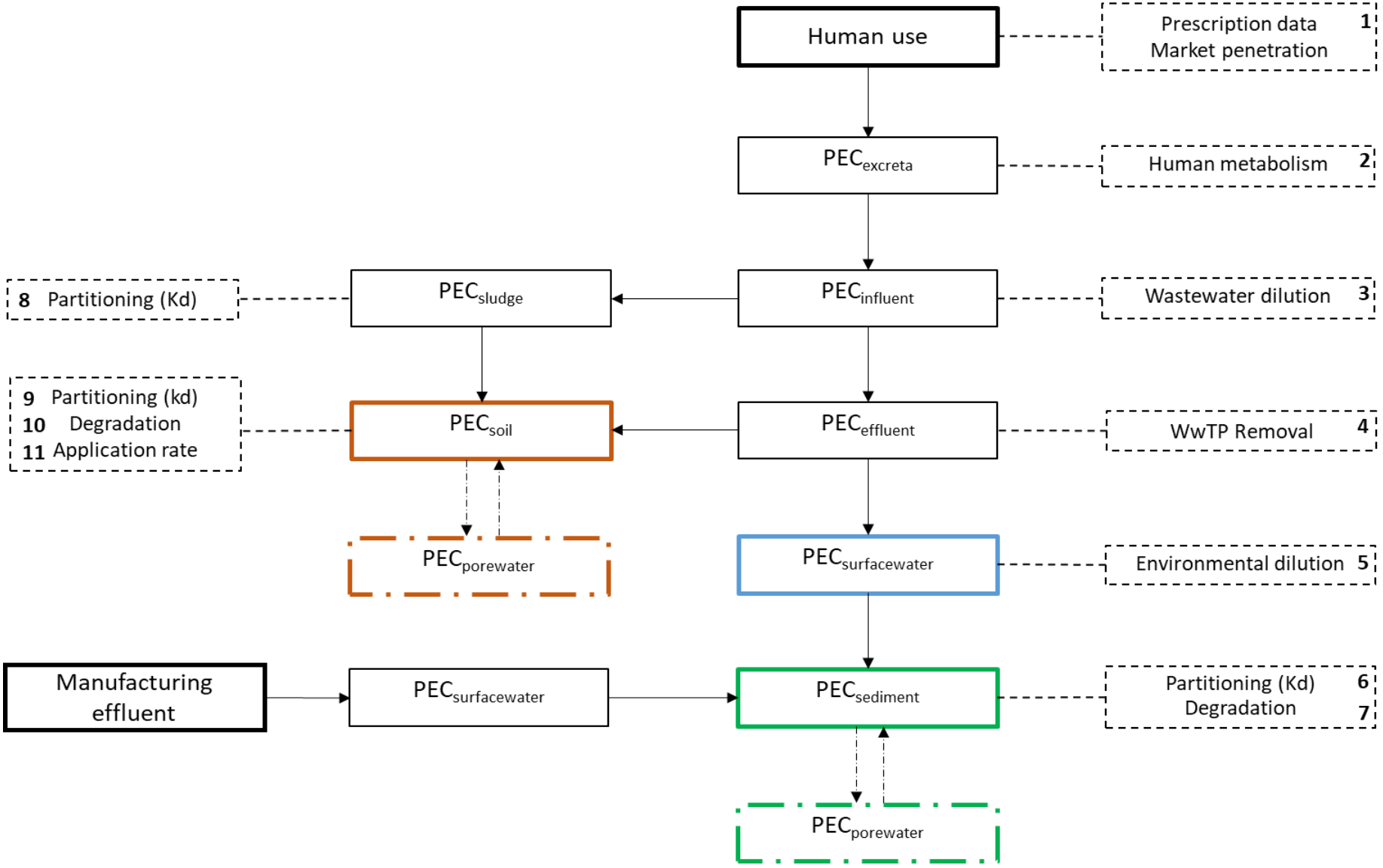

Figure 4. Breakdown of the relationship between exposure scenarios and the generalised parameters required to calculate the emissions. Numbers refer to Supplementary Tables S1 and S2 where greater of the derivation and limitations of each parameter is given.

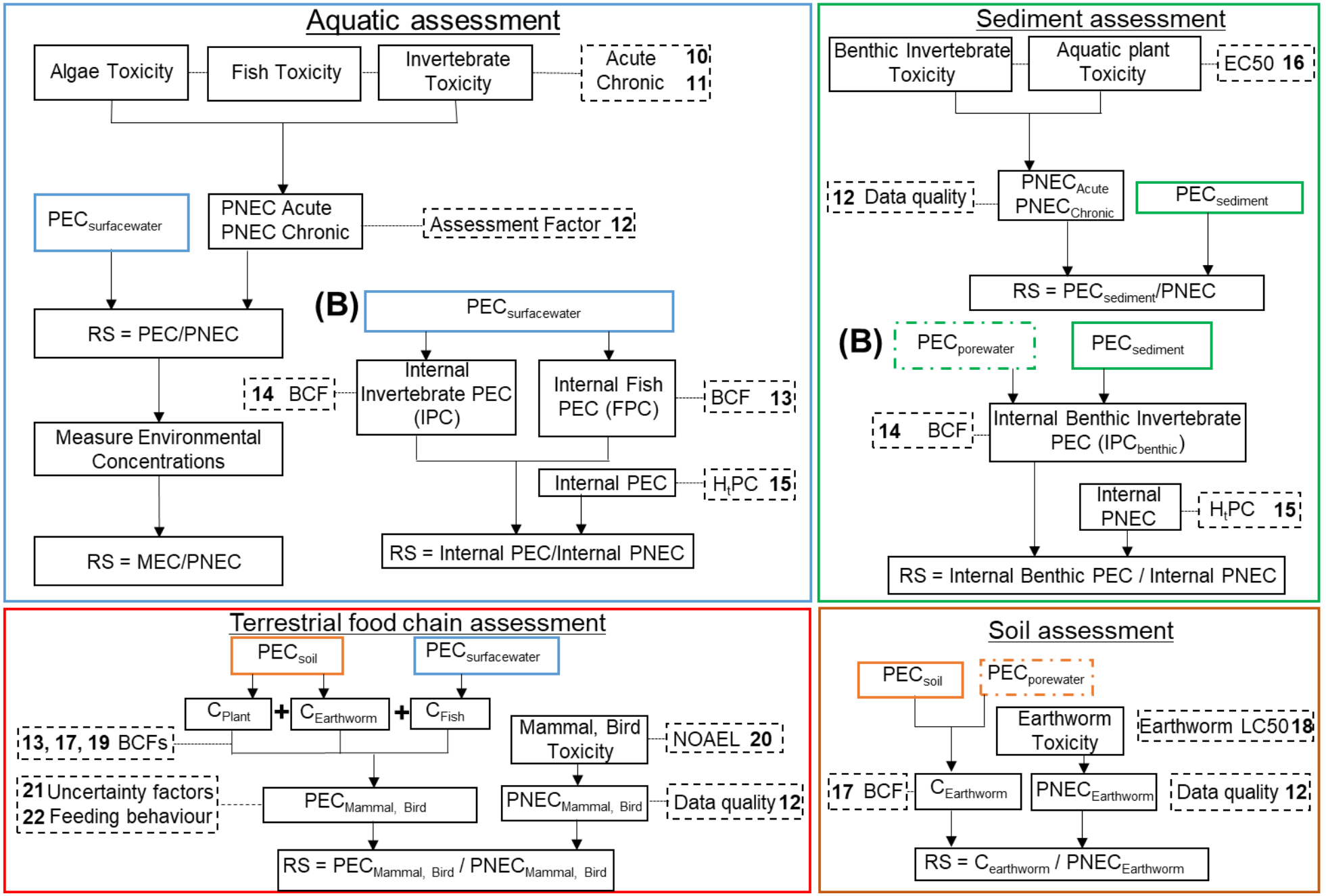
Aquatic assessment
Algae Toxicity
Fish Toxicity
Invertebrate Toxicity
Acute 10
Chronic 11
PEC surfacewater
PNEC Acute
PNEC Chronic
Assessment Factor 12
RS = PEC/PNEC
Measure Environmental Concentrations
RS = MEC/PNEC
(B)
PEC surfacewater
14 BCF
Internal Invertebrate PEC (IPC)
Internal Fish PEC (FPC)
BCF 13
Internal PEC
HtPC 15
RS = Internal PEC/Internal PNEC
Sediment assessment
Benthic Invertebrate Toxicity
Aquatic plant Toxicity
EC50 16
12 Data quality
PNEC Acute
PNEC Chronic
PEC sediment
RS = PEC sediment/PNEC
(B)
PEC porewater
PEC sediment
14 BCF
Internal Benthic Invertebrate PEC (IPC benthic)
Internal PNEC
HtPC 15
RS = Internal Benthic PEC / Internal PNEC
Terrestrial food chain assessment
PEC soil
PEC surfacewater
C Plant
C Earthworm
C Fish
13, 17, 19 BCFs
21 Uncertainty factors
22 Feeding behaviour
PEC Mammal, Bird
Mammal, Bird Toxicity
NOAEL 20
PNEC Mammal, Bird
Data quality 12
RS = PEC Mammal, Bird / PNEC Mammal, Bird
Soil assessment
PEC soil
PEC porewater
Earthworm Toxicity
Earthworm LC50 18
17 BCF
C Earthworm
PNEC Earthworm
Data quality 12
RS = C earthworm / PNEC Earthworm

Figure 5. High level schematics demonstrating the prioritisation of risk posed to three trophic levels in aquatic, sediment and soil systems. Secondary approaches to prioritising risks to aquatic/sediment systems based on pharmaceutical uptake and internal concentrations compared to human therapeutic concentrations are also shown (B). Predatory wildlife food chain risk prioritisation which considers exposure to multiple prey/environmental sources (terrestrial). Numbers refer to Supplementary Tables S1 and S2 where greater of the derivation and limitations of each parameter is given.

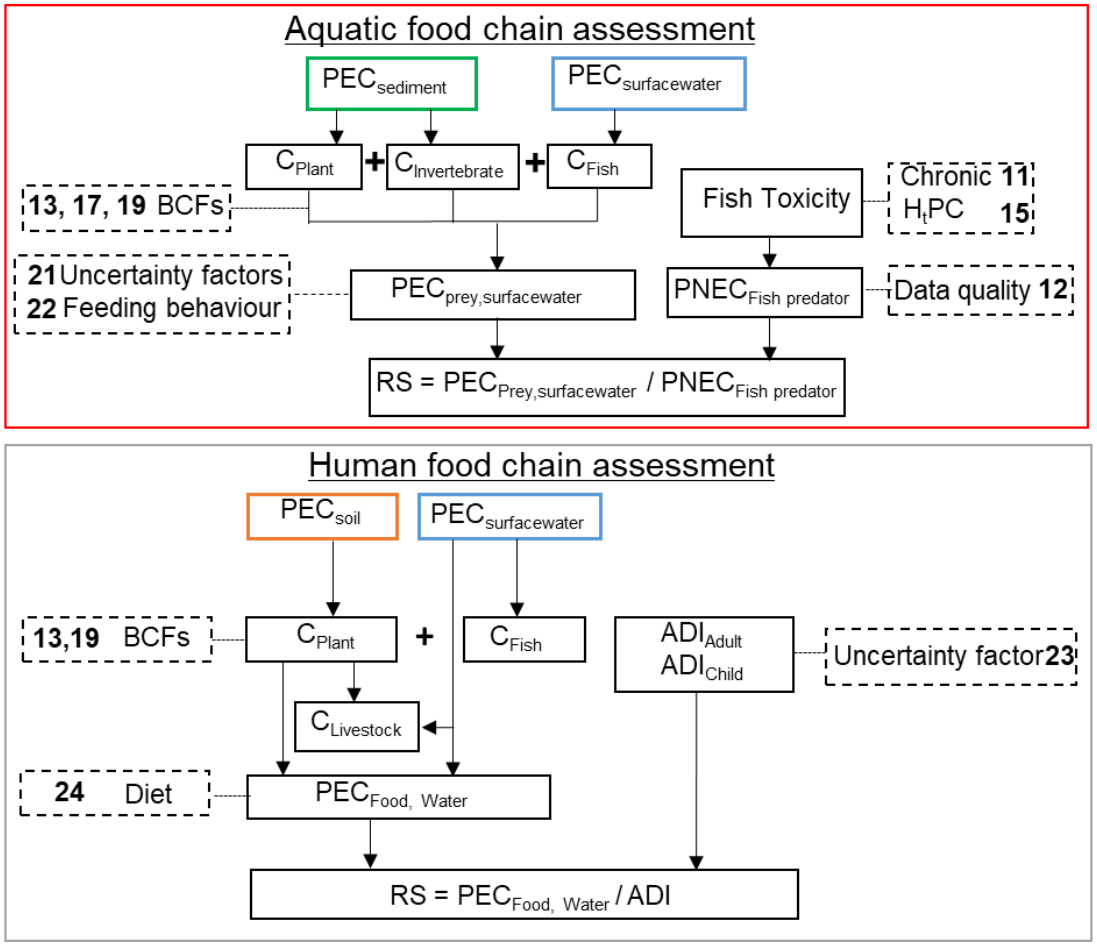

Figure 6. Prioritisation of pharmaceutical risks to humans considering both water intake or direct water exposure as well as other dietary sources such as plants and meat. Predatory wildlife food chain risk prioritisation which considers exposure to multiple prey/environmental sources (aquatic). Numbers refer to Supplementary Tables S1 and S2 where greater of the derivation and limitations of each parameter is given.

Table 3. Generalised overview of the availability of parameters required to estimate environmental pharmaceutical exposure and effects in multiple compartments based on the models contained within the prioritisation framework. Default refers to suggestions from the EMA (2006) guidelines. Models or methods to derive the parameter are listed in Table S2.

Model	Parameter		iPiE	Experimental source	Model	Default (Table S2)
Human use	(1) API consumption	mg/yr	Table S2	Table S2	Table S2	
$PEC_{excreta}$	(2) Human metabolism	$F_{excreta}$				
$PEC_{influent}$	(3) Wastewater dilution	L/person·day				
$PEC_{effluent}$	(4) WWTP Removal	% Biodegration % Sorption				
$PEC_{surface\ water}$	(5) Environmental dilution					
$PEC_{sediment}$	(6) Equilibrium partitioning	Sediment (Kd)				
	(7) Degradation	DT50 (sediment)				
PEC_{soil}	(6) Equilibrium partitioning	Soil (Kd)				
	(7) Degradation	DT50 (soil)				
	(8) Application rate	kg/ha·year				
Toxicity	(9) Algae/daphnia/fish	Acute EC50				
	(10) Algae/daphnia/fish	Chronic EC50				
PNEC	(11) Assessment factor					
Internal PEC	(12) Fish	FPC				
	(13) Invertebrate	IPC				
Internal PNEC	(14) Therapeutic plasma concentration	H_tPC				
Toxicity	(9) Benthic invertebrate	EC50				
$C_{Earthworm}$	(15) BCF					
Toxicity	(9) Earthworm	LC50				
C_{Plant}	(15) BCF_{plant}					
Toxicity	(16) Mammal	NOAEL				
Toxicity	(17) Bird	NOEC				
$PEC_{Diet(wildlife)}$	(18) Uncertainty factor					
	(19) Feeding behaviour					
Acceptable daily intake	(20) Uncertainty factor	ADI				
$PEC_{Diet(human)}$	(21) Diet					

Full dataset for pharmaceuticals released to market post 2006.
Available or applicable to majority pharmaceuticals. In iPiE column, relative to dataset (n=300).
Available but not applicable to ionizables or other applicability domain exist.
Available or applicable to few pharmaceuticals.
Model to predict parameter does not exist.

Table 4. Summary of the current reliability of models included in the optimum prioritisation framework based on the suitability of relevant parameter estimation and reported validation in the literature.

Endpoint	Exposure		Effects	
	Model	Model reliability	Model	Model reliability
Aquatic plant	$PEC_{surfacewater}$		Acute	
			Chronic	
Aquatic invertebrate	$PEC_{surfacewater}$		Acute	
			Chronic	
Aquatic invertebrate	Invertebrate plasma concentration (IPC)		Read across	
Aquatic wildlife (fish)	PEC_{sw}		Acute	
			Chronic	
Aquatic wildlife (fish)	Fish plasma concentration (FPC)		Read across	
Terrestrial plant	PEC_{soil}		Acute	
			Chronic	
Terrestrial invertebrate	PEC_{soil}		Acute	
			Chronic	
Terrestrial invertebrate	$PEC_{sediment}$		Acute	
			Chronic	
Terrestrial invertebrate	Invertebrate plasma concentration (IPC)		Read across	
Terrestrial wildlife (birds)	PEC_{diet}		Acute	
			Chronic	
Terrestrial wildlife (birds)	PEC_{bird}		Chronic	
Human	PEC_{diet}		ADI	
Human	$PEC_{surfacewater}$		ADI	

Model exists and is validated for pharmaceuticals.
Model exists and used for pharmaceuticals, but lacks validation.
Model exists, but not designed for pharmaceuticals.
No model has been developed yet.

Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals

Emily E. Burns,[†] Laura J. Cater,[‡] Jason Snape,[§] Jane Thomas-Oates,[†] Alistair B.A. Boxall*[‡]

[†]Chemistry Department, University of York, Heslington, YO10 5DD, United Kingdom

[‡]Environment Department, University of York, Heslington, YO10 5DD, United Kingdom

[§]AstraZeneca UK, Global Safety, Health and Environment, Macclesfield, SK10 4TG, United Kingdom

Supplementary Material

Availability of European Medicines Agency ERA data through a European Public Assessment Report (EPAR)

Table S3. Assessment of the availability of EPARs (see main text) for the top 350 prescribed pharmaceuticals by mass in England from the year 2012. Usage data was collected from the National Health Service Prescription Cost Analysis 2012 (NHS, 2012).

Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available
Acamprosate Calcium	4633.995	N	Amiodarone HCl	3129.719	N	Baclofen	848.1401	N
Acrivastine	40.1273	N	Amisulpride	2504.559	N	Balsalazide Sodium	8578.065	N
Acyclovir	15503.25	N	Amitriptyline HCl	10431.37	N	Bendroflumethiazide	1504.737	N
Adapalene	5.75915	N	Amlodipine	5623.418	Y	benzerazide	1711.785	N
Alendronic Acid	2485.896	Y	Amoxicillin	123080.7	N	Benzoyl Peroxide	2.777593	N
Alfuzosin HCl	198.6387	N	Anastrozole	19.01404	N	Benzydamine HCl	8.119974	N
Alimemazine Tartrate	42.47056	N	Aripiprazole	168.2959	Y	Betahistine HCl	1640.354	N
Allopurinol	35355.61	N	Acetylsalicylic acid	76766.37	Y	Betamethasone Valerate	0.103622	N
Alverine Citrate	2008.694	N	Atenolol	19849.26	N	Bezafibrate	1.102586	N
Amantadine HCl	577.1469	N	Atorvastatin	18301.26	N	Bicalutamide	7808.065	N
Amiloride	202.2389	N	Azathioprine	2824.994	N	Bisacodyl	662.9771	N
Aminophylline Hydrate	5359.066		Azithromycin	15020.11	N	Bisoprolol Fumarate	126.8647	N
Brinzolamide	1987.094	N	Cetomacrogol	65.58092	N	Centrimide	0.492776	N
Bumetanide	63.38782	N	Chloramphenicol	4.057731	N	Cetirizine HCl	1726.327	N

Table S4. Assessment of the availability of EPARs (see main text) for the top 350 prescribed pharmaceuticals by mass in England from the year 2012. Usage data was collected from the National Health Service Prescription Cost Analysis 2012 (see main text).

Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available
Budesonide	73.6161	Y	Chlohexidine Gluconate	0.047155	N	Clonazepam	24.876	N
Digoxin	12.81834	N	Erythromycin	17586.66	N	Flecainide Acetate	2029.77	N
Buprenorphine	65.85415	Y	Chlorphenamine Maleate	215.1903	N	Clonidine HCl	1086.108	N
Bupropion HCl	51.79441	Y	Chlorpromazine HCl	843.0926	N	Clopidogrel	13584.8	Y
Buspirone HCl	3.122872	N	Chlortalidone	297.7189	N	Clotrimazole	204.5456	N
Calcipotriol	3.116136	N	Ciclosporin	641.8038	Y	Codeine	47949.39	N
Calcium Acetate	1711.371	N	Cimetidine	2734.228	N	Colchicine	7.831715	N
Candesartan Cilexetil	2282.735	N	Cinnarizine	496.6023	N	Crotamiton	1.484619	N
Captopril	365.6421	N	Ciprofloxacin	6233.46	N	Cyclizine HCl	1750.654	N
Carbamazepine	37897.98	N	Citalopram Hydrobromide	8734.843	N	Cyprote Acetate	38.63865	N
Carbidopa	2875.356	Y	Clarithromycin	14320.11	N	Dabigatran Etexilate	1222.095	Y
Carbimazole	204.5619	N	Clavulanate	818.0046	N	Dantrolene	140.8969	N
Carbocisteine	62872.02	N	Clindamycin	-	N	Desmopressin Acetate	1.849407	N
Carvedilol	327.1891	N	Clobazam	107.8139	N	Desogestrel	16.96663	N
Cefalexin	9965.047	N	Clobetasol Propionate	2.279332	N	Desoloratidine	58.47969	N
Celecoxib	2534.791	Y	Clomipramine HCl	730.8683	N	Dexamethasone	17.56267	Y

Table S5. Assessment of the availability of EPARs (see main text) for the top 350 prescribed pharmaceuticals by mass in England from the year 2012. Usage data was collected from the National Health Service Prescription Cost Analysis 2012 (see main text).

Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available
Dexamfetamine Sulfate	24.88827	N	Doxazosin Mesilate	1027.151	N	Famotidine	-	N
Dexketoprofen	4.034275	N	Doxycycline Hyclate	3430.624	N	Felodipine	815.3964	N
Dextromethorphan Hydrobromide	OTC	Y	Duloxetine HCl	1991.763	Y	Fenofibrate	3771.716	Y
Dextroprop HCl	571.3053	N	Dutasteride	8.334655	N	Fentanyl	-	Y
Diazepam	619.8726	N	Enalapril Maleate	1346.481	N	Fesoterodine Fumarate	39.92008	Y
Diclofenac Sodium	8240.328	N	Entacapone	4430.08	Y	Fexofenadine HCl	9935.872	N
Dicycloverine HCl	184.5628	N	Eplerenone	230.6903	N	Finasteride	376.9499	N
Gabapentin	124353.5	N	Ibuprofen	99212.55	Y	Lercanidipine HCl	846.4954	N
Dihydrocodeine Tartrate	9609.232	N	Escitalopram	368.8627	N	Flucloxacillin Sodium	53702.76	N
Diltiazem HCl	21015.41	N	Estriol	5.740766	N	Fluconazole	-	N
Dimeticone	21.90098	N	Ethinylestradiol	14.66202	N	Fludrocortisone acetate	1.274797	N
Dipyridamole	2527.264	N	Ethosuximide	779.641	N	Fluorouracil	1.001543	N
Docusate Sodium	9354.674	N	Etodolac	3335.156	N	Fluoxetine HCl	5236.459	N
Domperidone	1320.033	N	Etoricoxib	892.8282	N	Flupentixol HCl	8.633705	N
Donepezil HCl	305.721	Y	Etynodiol Diacetate	2.65181	N	Fluticasone Propionate	5.465809	Y
Dorzolamide	0.183812	N	Exemestane	99.7522	N	Folic Acid	644.0475	N
Dosulepin HCl	3032.475	N	Ezetimibe	685.6289	N	Frusemide	155.3189	N

Table S6. Assessment of the availability of EPARs (see main text) for the top 350 prescribed pharmaceuticals by mass in England from the year 2012. Usage data was collected from the National Health Service Prescription Cost Analysis 2012 (see main text).

Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available
Mebendazole	112.712	N	Metoclopramide HCl	637.5506	N	Neomycin Sulfate	62.92856	N
Gemfibrozil	-	N	Imipramine HCl	299.5535	N	Letrozole	38.31931	N
Gilbenclamide	27.25068	N	Indapamide	220.0683	N	Levetiracetam	44519.27	Y
Gliclazide	36347.48	N	Indometacin	640.33	N	Levocetirizine	27.01289	N
Glimepiride	74.04899	Y	Indoramin	119.0657	N	Levodopa	19906.56	Y
Glipizide	57.49691	N	Ipratropium Bromide	3.282406	N	Levofloxacin	-	Y
Glyceryl Trinitrate	50.02094	N	Irbesartan	16480.61	Y	Levonorgestrel	0.437523	N
Haloperidol	24.58707	N	Isosorbide Mononitrate	6874.212	N	Levothyroxine Sodium	65.59779	N
Hydralazine HCl	257.4103	N	Itraconazole	475.082	N	Lidocaine HCl	0.565125	Y
Hydrochlorothiazide	-	Y	Ivabradine	71.02108	Y	Lisdexamfetamine Dimesylate	-	N
Hydrocortisone	--	Y	Ketoconazole	23.99151	Y	Lisinopril	4759.135	N
Hydroxycarbamide	2954.171	Y	Ketoprofen	235.9665	N	Lofepramine HCl	1129.279	N
Hydroxychloroquine Sulfate	533.517	N	Labetalol HCl	1644.713	N	Loperamide HCl	236.7046	N
Hydroxyzine HCl	536.2263	N	Lacidipine	62.06591	N	Loratadine	819.2082	N
Hyoscine Butylbromide	865.77	N	Lamotrigine	8726.156	N	Lorazepam	36.56924	N
Hypromellose	0.387105	N	Lansoprazole	16175.15	N	Losartan Potassium	16690.98	N
Ibandronate Sodium	-	N	Lantanoprost	0.531841	N	Lymecycline	20293.65	N

Table S7. Assessment of the availability of EPARs (see main text) for the top 350 prescribed pharmaceuticals by mass in England from the year 2012. Usage data was collected from the National Health Service Prescription Cost Analysis 2012 (see main text).

Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available
Oxazepam	76.3154	N	Pramipexole	103.1683	Y	Quinine Bisulfate	6206.635	N
Mebeverine HCl	23210.73	N	Metoprolol Tartrate	2294.196	N	Nicorandil	1646.397	N
Medroxyprogesterone acetate	10027.43	N	Metronidazole	11153.06	N	Nicotine	384.8292	N
Mefenamic Acid	55.98768	N	Miconazole Nitrate	185.0328	N	Nifedipine	2999.857	N
Melatonin	289.0645	Y	Mirtazapine	3693.804	N	Nitrazepam	118.9559	N
Meloxicam	172.5621	N	Mometasone Furoate	0.155947	N	Nitrofurantoin	3179.265	N
Memantine HCl	10027.43	Y	Montelukast	502.6383	N	Norethisterone	189.848	N
Meptazinol HCl	1194.181	N	Morphine Sulfate	4215.292	N	Nortriptyline	482.7553	N
Mesalazine	77618.76	N	Moxifloxacin HCl		N	Nystatin	-	N
Metformin	937082.8	Y	Moxonidine	5.73321	N	Oestrogens Conjugated	34.36688	Y
Methadone	1557.91	N	Mycophenolate Mofetil	8471.95	Y	Olanzapine	423.4855	Y
Methocarbamol	9850.463	N	Nabumetone	1900.28	N	Olmesartan Medoxomil	480.2685	N
Methotrexate	159.9306	Y	Naftidrofuryl Oxalate	1315.567	N	Olopatadine HCl		Y
Methycellulose	2211.906	N	Naloxone HCl		N	Omeprazole	20213.56	N
Methyldopa	2485.886	N	Naproxen	144631.8	N	Ondansetron HCl		N
Methylphenidate HCl	770.8237	N	Nebivolol	82.73712	N	Orlistat	6022.41	Y
Methylpredisolone	-	N	Nefopam HCl	863.1576	N	Oseltamivir Phosphate	-	Y

Table S8. Assessment of the availability of EPARs (see main text) for the top 350 prescribed pharmaceuticals by mass in England from the year 2012. Usage data was collected from the National Health Service Prescription Cost Analysis 2012 (see main text).

Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available
Simeticone	649.7117	N	Tamsulosin HCl	198.2635	N	Tranexamic Acid	13377.8	N
Oxybutynin	357.7791	Y	Pravastatin Sodium	2858.58	Y	Quinine Sulfate	23334.29	N
Oxycodone HCl	1252.609	N	Prazosin HCl	5.749455	N	Raberprazole sodium	254.6749	N
Oxytetracycline	17705.12	N	Prednisolone	1447.857	N	Raloxifene	-	Y
Pantoprazole	1031.968	Y	Pregabalin	21033.26	Y	Ramipril	5454.358	N
Paracetamol	2222361	N	Primidone	1738.296	N	Ranitidine HCl	34853.71	N
Paroxetine HCl	1168.383	N	Prochlorperazine Maleate	398.1138	N	Rasagiline Mesilate	4.18359	Y
Perindopril Arginine	26.24768	N	Procyclidine HCl	163.6549	N	Repaglinide	10.79511	Y
Perindopril Erbumine	927.4732	N	Promazine HCl	183.0343	N	Risedronate Sodium	-	N
Permethrin	0.645626	N	Promethazine HCl	372.5662	N	Risperidone	82.93323	N
Phenobarbital	566.2101	N	Propranolol HCl	9604.497	Y	Ropinirole HCL	73.94691	N
Phenoxymethylpenicillin	30213.85	N	Propylthiouracil	193.4775	N	Rosuvastatin Calcium	785.6995	N
Phenytoin	12046.42	N	Pseudoephedrine HCl	329.8656	Y	Salbutamol	78.13675	N
Pholcodine	103.1683	N	Pyridostigmine bromide	717.8097	N	Saxagliptin	40.0278	Y
Pioglitazone HCl	1285.504	Y	Pyridoxine HCl	242.4529	N	Sertraline HCl	14646.35	N
Piroxicam	24.32061	N	Quetiapine	9937.301	N	Sevelamer	7370.68	Y
Pizotifen Malate	24.88417	N	Quinapril HCl		N	Sildenafil Citrate	-	Y

Table S9. Assessment of the availability of EPARs (see main text) for the top 350 prescribed pharmaceuticals by mass in England from the year 2012. Usage data was collected from the National Health Service Prescription Cost Analysis 2012 (see main text).

Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available	Pharmaceutical	Mass prescribed (2012)	EPAR available
Simvastatin	43228.17	Y	Telmisartan	942.8226	Y	Trazodone HCl	3261.608	N
Sitagliptin	6084.335	Y	Temazepam	660.796	N	Triamcinolone Acetonide	-	N
Sodium Cromoglicate	165.2364	N	Terazosin Hydrochloride	-	N	Triamterene	-	Y
Sodium Feredate	2654.143	N	Terbinafine HCl	6419.333	N	Trifluoperazine	14.17442	N
Sodium Fluoride	3.177142	N	Testosterone	158.8291	Y	Trihexyphenidyl HCl	19.41714	N
Sodium Picosulfate	301.9395	N	Tetracycline	945.4462	N	Trimethoprim	9618.376	N
Solifenacin	452.7087	N	Theophylline	7152.281	N	Trosoium chloride	350.868	N
Sotalol HCl	2722.237	N	Thiamine HCl	8037.643	N	Ursodeoxycholic Acid	5716.05	N
Spironolactone	2345.547	N	Tibolone	31.1085	N	Valaciclovir	467.6434	N
Sulfamethoxazole	-	N	Ticagrelor	777.7494	Y	Valproic Acid	10533.69	N
Sulfasalazine	53559.59	N	Tiotropium	2.634269	N	Valsartan	6512.622	Y
Sulpiride	1961.786	N	Tizanidine HCl	29.67087	N	Verapamil HCl	5771.087	N
Sumatriptam Succinate	749.3011	N	Tolbutamide	2603.915	N	Varenicline Tartrate	18.53741	Y
Tacrolimus	23.43627	Y	Tolterodine	118.3774	N	Venlafaxine	11206.86	N
Tadalafil	92.56042	Y	Topiramate	2315.892	Y	Warfarin Sodium	1192.922	N
Tamoxifen Citrate	456.7937	N	Tramadol	43206.84	N	Zolpidem Tartrate	141.9548	N
Zonisamide	509.5191	Y	Zopiclone	721.6331	N	Zuclopenthixol hydrochloride	74.3017	N

National Health Service, 2012. Prescription Cost Analysis - England 2012. https://digital.nhs.uk/catalogue/PUB10610 (accessed January 3, 2018).

1. Al-Khazrajy OSA, Boxall ABA. 2016. Risk-based prioritization of pharmaceuticals in the natural environment in Iraq. *Environ. Sci. Pollut. Res.* 23:15712–15726.

2. Ashton D, Hilton M, Thomas K V. 2004. Investigating the environmental transport of human pharmaceuticals to streams in the United Kingdom. *Sci. Total Environ.* 333:167–184.

3. Aubakirova B, Beisenova R, Boxall AB. 2017. Prioritization of pharmaceuticals based on risks to aquatic environments in Kazakhstan. *Integr. Environ. Assess. Manag.* 9999:1–8.

4. Al Aukidy M, Verlicchi P, Jelic A, Petrovic M, Barcelò D. 2012. Monitoring release of pharmaceutical compounds: Occurrence and environmental risk assessment of two WWTP effluents and their receiving bodies in the Po Valley, Italy. *Sci. Total Environ.* 438:15–25.

5. Berninger JP, Lalone CA, Villeneuve DL, Ankley GT. 2016. Prioritization of pharmaceuticals for potential environmental hazard through leveraging a large-scale mammalian pharmacological dataset. *Environ. Toxicol. Chem.* 35:1007–1020.

6. Besse JP, Garric J. 2008. Human pharmaceuticals in surface waters. Implementation of a prioritization methodology and application to the French situation. *Toxicol. Lett.* 176:104–123.

7. Besse JP, Latour JF, Garric J. 2012. Anticancer drugs in surface waters. What can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs? *Environ. Int.* 39:73–86.

8. Besse J-P, Kausch-Barreto C, Garric J. 2008. Exposure Assessment of Pharmaceuticals and Their Metabolites in the Aquatic Environment: Application to the French Situation and Preliminary Prioritization. *Hum. Ecol. Risk Assess. An Int. J.* 14:665–695.

9. Booker V, Halsall C, Llewellyn N, Johnson A, Williams R. 2014. Prioritising anticancer drugs for environmental monitoring and risk assessment purposes. *Sci. Total Environ.* 473–474:159–170.

10. Bouissou-Schurtz C, Houeto P, Guerbet M, Bachelot M, Casellas C, Mauclaire AC, Panetier P, Delval C, Masset D. 2014. Ecological risk assessment of the presence of pharmaceutical residues in a French national water survey. *Regul. Toxicol. Pharmacol.* 69:296–303.

11. Carlsson C, Johansson AK, Alvan G, Bergman K, Kühler T. 2006. Are pharmaceuticals potent environmental pollutants?. Part I: Environmental risk assessments of selected active pharmaceutical ingredients. *Sci. Total Environ.* 364:67–87.

12. Castiglioni S, Bagnati R, Fanelli R, Pomati F, Calamari D, Zuccato E. 2006. Removal of pharmaceuticals in sewage treatment plants in Italy. 40:357–363.

13. Christen V, Hickmann S, Rechenberg B, Fent K. 2010. Highly active human pharmaceuticals in aquatic systems: A concept for their identification based on their mode of action. *Aquat. Toxicol.* 96:167–181.

14. Coutu S, Rossi L, Barry DA, Chèvre N. 2012. Methodology to account for uncertainties and tradeoffs in pharmaceutical environmental hazard assessment. *J. Environ. Manage.* 98:183–190.

15. Daouk S, Chèvre N, Vernaz N, Bonnabry P, Dayer P, Daali Y, Fleury-Souverain S. 2015. Prioritization methodology for the monitoring of active pharmaceutical ingredients in hospital effluents. *J. Environ. Manage.* 160:324–332.

16. Diamond JM, Latimer HA, Munkittrick KR, Thornton KW, Bartell SM, Kidd KA. 2011. Prioritizing contaminants of emerging concern for ecological screening assessments. *Environ. Toxicol. Chem.* 30:2385–94.

17. Dong Z, Senn DB, Moran RE, Shine JP. 2013. Prioritizing environmental risk of prescription pharmaceuticals. *Regul. Toxicol. Pharmacol.* 65:60–67.

18. Donnachie RL, Johnson AC, Sumpter JP. 2016. A rational approach to selecting and ranking some pharmaceuticals of concern for the aquatic environment and their relative importance compared with other chemicals. *Environ. Toxicol. Chem.* 35:1021–1027.

19. Escher BI, Baumgartner R, Koller M, Treyer K, Lienert J, McArdell CS. 2011. Environmental toxicology and risk assessment of pharmaceuticals from hospital wastewater. *Water Res.* 45:75–92.

20. Fàbrega F, Marquès M, Ginebreda A, Kuzmanovic M, Barceló D, Schuhmacher M, Domingo JL, Nadal M. 2013. Integrated risk index of chemical aquatic pollution (IRICAP): Case studies in Iberian rivers. *J. Hazard. Mater.* 263:187–196.

21. Fent K. 2015. Progestins as endocrine disrupters in aquatic ecosystems: Concentrations, effects and risk assessment. *Environ. Int.* 84:115–130.

22. Ferrari B, Paxéus N, Giudice R Lo, Pollio A, Garric J. 2003. Ecotoxicological impact of pharmaceuticals found in treated wastewaters: Study of carbamazepine, clofibric acid, and diclofenac. *Ecotoxicol. Environ. Saf.* 55:359–370.

23. Fick J, Lindberg RH, Tysklind M, Larsson DGJ. 2010. Predicted critical environmental concentrations for 500 pharmaceuticals. *Regul. Toxicol. Pharmacol.* 58:516–523.

24. Orias F, Perrodin Y. 2014. Pharmaceuticals in hospital wastewater: Their ecotoxicity and contribution to the environmental hazard of the effluent. *Chemosphere*. 115:31–39.

25. Ginebreda A, Jelić A, Petrović M, López de Alda M, Barceló D. 2012. New indexes for compound prioritization and complexity quantification on environmental monitoring inventories. *Environ. Sci. Pollut. Res.* 19:958–970.

26. Götz CW, Stamm C, Fenner K, Singer H, Schärer M, Hollender J. 2010. Targeting aquatic microcontaminants for monitoring: exposure categorization and application to the Swiss situation. *Environ. Sci. Pollut. Res.* 17:341–354.

27. Grill G, Khan U, Lehner B, Nicell J, Ariwi J. 2016. Risk assessment of down-the-drain chemicals at large spatial scales: Model development and application to contaminants originating from urban areas in the Saint Lawrence River Basin. *Sci. Total Environ.* 541:825–838.

28. Grung M, Källqvist T, Sakshaug S, Skurtveit S, Thomas K V. 2008. Environmental assessment of Norwegian priority pharmaceuticals based on the EMEA guideline. *Ecotoxicol. Environ. Saf.* 71:328–340.

29. Guo J, Sinclair CJ, Selby K, Boxall ABA. 2016. Toxicological and ecotoxicological risk-based prioritization of pharmaceuticals in the natural environment. *Environ. Toxicol. Chem.* 35:1550–1559.

30. Helwig K, Hunter C, MacLachlan J, McNaughtan M, Roberts J, Cornelissen A, Dagot C, Evenblij H, Klepiszewski K, Lyko S, Nafo I, McArdell CS, Venditti S, Pahl O. 2013. Micropollutant Point Sources in the Built Environment: Identification and Monitoring of Priority Pharmaceuticals Substances in Hospital Effluents. *J. Anal. Toxicol.* 3:177.

31. Helwig K, Hunter C, Mcnaughtan M, Roberts J, Pahl O. 2016. Ranking prescribed pharmaceuticals in terms of environmental risk: Inclusion of hospital data and the importance of regular review. *Environ. Toxicol. Chem.* 35:1043–1050.

32. Howard P, Muir D. 2010. Identifying New Persistent and Bioaccumulative Organics Among Chemicals in Commerce. *Environ. Sci. Technol.* 44:2277–2285.

33. Huber S, Remberger M, Kaj L, Schlabach M, Jörundsdóttir HÓ, Vester J, Arnórsson M, Mortensen I, Schwartson R, Dam M. 2016. A first screening and risk assessment of pharmaceuticals and additives in personal care products in waste water, sludge, recipient water and sediment from Faroe Islands, Iceland and Greenland. *Sci. Total Environ.* 562:13–25.

34. Huschek G, Hansen PD, Maurer HH, Krengel D, Kayser A. 2004. Environmental risk assesssment of medicinal products for human use according to European Commission recommendations. *Environ. Toxicol.* 19:226–240.

35. Isidori M, Lavorgna M, Nardelli A, Pascarella L, Parrella A. 2005. Toxic and genotoxic evaluation of six antibiotics on non-target organisms. *Sci. Total Environ.* 346:87–98.

36. Jean J, Perrodin Y, Pivot C, Trepo D, Perraud M, Droguet J, Tissot-Guerraz F, Locher F. 2012. Identification and prioritization of bioaccumulable pharmaceutical substances discharged in hospital effluents. *J. Environ. Manage.* 103:113–121.

37. Ji K, Han EJ, Back S, Park J, Ryu J, Choi K. 2016. Prioritizing human pharmaceuticals for ecological risks in

the freshwater environment of Korea. *Environ. Toxicol. Chem.* 35:1028–1036.

38. Jones OAH, Voulvoulis N, Lester JN. 2002. Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. *Water Res.* 36:5013–5022.

39. Kim MH, Park J, Kim YH, Choi K. 2006. Prioritising Human Use Antibiotics for Environmental Health Management and Estimating Their Environmental Concentrations in Korean Waterway. *Korean J. Environ. Heal. Sci.* 32:462–468.

40. Kosma CI, Lambropoulou DA, Albanis TA. 2014. Investigation of PPCPs in wastewater treatment plants in Greece: Occurrence, removal and environmental risk assessment. *Sci. Total Environ.* 466–467:421–438.

41. Kostich MS, Batt AL, Lazorchak JM. 2014. Concentrations of prioritized pharmaceuticals in effluents from 50 large wastewater treatment plants in the US and implications for risk estimation. *Environ. Pollut.* 184:354–359.

42. Kostich MS, Lazorchak JM. 2008. Risks to aquatic organisms posed by human pharmaceutical use. *Sci. Total Environ.* 389:329–339.

43. Kumar A, Xagoraraki I. 2010.Pharmaceuticals, personal care products and endocrine-disrupting chemicals in U.S. surface and finished drinking waters: A proposed ranking system. *Sci. Total. Environ.* 408: 5972–5989.

44. Kuzmanović M, Ginebreda A, Petrović M, Barceló D. 2015. Risk assessment based prioritization of 200 organic micropollutants in 4 Iberian rivers. *Sci. Total Environ.* 503–504:289–299.

45. Leung HW, Jin L, Wei S, Tsui MMP, Zhou B, Jiao L, Cheung PC, Chun YK, Murphy MB, Lam PKS. 2013. Pharmaceuticals in tap water: Human health risk assessment and proposed monitoring framework in China. *Environ. Health Perspect.* 121:839–846.

46. Li Z, Li M, Liu X, Ma Y, Wu M. 2014. Identification of priority organic compounds in groundwater recharge of China. *Sci. Total Environ.* 493:481–486.

47. Lin AY-C, Yu T-H, Lin C-F. 2008. Pharmaceutical contamination in residential, industrial, and agricultural waste streams: Risk to aqueous environments in Taiwan. *Chemosphere*. 74:131–141.

48. Lienert J, Güdel K, Escher BI. 2007. Screening method for ecotoxicological hazard assessment of 42 pharmaceuticals considering human metabolism and excretory routes. *Environ. Sci. Technol.* 41:4471–4478.

49. Lolić A, Paíga P, Santos LHMLM, Ramos S, Correia M, Delerue-Matos C. 2015. Assessment of non-steroidal anti-inflammatory and analgesic pharmaceuticals in seawaters of North of Portugal: Occurrence and environmental risk. *Sci. Total Environ.* 508:240–250.

50. Mansour F, Al-Hindi M, Saad W, Salam D. 2016. Environmental risk analysis and prioritization of pharmaceuticals in a developing world context. *Sci. Total Environ.* 557–558:31–43.

51. Morais SA, Delerue-Matos C, Gabarrell X. 2014. An uncertainty and sensitivity analysis applied to the prioritisation of pharmaceuticals as surface water contaminants from wastewater treatment plant direct emissions. *Sci. Total Environ.* 490:342–350.

52. Muñoz I, José Gómez M, Molina-Díaz A, Huijbregts MAJ, Fernández-Alba AR, García-Calvo E. 2008. Ranking potential impacts of priority and emerging pollutants in urban wastewater through life cycle impact assessment. *Chemosphere*. 74:37–44.

53. Murray KE, Thomas SM, Bodour AA. 2010. Prioritizing research for trace pollutants and emerging contaminants in the freshwater environment. *Environ. Pollut.* 158:3462–3471.

54. Ncube E, Voyi K, du Preez H. 2012. Implementing a protocol for selection and prioritisation of organic contaminants in the drinking water value chain: Case study of Rand Water, South Africa. *Water SA*. 38:487–504.

55. Ngumba E, Gachanja A, Tuhkanen T. 2016. Occurrence of selected antibiotics and antiretroviral drugs in Nairobi River Basin, Kenya. *Sci. Total Environ.* 539:206–213.

56. Oğuz M, Mihçiokur H. 2014. Environmental risk assessment of selected pharmaceuticals in Turkey. *Environ. Toxicol. Pharmacol.* 38:79–83.

57. Oldenkamp R, Huijbregts MAJ, Hollander A, Versporten A, Goossens H, Ragas AMJ. 2013. Spatially explicit

prioritization of human antibiotics and antineoplastics in Europe. *Environ. Int.* 51:13–26.

58. Olsen L., J.F. V, Carter JM, Zogorski JS. 2013. *Prioritization of constituents for national- and region-scale amibient monitoring of water and sediment in the United States: U.S. Geological Survey Scientific Investigations Report 2012-5218*.

59. Ortiz de García S, Pinto GP, García-Encina PA, Mata RI. 2013. Ranking of concern, based on environmental indexes, for pharmaceutical and personal care products: An application to the Spanish case. *J. Environ. Manage.* 129:384–397.

60. Perazzolo C, Morasch B, Kohn T, Magnet A, Thonney D, Chèvre N. 2010. Occurrence and fate of micropollutants in the Vidy Bay of Lake Geneva, Switzerland. Part I: Priority list for environmental risk assessment of pharmaceuticals. *Environ. Toxicol. Chem.* 29:1649–1657.

61. Pereira AMPT, Silva LJG, Lino CM, Meisel LM, Pena A. 2016. Assessing environmental risk of pharmaceuticals in Portugal: An approach for the selection of the Portuguese monitoring stations in line with Directive 2013/39/EU. *Chemosphere*. 144:2507–2515.

62. Riva F, Zuccato E, Castiglioni S. 2015. Prioritization and analysis of pharmaceuticals for human use contaminating the aquatic ecosystem in Italy. *J. Pharm. Biomed. Anal.* 106:71–78.

63. Roos V, Gunnarsson L, Fick J, Larsson DGJ, Rudén C. 2012. Prioritising pharmaceuticals for environmental risk assessment: Towards adequate and feasible first-tier selection. *Sci. Total Environ.* 421–422:102–110.

64. Sangion A, Gramatica P. 2016. Hazard of pharmaceuticals for aquatic environment: Prioritization by structural approaches and prediction of ecotoxicity. *Environ. Int.* 95:131–143.

65. Stuer-Lauridsen F, Birkved M, Hansen LP, Lützhøft HC, Halling-Sørensen B. 2000. Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. *Chemosphere*. 40:783–93.

66. Sui Q, Wang B, Zhao W, Huang J, Yu G, Deng S, Qiu Z, Lu S. 2012. Identification of priority pharmaceuticals in the water environment of China. *Chemosphere*. 89:280–286.

67. Tauxe-Wuersch A, De Alencastro LF, Grandjean D, Tarradellas J. 2005. Occurrence of several acidic drugs in sewage treatment plants in Switzerland and risk assessment. *Water Res.* 39:1761–1772.

68. Tewari S, Jindal R, Kho YL, Eo S, Choi K. 2013. Major pharmaceutical residues in wastewater treatment plants and receiving waters in Bangkok, Thailand, and associated ecological risks. *Chemosphere*. 91:697–704.

69. von der Ohe PC, Dulio V, Slobodnik J, De Deckere E, Kuhne R, Ebert RU, Ginebreda A, De Cooman W, Schuurmann G, Brack W. 2011. A new risk assessment approach for the prioritization of 500 classical and emerging organic microcontaminants as potential river basin specific pollutants under the European Water Framework Directive. *Sci. Total Environ.* 409:2064–2077.

70. Webb S. 2004. A Data-based Perspective on the Environmental Risk Assessment of Human Pharmaceuticals I- Collation of Available Ecotoxicity Data. In Kümmerer, K, ed., *Pharm. Environ.*, pp 317–343.

71. Wennmalm Å, Gunnarsson B. 2005. Public health care management of water pollution with pharmaceuticals: Environmental classification and analysis of pharmaceutical residues in sewage water. 39:291–297.

72. Zhou H, Zhang Q, Wang X, Zhang Q, Ma L, Zhan Y. 2014. Systematic screening of common wastewater-marking pharmaceuticals in urban aquatic environments: implications for environmental risk control. *Environ. Sci. Pollut. Res.* 21:7113–7129.

73. Zuccato E, Castiglioni S, Fanelli R. 2005. Identification of the pharmaceuticals for human use contaminating the Italian aquatic environment. *J. Hazard. Mater.* 122:205–209.

Table S10. Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

Number	Variable	Experimental source	Model/ predictive tool/ default	Applicability domain	Experimental validation	Method limitations/ Suggestions
(1) API usage in specific region	Consumption (mg/yr)	Prescription analysis	N/A	N/A	1. Found good agreement between PECs/MECs in WwTP effluent (11 APIs) [1].	• No over-the-counter API usage. • Hospital usage should be included if possible [2]. • Method can be paired with the Fpen approach to cover all APIs. • Route of administration can affect metabolism, the highest fraction excreted unchanged found in the literature should be used for a worst case approach. • Ensure combination drugs are split into constituent parts. • Run the prioritisation with no metabolism to identify whether the metabolites of particular highly metabolised parent pharmaceuticals require research, as metabolites are rarely more potent than the parent pharmaceutical.
		Sales data	N/A	N/A	PECs derived from sales data are greater than local maximum MECs in study of 56 APIs [3].	• Not publicly available.
		Market penetration (Fpen) estimate	Fpen 1% (default) [4]	• All APIs.	1.) Derived 1% Fpen default based on 95th percentile of 800 APIs [4]. 2.) Evaluated 10 MECs with PECs derived using default Fpen, PECs were conservative [5].	• Generalised, consumption over/under estimations likely. • Limited to a specific product, not additive across pharmaceuticals in multiple formulations or prodrugs.
(2) API emission to sewage	% excreted unchanged ($F_{excreta}$)	In vivo metabolism studies in man	N/A	• All administered internally (including metabolites).	Variation in reported $F_{excreta}$ identified as source of PEC error (0-200% change in PEC) [6].	• Topical and ophthalmic preparations generally no metabolism, assume 100% excretion [7]. • Sulfato-and glucuronide metabolites (cleaving) possible in WwTP, could increase wastewater parent API loads, include this fraction in PEC [8]. • Suggested that largest reported $F_{excreta}$ value in literature generates the most relevant PECs [9].

Table S11. (continued) Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

Number	Variable	Experimental source	Model/ predictive tool/	Applicability domain	Experimental validation	Method limitations/ Suggestions
(3) Wastewater dilution	Wastewater (L/person·day)	Wastewater entering WWTP averaged per capita	Default: 200 L/day [10,11]	Europe	1.)Validated 200 L/day per capita wastewater generation for Germany [12]. 2.) Wastewater dilution will vary based on water usage practices throughout world, 50-400 L/day [13].	Consider regional water usage patterns to not overestimate environmental dilution.
(4) WWTP removal	% removal efficiency (%RE), split into % sorption to sludge and % biodegredation	Estimated removals based on difference between influent and effluent concentrations	SimpleTreat 4.0 [14]	• Monovalent organic acids, bases, neutrals • pH 3-7, -1 < logKow >3). • Koc may be underestimated for organic acids, more so for bases. • Not suitable for ionic surfactants.	1.) Neutral organics, predicted within +/- 5% removal [15]. 2.) 10 compounds to challenge applicability domain, found K_{OC} regressions good for acids, but not for bases (K_{OC} better to be experimentally determined [16].	• Improvements in mechanistic understanding and modelling of sorption for ionsables still needed [17]. • Experimental values vary substantially, if used, use lowest % RE reported in literature. • Organic bases preform more poorly than acids because when ionised, cations could have electrostatic interactions with negatively charged particles (ie. sediment, colloids, sludge), so use experimental K_{oc} when possible. • SimpleTreat 3.1 (and newer) suggested for first tier risk assessment (considers ionic state of API) [4].
(5) Environmental Dilution	Dilution factor	Monitor river flow and WWTP discharge rate	Default:10 [4]	Rivers (up to dilution factor of 1000).	1.) Site specific dilution is prefered to calculate PEC.[18] 2.)Dilution factor can lead to an uncertainty of up to 695% in calculation of PECs.[6]	• In general, a 10 default dilution factor will provide the worst-case assumption (Europe). • Caution should be taken using this value to estimate the dilution factor of small rivers with seasonal fluctuations.
(6) Equilibrium partitioning	Soil-water partition coefficient (Kd)	OECD 106	QSAR [19]	• Includes ionisables and neutral organics • Bases: pKa>2, -1.66< logKow >7.03 • Acids: pKa 0-12, -2.19 < logKow > 8.50	1.) QSARs applied to realistic exposure scenario of 3 compounds, results compared with monitoring data and output from conventional fugacity modelling [20]. 2.) QSARs applied to 415 acids and 496 bases in a multimedia fate and effect model (USES-LCA), indicated partitioning to solid-phase underestimated when ionisables not considered, (e.g. TGD method) [21].	• $PEC_{porewater}$ is also calculated with this Kd estimation approach. • Further model refinement required for APIs specifically. • The multimedia fate model SimpleBox 4.0 has also been updated with this approach [22].
	Sediment-water partition coefficient (Kd)	OECD 106 (modified) OPPTS 835.110	QSAR [19]	N/A	N/A	• The water-soil Kd QSARs [19] has been suggested to use, nothing specifically developed for water-sediment partitioning [20].
	Sludge-water partition coefficient (Kd)					•

Table S12. (continued) Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

Number	Variable	Experimental source	Model/ predictive tool/	Applicability domain	Experimental validation	Method limitations/ Suggestions
(7) Degradation	DT50 (soil)	OECD 307 (degradation test)	BIOWIN	• Able to predict not-readily biodegradable substances with high accuracy in contrast to ready biodegradability [23].	1.) Compared API experimental anaerobic biodegradation with BIOWIN estimates, found a similar order in anaerobic biodegradability (n=4) [24]. 2.)Validated the BIOWIN model using experimental data from 110 compounds [23].	• Poor model predictions for chemicals that contain moieties or combinations of moieties that are not adequately represented in database to build models (e.g. pharmaceuticals). • Does not account for stereochemistry in predictions which is important for chiral molecules (e.g. pharmaceuticals) [25].
	DT50 (sediment)	OECD 308 (309) (degradation test)	BIOWIN	• Can be applied for sediments, but not validated.	N/A	• Degradation in sediment will be subject variety of environmental conditions, for example experimental differences in degradation rates between moving and flat bed sediments observed [26]. • More work is needed to determine the appropriateness of BIOWIN for API degradation in sediment.
(8) Application rate	Application (kg/hectare (dry weight) per year)	Localised application rate	Default: • 5000 kg/ha·yr agricultural • 1000 kg/ha·yr grassland (dry weight)	• Europe, however the Danish EPA suggest 6000 kg/ha·yr (dry weight) application for risk assessment.	N/A	• The suitability of the defaults is dependent on the country-specific biosolid practices and legislation, for example the US applied 4.0×10^6 tons of dry weight biosolids, while Europe applied 2.39×10^6 tons in 2006 [27]. • The magnitude and impact of the application rate of biosolids throughout the world in terms of APIs is largely unexplored.

Table S13. (continued) Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

Number	Variable	Experimental source	Model/ predictive tool	Applicability domain	Experimental validation	Method limitations
(9) Acute	Fish LC_{50}	OECD 203	1.API specific ecotoxicity QSARs [28] 2. ECOSAR [29]	1. Applied QSAR to 1267 APIs and the percent of APIs that fell in the applicability domain (AD) was ≥ 74% 2. ECOSAR -3 < LogKow < 5. 8 Molecular weight <1000	1. Relatively new QSARs, no external validation yet published. 2. Limitations of ECOSAR demonstrated by many, notably Hulzebos and Posthumus (2003) [30].	• ECOSAR was developed with a small set of industrial chemicals with simple structures [31]. • APIs have complex structures with multiple functional groups, which could have a specific mode of action [28,32]. • Experimental ecotoxicity data is limited.
	Invertebrate EC_{50}	OECD 202				
	Algae EC_{50}	OECD 201				
	Benthic Invertebrate EC_{50}	OECD 218	Not yet developed	N/A	N/A	• Unique exposure scenario where organisms could be exposed to water column, sediments and pore water.
	Earthworm LC_{50}	OECD 207	1. Equilibrium partitioning concept applied to aquatic data for screening. 2. Earthworm QSAR reported in Guo (2016) [33].	1. QSARs developed based on 11 compounds is valid for short-term toxicity of several chlorophenols, chlorobenzenes and chloroanilines [34]. 2. None reported.	1. API specific validation of this approach has not been attempted. 2. None reported.	• Equilibrium partitioning method may not be suitable for lipophilic compounds or substances with a specific mode of action (e.g. APIs) [34]. • Does not consider the effects on soil organisms for chemicals that are adsorbed to soil particles and taken up by ingestion or contact with soil or sediment adsorbing chemicals (log Kow > than 3).
	Soil Invertebrate EC_{50}	OECD 218	Not yet developed	N/A	N/A	• Despite experimental field evidence of exposure, modelling consideration of this exposure pathway is largely unexplored for APIs.
	Terrestrial Plant EC_{50}	OECD 208	Not yet developed	N/A	N/A	

Table S14. (continued) Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

Number	Variable	Experimental source	Model/ predictive tool	Applicability domain	Experimental validation	Method limitations
(10) Chronic	Fish	OECD 210	1. ECOSAR: ChV (geometric mean of LOEC and NOEC) 2. Claey (2013) [35]: QSARs for substances acting via nonpolar and polar narcosis.	1. LogKow < 5.8, neutral organics. When chronic data is lacking acute to chronic ratios are used. 2. Nonpolar narcosis: 0.92 < logKow < 6.8 Polar narcosis: 6.83 < pKa <10.7 1.46 < logKow < 5.76	1. Validated for 23 neutral organics (not APIs). Concluded when functional groups could have a specific mode of action (e.g. pharmaceuticals), ECOSAR not suitable and only when a compound is within the AD the QSAR is suitable [32]. 2. Method has not been externally validated for APIs by others.	• Chronic experimental data is rare putting a reliance on acute to chronic ratios for many structural classes in ECOSAR. • ECOSAR was creating using a limited number of compounds whose relevance to APIs is questioned [31]. • De Haas (2011) [32] and Claeys (2013) [35], suggest chronic ECOSAR is not robust.
	Invertebrate	OECD 211	ECOSAR Chv	1. LogKow < 5.8, neutral organics. When chronic data is lacking acute to chronic ratios are used.	Not validated for APIs	• Chronic experimental data for invertebrates and aquatic plants, validation and development has focused on fish.
	Algae	OECD 221				
	Benthic Invertebrate	OECD 219	No QSAR for APIs developed	N/A	N/A	• Despite experimental field evidence of exposure, modelling consideration of this exposure pathway is largely unexplored for APIs.
(11) Assessment Factors	Acute assessment factor (AF)		Defaults suggested: EPA (1995) [36] EMEA 2006 [37] OECD 1992 [38]	AF: No greater than 1000, regardless of whether species is a standard test organism. AF: No less than 100 even when acute $LC(EC)_{50}$ is from most sensitive species.	• Fish are most sensitive species and assessment factors applied to acute data may be acceptable when chronic data is missing (unless a mode of action concern is present) [39].	• Account for inter- and intra-species variability and extrapolate from lab to field or in silico prediction to field. • Derived from policy, assessment factors are arbitrary values which may have little scientific relevance, but reduce the likelihood of underestimating risk [40].
	Chronic AF		ECHA (2008) [41]	AF: 10 if ecotoxicity is available for 3 trophic levels. AF: 50 if ecotoxicity available for 2 trophic levels.		

Table S15. (continued) Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

Number	Variable	Experimental source	Model/ predictive tool	Applicability domain	Experimental validation	Method limitations
(12) Fish plasma concentration	FPC		1. $logP_{blood:water}$ [42] 2. BCF estimation (ionisables) [43]	1. 0 < LogKow < 8 2. Three equations covering acids, bases and neutral compounds: 1< logKow <7 Acid: -0.36 < pKa <10.6 Base: 2 < pKa < 11.4	1. Tested the read across hypothesis (using pH corrected logKow) for Fluoxetine, concluded powerful tool for risk assessment [44]. 1b. Tested read across hypothesis for ibuprofen, provided evidence to support it [45]. 2. Investigation of parameters used to model FPC, suggested approach (2) with logDow most robust [46].	• BCF method that considers ionisables preferred [43,46]. • C_{max} values are more readily available[46]. • The read-across approach for risk assessment has limited validation [44,45].
(13) Internal concentration invertebrate	IPC	Method not yet suggested	Not yet developed	N/A	N/A	• An invertebrate internal concentration estimation method needs to be developed for invertebrates associated with the benthos and the water column. • A similar approach like the FPC could be possibility [47].
	$IPC_{benthic}$	Method not yet suggested	Not yet developed	N/A	N/A	
(14) Therapeutic plasma concentration	H_tPC	C_{max} (peak plasma concentration) AUC_{conc} (area under the time-concentration curve)	N/A	N/A	The area under the curve (AUC) compared to C_{max} does not have a large impact of FPC results [46].	• Highly dependent on the administered therapeutic dose/brand. • Lowest reported values taken to represent worst case. • Available in peer-reviewed pharmacokinetic literature or drug approval reports (EMA, FDA).

Table S16. (continued) Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

Number	Variable	Experimental source	Model/ predictive tool	Applicability domain	Experimental validation	Method limitations
(15) Bioconcentration factors (BCF)	Fish BCF	OECD 305	1. See FPC 2. QSAR [48]	1. See FPC 2. 1< LogKow <10	1. Not validated specifically for pharmaceuticals. 2. Meylan evaluated 694 logBCF/logKow data values 610 non-ionic and 84 ionic covering a logKow range of 3.98-13.98 to derive QSARs.	• Linear and parabolic approaches to cover logKow 2- 10 suggested [48], LogKow >10 BCFs should be treated as qualitative. • These models are not applicable to ionisable compounds [49]. • Neither approach validated explicitly for pharmaceuticals.
	Invertebrate BCF	BCF minimised design [50]	Not yet developed	N/A	N/A	• Uptake of APIs in invertebrate has been shown [51,52], but a suitable predictive model for neutrals and ionisables has yet to be developed. • OECD 305 methods may be inappropriate for invertebrates.
	Benthic Invertebrate BCF	Test method not yet suggested	Not yet developed	N/A	N/A	• QSARs are only available to predict fish and algal BCFs. • Field studies demonstrated pharmaceutical accumulation in benthic invertebrates [53,54].
	Earthworm BCF	OECD 317	QSAR [55,56]	0 < logKow < 8	BCF/BAF estimation approach has been validated, but not for pharmaceuticals specifically [57].	• Current predictive method not suitable for ionisable organic chemicals and poor performance for chemicals of moderate to high hydrophobicity [11,55].
	Plant BCF	Test method not yet suggested	Not yet developed	N/A	N/A	• Pharmaceutical uptake has been demonstrated in the lab and in the field [58,59]. • Developing a predictive tool for this uptake pathway will be especially important as human intake stemming from biosolid use and reclaimed wastewater on cropland has been demonstrated [60].
(16) NOAEL	Mammal	Clinical and pre-clinical data Toxicity studies –repeated-dose toxicity (NOAEL 28, 90 day) or chronic study	Assessment factor : $NOEC_{mammal}$, 28 days=300 90 days =90 Chronic=30	N/A	N/A	• Available as pre-clinical data. • Convert NOAEL to NOEC but not appropriate to extrapolate LC50 tests to derive NOEC unlike birds [11].

Table S17. (continued) Parameters needed to estimate environmental active pharmaceutical ingredient (API) exposure and effects in multiple compartments. Summarised in Table 3 of the main text. Numbers refer to the framework presented in Figure 4-6. Default refers to suggestions from the EMA (2006) guidelines.

(17) NOEC	Bird	OECD 205, 206, 223 (1984hr, LC50 acute avian bird study)	Assessment factor: LC_{50} bird = 3000 NOEC bird (chronic) =30	Extrapolate toxicity tests to get conversion to NOEC		• Extrapolate toxicity tests (LC_{50}) for conversion to NOEC (OECD 205, 206)
(18) Multiple prey types	Uncertainty factors	Not yet derived	N/A	N/A	N/A	• Applying an uncertainty factor to the feeding habit. • Uncertainty in uptake across prey species, e.g. different type of plants invertebrates consume.
(19) Feeding behaviour	Dietary inputs	Not yet derived	N/A	N/A	N/A	• Assessment of the diet for the species in question is (i.e. how much fish, plant, worm does it generally consume to calculate the exposure).
(20) Acceptable daily intake	ADI	Mammalian chronic toxicity studies	1. Calculate from NOAEL from most sensitive species in most sensitive test.[61] (EQ. SX) 2. Calculate ADI from LOEL and series of uncertainty factors.[62] (EQN. SX)	N/A	N/A	• This is based on arbitrary uncertainty factors to ensure conservative risk assessment, which may be modified when adequate human data or comparative pharmacokinetic or toxicodynamic data are available.[61]
(21) Human diet	Agricultural practice	Not yet derived	N/A	N/A	N/A	• Human exposure has only included contamination of fish or drinking water.[62] • Regions which rely on application of biosolids or wastewater reclamation for agriculture will need combination of PICplant and an assessment factor to be applied.

Supplemental Material References

1. Coetsier CM, Spinelli S, Lin L, Roig B, Touraud E. 2009. Discharge of pharmaceutical products (PPs) through a conventional biological sewage treatment plant: MECs vs PECs? *Environ. Int.* 35:787–792.

2. Helwig K, Hunter C, Mcnaughtan M, Roberts J, Pahl O. 2016. Ranking prescribed pharmaceuticals in terms of environmental risk: Inclusion of hospital data and the importance of regular review. *Environ. Toxicol. Chem.* 35:1043–1050.

3. Kostich MS, Batt AL, Lazorchak JM. 2014. Concentrations of prioritized pharmaceuticals in effluents from 50 large wastewater treatment plants in the US and implications for risk estimation. *Environ. Pollut.* 184:354–359.

4. EMA. 2006. GUIDELINE ON THE ENVIRONMENTAL RISK ASSESSMENT OF MEDICINAL PRODUCTS FOR HUMAN USE. EMEA/CHMP/SWP/4447/00:1–12.

5. Bouissou-Schurtz C, Houeto P, Guerbet M, Bachelot M, Casellas C, Mauclaire AC, Panetier P, Delval C, Masset D. 2014. Ecological risk assessment of the presence of pharmaceutical residues in a French national water survey. *Regul. Toxicol. Pharmacol.* 69:296–303.

6. Verlicchi P, Al Aukidy M, Jelic A, Petrović M, Barceló D. 2014. Comparison of measured and predicted concentrations of selected pharmaceuticals in wastewater and surface water: A case study of a catchment area in the Po Valley (Italy). *Sci. Total Environ.* 470–471:844–854.

7. Perazzolo C, Morasch B, Kohn T, Magnet A, Thonney D, Chèvre N. 2010. Occurrence and fate of micropollutants in the Vidy Bay of Lake Geneva, Switzerland. Part I: Priority list for environmental risk assessment of pharmaceuticals. *Environ. Toxicol. Chem.* 29:1649–1657.

8. Jelić A, Gros M, Petrović M, Ginebreda A, Barceló D. 2012. Occurrence and Elimination of Pharmaceuticals During Conventional Wastewater Treatment. *Emerg. Prior. Pollut. Rivers*., pp 1–23. doi:10.1007/978-3-642-25722-3_1.

9. Grung M, Källqvist T, Sakshaug S, Skurtveit S, Thomas K V. 2008. Environmental assessment of Norwegian priority pharmaceuticals based on the EMEA guideline. *Ecotoxicol. Environ. Saf.* 71:328–340.

10. Struijs J. 1996. *SimpleTreat 3.0: a model to predict the distribution and elimination of chemicals by sewage treatment plants*. Bilthoven.

11. European Chemicals Bureau. 2003. *Technical Guidance Document on Risk Assessment, Part 2, Chapter 3. EUR 20418 EN/2*.

12. Ahting M, Mueller-Knoche S. 2014. *The assessment of direct emission to surface water in urban areas (PT 6.2/6.3 and 7-10)*.

13. Henze M, Comeau Y. 2008. *Biological Wastewater Treatment Principles, Modelling and Design*. In Henze, M, van Loosdrecht, MC., Ekama, GA and Brdjanovic, D, eds. IWA Publishing, London.

14. SimpleTreat 4.0: a model to predict fate and emission of chemicals in wastewater treatment plants SimpleTreat 4.0: a model to predict the fate and emission of chemicals in wastewater treatment plants.

15. Crechem Technologies. 2006. *Validation of Sewage Treatment Plant Emission Models. Volume I/II - Main Text*. Ottawa, Ontario.

16. Franco A, Struijs J, Gouin T, Price OR. 2013. Evolution of the sewage treatment plant model SimpleTreat: Applicability domain and data requirements. *Integr. Environ. Assess. Manag.* 9:560–568.

17. Chemicals EC for E and T of. 2013. *Environmental Exposure Assesment of Ionisable Organic Compounds. Technical Report: 123*. Brussels.

18. Celle-Jeanton H, Schemberg D, Mohammed N, Huneau F, Bertrand G, Lavastre V, Le Coustumer P. 2014. Evaluation of pharmaceuticals in surface water: Reliability of PECs compared to MECs. *Environ. Int.* 73:10–21.

19. Franco A, Trapp S. 2008. Environmental Chemistry ESTIMATION OF THE SOIL–WATER PARTITION COEFFICIENT NORMALIZED TO ORGANIC CARBON FOR IONIZABLE ORGANIC CHEMICALS. *Environ. Toxicol. Chem.* 27.

20. Franco A, Trapp S. 2010. A multimedia activity model for ionizable compounds: Validation study with 2,4-dichlorophenoxyacetic acid, aniline, and trimethoprim. *Environ. Toxicol. Chem.* 29:789–799.

21. van Zelm R, Stam G, Huijbregts MAJ, van de Meent D. 2013. Making fate and exposure models for freshwater ecotoxicity in life cycle assessment suitable for organic acids and bases. *Chemosphere*. 90:312–317.

22. Hollander A, Schoorl M, van de Meent D. 2016. SimpleBox 4.0: Improving the model while keeping it simple…. *Chemosphere*. 148:99–107.

23. Posthumus R, Traas TP, Peijnenburg WJGM, Hulzebos EM. 2005. External validation of EPIWIN biodegradation models. *SAR QSAR Environ. Res.* 16:135–148.

24. Musson SE, Campo P, Tolaymat T, Suidan M, Townsend T. 2010. Assessment of the anaerobic degradation of six active pharmaceutical ingredients. *Sci. Total Environ.* 408:2068–2074.

25. MacLeod SL, Wong CS. 2010. Loadings, trends, comparisons, and fate of achiral and chiral pharmaceuticals in wastewaters from urban tertiary and rural aerated lagoon treatments. *Water Res.* 44:533–544.

26. Kunkel U, Radke M. 2008. Biodegradation of Acidic Pharmaceuticals in Bed Sediments: Insight from a Laboratory Experiment. *Environ. Sci. Technol.* 42:7273–7279.

27. Kinney CA, Furlong ET, Kolpin DW, Burkhardt MR, Zaugg SD, Werner SL, Bossio JP, Benotti MJ. 2008. Bioaccumulation of pharmaceutical and other anthropogenic waste indicators in earhtworms from agricultural soil amended with biosolid or swine manure. *Environ. Sci. Technol.* 42:1863–1870.

28. Sangion A, Gramatica P. 2016. Hazard of pharmaceuticals for aquatic environment: Prioritization by structural approaches and prediction of ecotoxicity. *Environ. Int.* 95:131–143.

29. Envirometal Protection Agency. ECOlogical Structure-Activity Relationship Model (ECOSAR) Class Program. *Epa*.

30. Hulzebos EM, Posthumus R. 2003. (Q)SARs: gatekeepers against risk on chemicals? *SAR QSAR Environ. Res.* 14:285–316.

31. Madden JC, Enoch SJ, Hewitt M, Cronin MTD. 2009. Pharmaceuticals in the environment: Good practice in predicting acute ecotoxicological effects. *Toxicol. Lett.* 185:85–101.

32. de Haas EM, Eikelboom T, Bouwman T. 2011. Internal and external validation of the long-term QSARs for neutral organics to fish from ECOSAR™. *SAR QSAR Environ. Res.* 22:545–559.

33. Guo J, Sinclair CJ, Selby K, Boxall ABA. 2016. Toxicological and ecotoxicological risk-based prioritization of pharmaceuticals in the natural environment. *Environ. Toxicol. Chem.* 35:1550–1559.

34. Van Gestel CAM, Ma W-C. 1993. Development of QSAR's in soil ecotoxicology: Earthworm toxicity and soil sorption of chlorophenols, chlorobenzenes and chloroanilines. *Water. Air. Soil Pollut.* 69:265–276.

35. Claeys L, Iaccino F, Janssen CR, Van Sprang P, Verdonck F. 2013. Development and validation of a quantitative structure-activity relationship for chronic narcosis to fish. *Environ. Toxicol. Chem.* 32:2217–2225.

36. Zeeman M. 1995. EPA's framework for ecological effects assessment. In Herd, R, ed., *Screen. Test. Chem. Commer.*, pp 69–78.

37. European Medicines Agency. 2006. *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use*. London, UK.

38. Organisation for Economic CO-Operation and Development. 1992. *Report of the OECD Workshop on the extrapolation of laboratory aquatic toxicity data to the real environment. OCDE/GD(92)169*. Paris.

39. Vestel J, Caldwell DJ, Constantine L, D'Aco VJ, Davidson T, Dolan DG, Millard SP, Murray-Smith R, Parke NJ, Ryan JJ, Straub JO, Wilson P. 2016. Use of acute and chronic ecotoxicity data in environmental risk assessment of pharmaceuticals. *Environ. Toxicol. Chem.* 35:1201–1212.

40. Chapman PM, Fairbrother A, Brown D. 1998. A critical evaluation of safety (uncertainty) factors for ecological risk assessment. *Environ. Toxicol. Chem.* 17:99–108.

41. European Chemicals Agency. 2008. *Guidance on information requiremens and chemical safety assessment*.

42. Huggett DB, Cook JC, Ericson JF, Williams RT. 2003. A Theoretical Model for Utilizing Mammalian Pharmacology and Safety Data to Prioritize Potential Impacts of Human Pharmaceuticals to Fish. *Hum. Ecol. Risk Assess. An Int. J.* 9:1789–1799.

43. Fu W, Franco A, Trapp S. 2009. Methods for estimating the bioconcentration factor of ionizable organic chemicals. *Env. Toxicol Chem*. 28:1372–1379.

44. Margiotta-Casaluci L, Owen SF, Cumming RI, de Polo A, Winter MJ, Panter GH, Rand-Weaver M, Sumpter JP. 2014. Quantitative Cross-Species Extrapolation between Humans and Fish: The Case of the Anti-Depressant Fluoxetine. In Pawluski, J, ed., *PLoS One*. 9:e110467.

45. Patel A, Panter GH, Trollope HT, Glennon YC, Owen SF, Sumpter JP, Rand-Weaver M. 2016. Testing the 'read-across hypothesis' by investigating the effects of ibuprofen on fish. *Chemosphere*. 163:592–600.

46. Schreiber R, Gündel U, Franz S, Küster A, Rechenberg B, Altenburger R. 2011. Using the fish plasma model for comparative hazard identification for pharmaceuticals in the environment by extrapolation from human therapeutic data. *Regul. Toxicol. Pharmacol.* 61:261–75.

47. Furuhagen S, Fuchs A, Lundström Belleza E, Breitholtz M, Gorokhova E. 2014. Are pharmaceuticals with evolutionary conserved molecular drug targets more potent to cause toxic effects in non-target organisms? *PLoS One*. 9:e105028.

48. Meylan W, Oward P, Oethling R. 1999. Improved Method for Estimating Water Solubility From Octanol / Water Partition Coefficient. *Environ. Toxicol. Chem.* 18:664–672.

49. European Centre for Ecotoxicology and Toxicology of Chemicals. 2013. *Environmental Exposure Assessment of Ionisable Organic Compounds: Technical Report No. 123*. Brussels.

50. Carter LJ, Ashauer R, Ryan JJ, Boxall ABA. 2014. Minimised Bioconcentration Tests: A Useful Tool for Assessing Chemical Uptake into Terrestrial and Aquatic Invertebrates? *Environ. Sci. Technol.* 48:13497–13503.

51. Miller TH, McEneff GL, Stott LC, Owen SF, Bury NR, Barron LP. 2016. Assessing the reliability of uptake and elimination kinetics modelling approaches for estimating bioconcentration factors in the freshwater invertebrate, Gammarus pulex. *Sci. Total Environ.* 547:396–404.

52. Meredith-Williams M, Carter LJ, Fussell R, Raffaelli D, Ashauer R, Boxall ABA. 2012. Uptake and depuration of pharmaceuticals in aquatic invertebrates. *Environ. Pollut.* 165:250–258.

53. Grabicova K, Grabic R, Blaha M, Kumar V, Cerveny D, Fedorova G, Randak T. 2015. Presence of pharmaceuticals in benthic fauna living in a small stream affected by effluent from a municipal sewage treatment plant. *Water Res.* 72:145–153.

54. Ruhí A, Acuña V, Barceló D, Huerta B, Mor J-R, Rodríguez-Mozaz S, Sabater S. 2016. Bioaccumulation and trophic magnification of pharmaceuticals and endocrine disruptors in a Mediterranean river food web. *Sci. Total Environ.* 540:250–259.

55. Jager T. 1998. Mechanistic approach for estimating bioconcentration of organic chemicals in earthworms (oligochaeta). *Environ. Toxicol. Chem.* 17:2080–2090.

56. EC. 2003. *Technical guidance document on risk assessment in support of Commission Directive 93/67/ EEC on risk assessment for new notified substances and Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances. Part II.* Luxembourg.

57. Fragoulis G, Merli A, Reeves G, Meregalli G, Stenberg K, Tanaka T, Capri E. 2011. A Bayesian approach to assessing the uncertainty in estimating bioconcentration factors in earthworms-the example of quinoxyfen. *Pest Manag. Sci.* 67:656–664.

58. Paz A, Tadmor G, Malchi T, Blotevogel J, Borch T, Polubesova T, Chefetz B. 2016. Fate of carbamazepine, its metabolites, and lamotrigine in soils irrigated with reclaimed wastewater: Sorption, leaching and plant uptake. *Chemosphere*. 160:22–29.

59. Carter LJ, Harris E, Williams M, Ryan JJ, Kookana RS, Boxall ABA. 2014. Fate and Uptake of Pharmaceuticals in Soil–Plant Systems. *J. Agric. Food Chem.* 62:816–825.

60. Paltiel O, Fedorova G, Tadmor G, Kleinstern G, Maor Y, Chefetz B. 2016. Human Exposure to Wastewater-Derived Pharmaceuticals in Fresh Produce: A Randomized Controlled Trial Focusing on Carbamazepine. *Environ. Sci. Technol.* 50:4476–4482.

61. Walker R. 1998. Toxicity testing and derivation of the ADI. *Food Addit. Contam.* 15:11–16.

62. Schwab BW, Hayes EP, Fiori JM, Mastrocco FJ, Roden NM, Cragin D, Meyerhoff RD, D'Aco VJ, Anderson PD. 2005. Human pharmaceuticals in US surface waters: A human health risk assessment. *Regul. Toxicol. Pharmacol.* 42:296–312.