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

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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 $\mu\text{g/L}$ 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 Xagorarakis 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.

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

Pharmaceutical consumption (Mass) per capita ($\mu\text{g}/\text{person}\cdot\text{day}$) is estimated based upon sales or prescription data. The F_{excreta} 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 Xagorarakis 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 *PhATE* (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), cardiovascular 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), highlighting 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. $\log K_{ow} > 4$), 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, aquaculture 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 $PEC_{\text{surfacewater}}$ 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, $PEC_{\text{surfacewater}}$ is employed in this assessment to reflect the worst case scenario or direct exposure such as wildlife swimming or drinking. In addition to $PEC_{\text{surfacewater}}$, 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 $PEC_{\text{surfacewater}}$ 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 comprehensive 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 it is 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.

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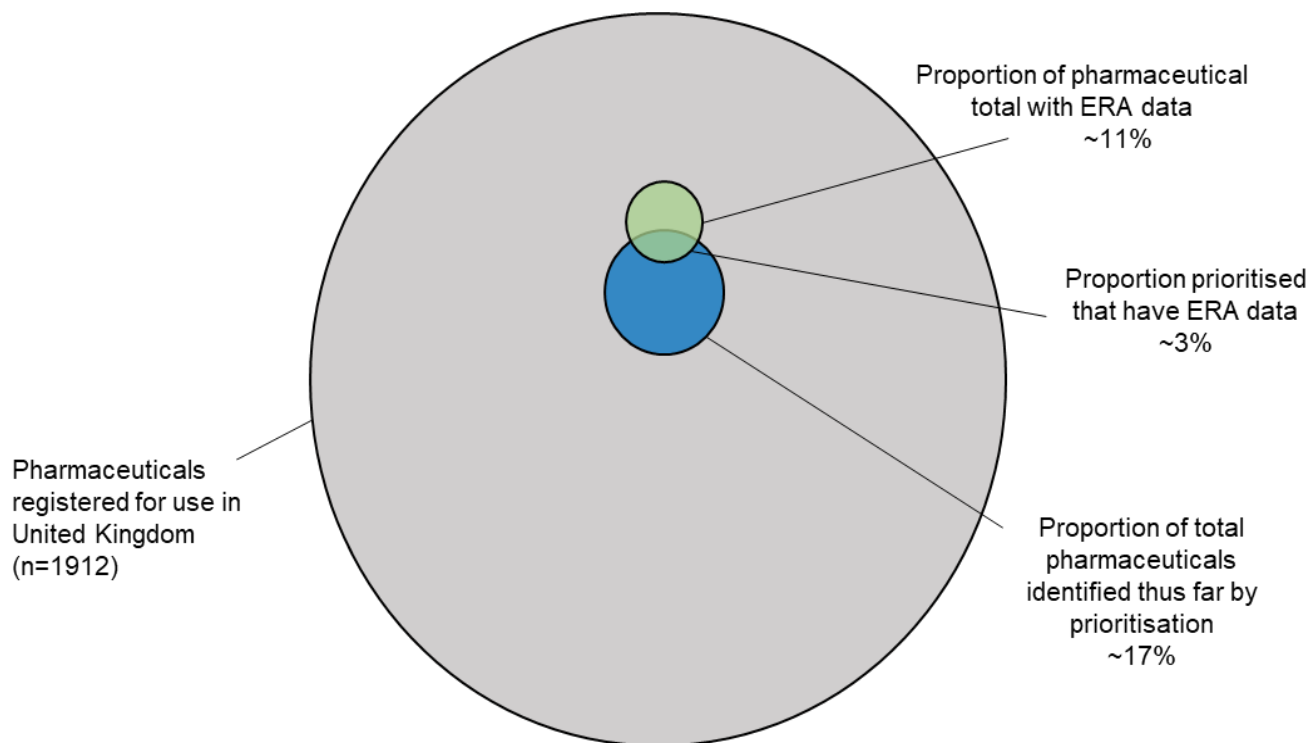


Figure 1. A qualitative representation of the estimated active pharmaceutical ingredients (APIs) registered for market use in the UK (eMC, 2017) (grey, n=1912), proportion of pharmaceuticals identified thus far by prioritisation exercises (blue, n=332), roughly the portion of total UK registered APIs 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).

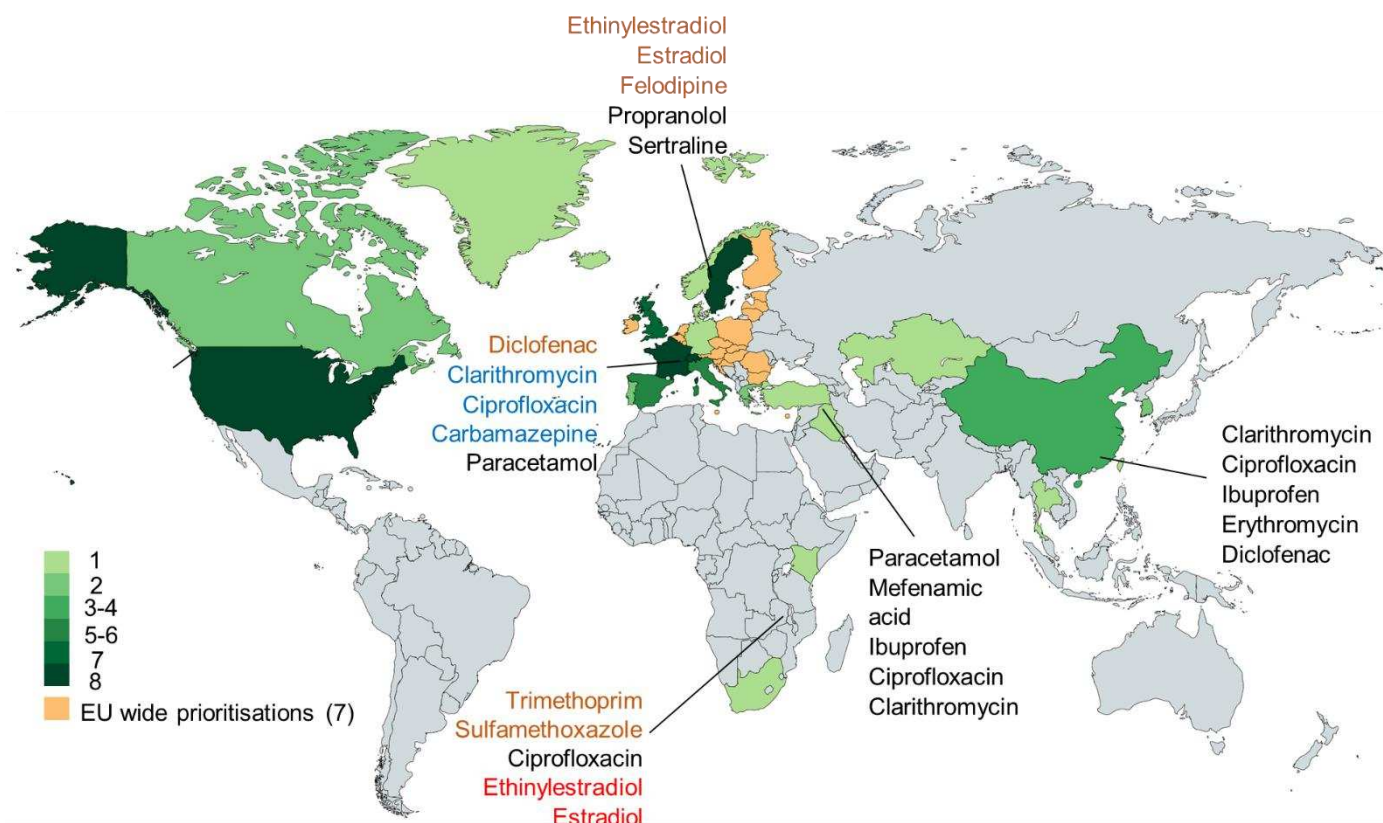


Figure 2. Areas of the world where priority pharmaceuticals have been identified by either risk-, hazard- or exposure-based approaches. Colouring corresponds to the number of prioritisations undertaken within that region (i.e. 1 to 8). The top 5 priorities selected for each region are based on the number 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, Oxytetracycline, Sulfamethoxazole, Trimethoprim
	Hormones (including synthetic) (10)	Equilenin, Estradiol, Estriol, Estrone, Ethinylestradiol, Levonorgestrel, Medoxyprogesterone, Mestranol, Noreisterone, 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)	Cyclophosphamide, 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)	Cyclophosphamide, 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

No. of times selected as priority pharmaceutical

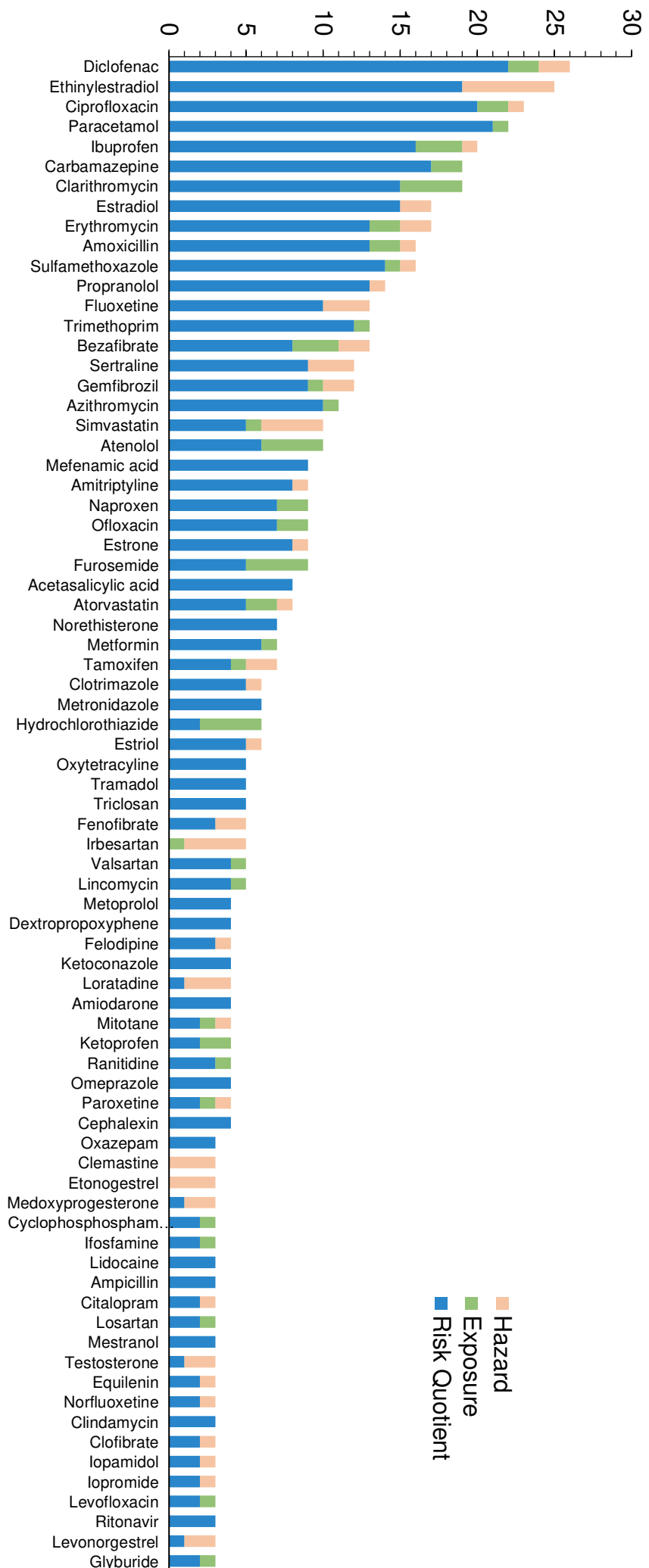


Figure 3. Pharmaceuticals identified as priorities three or more times (n=76) from on the 76 approaches reviewed in the literature.

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	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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. 	<ul style="list-style-type: none"> • First tier may unknowingly eliminate compounds (e.g. assessment trigger values) • Unsuitable exposure models (e.g. ionisable)
	Higher tier spatial PEC	<ul style="list-style-type: none"> • Multiple pharmaceutical sources • Incorporate mixing with pharmaceuticals transported from upstream • Identify local concentration hot spots • Incorporate hydrological characteristics/long term flow trends 	<ul style="list-style-type: none"> • Only developed for specific regions/watersheds • Access limited • Similar pharmaceutical consumption, WWTP removal and metabolisms issues to simple PEC 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Confidence in results • All environmental pathways considered (when representative sampling used) • Localised 	<ul style="list-style-type: none"> • Limited number of APIs/compounds • Costly • Maximal MECs • Limits of detection • Unrepresentative sampling • Limited to pharmaceuticals already detected/already of concern 	<ul style="list-style-type: none"> • Lower cost monitoring approaches • Improved limits of detection • Use to confirm risky predictions 	<ul style="list-style-type: none"> • 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.

Experimental	<ul style="list-style-type: none"> • Regulatory relevance 	<ul style="list-style-type: none"> • Limited availability 	<ul style="list-style-type: none"> • Create comprehensive database of industry held data to prevent 'Matthew 	<ul style="list-style-type: none"> • Missing specific MoA concerns
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(chronic/acute)	<ul style="list-style-type: none"> Confidence in results 	<ul style="list-style-type: none"> Limited relevance of acute data Chronic ECOSAR not yet validated for APIs and likely not robust Considers only apical endpoints (mortality, reproduction, growth) 	Effect'	<ul style="list-style-type: none"> Experimentally filling data gaps defeats purpose of desk-based prioritisation.
ECOSAR	<ul style="list-style-type: none"> Rapid, can be applied to all APIs. 	<ul style="list-style-type: none"> Heavy reliance on predicted data, 'Matthew Effect' Large arbitrary safety factors 	<ul style="list-style-type: none"> Improve chronic QSAR 	<ul style="list-style-type: none"> 'Matthew effect' Missing specific MoA concerns
FPM	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> BCFs not experimentally available for most APIs Applicability of BCF QSAR Only relevant for fish Experimental validation limited, but growing 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Unsuitable uptake models (e.g. ionisables) Miss specific MoA concerns pertaining to an API's side effect/off label use
ADI	<ul style="list-style-type: none"> Can calculate for all APIs which have mammalian toxicity studies 	<ul style="list-style-type: none"> Based on arbitrary uncertainty factors to ensure conservative risk assessment Focuses on water exposure (surface and drinking) 	<ul style="list-style-type: none"> Include a diet component (fish, meat, water, crops) 	<ul style="list-style-type: none"> Diet (fish, meat, water, crops)

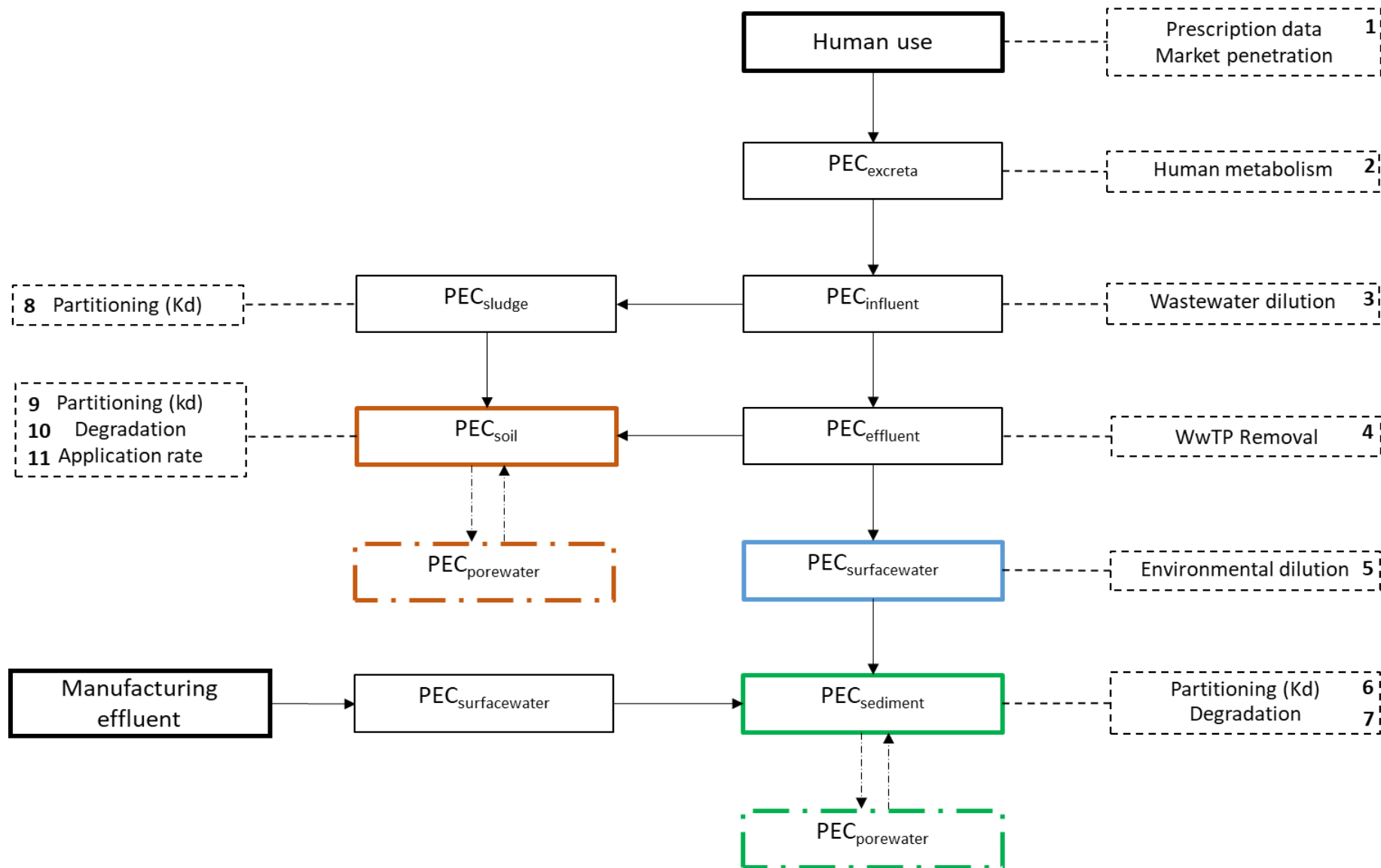


Figure 4. Breakdown of the relationship between exposure scenarios and the generalised parameters required to calculate the emissions. Numbers refer to Supplementary Tables S1 and S2 where greater of the derivation and limitations of each parameter is given.

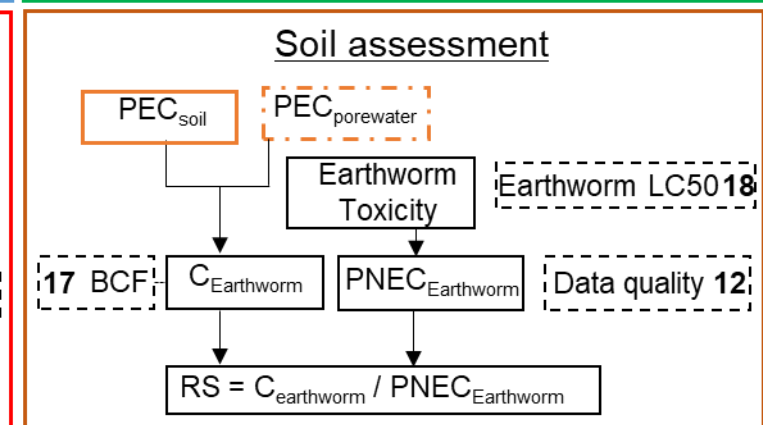
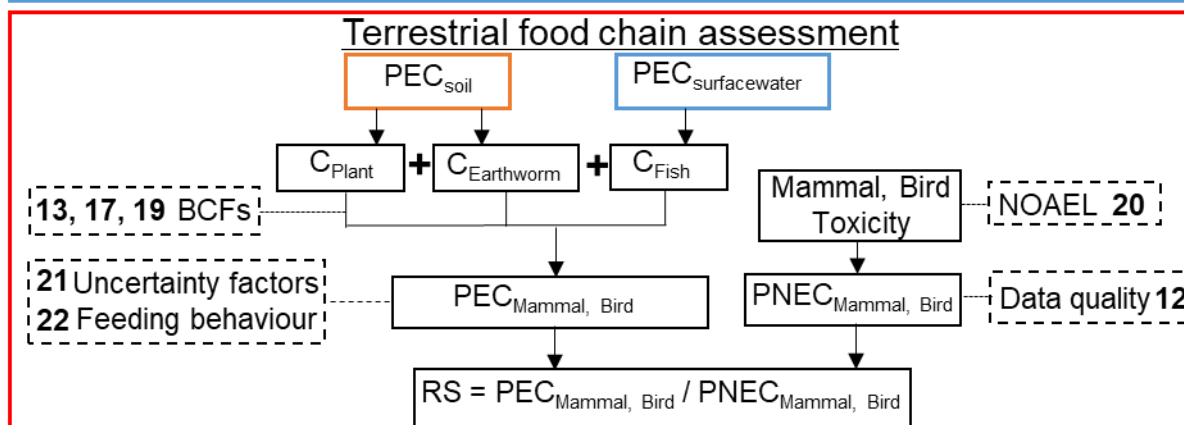
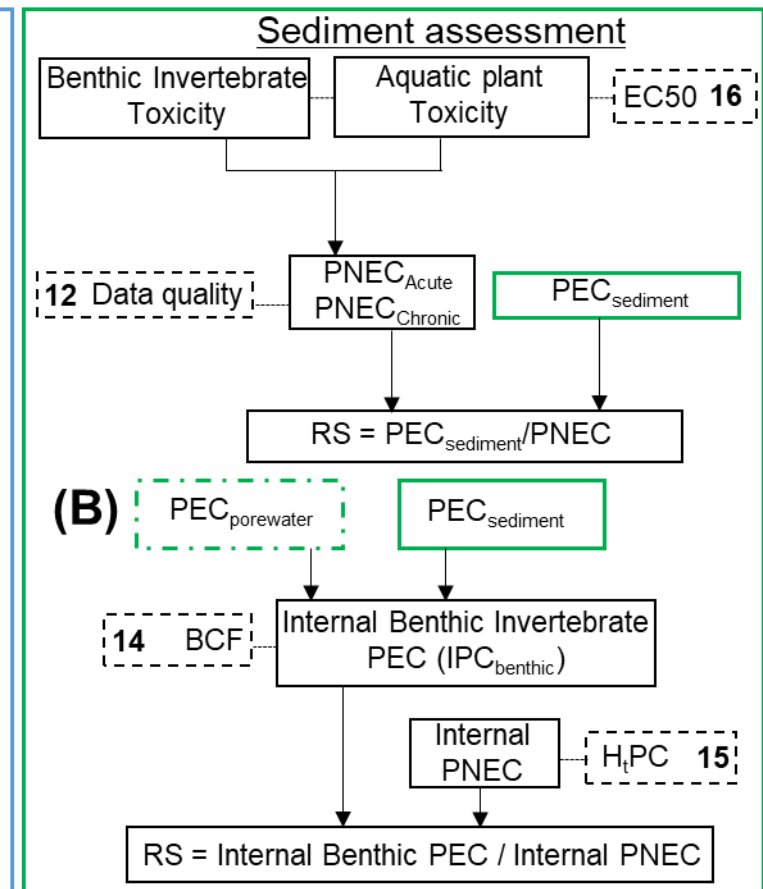
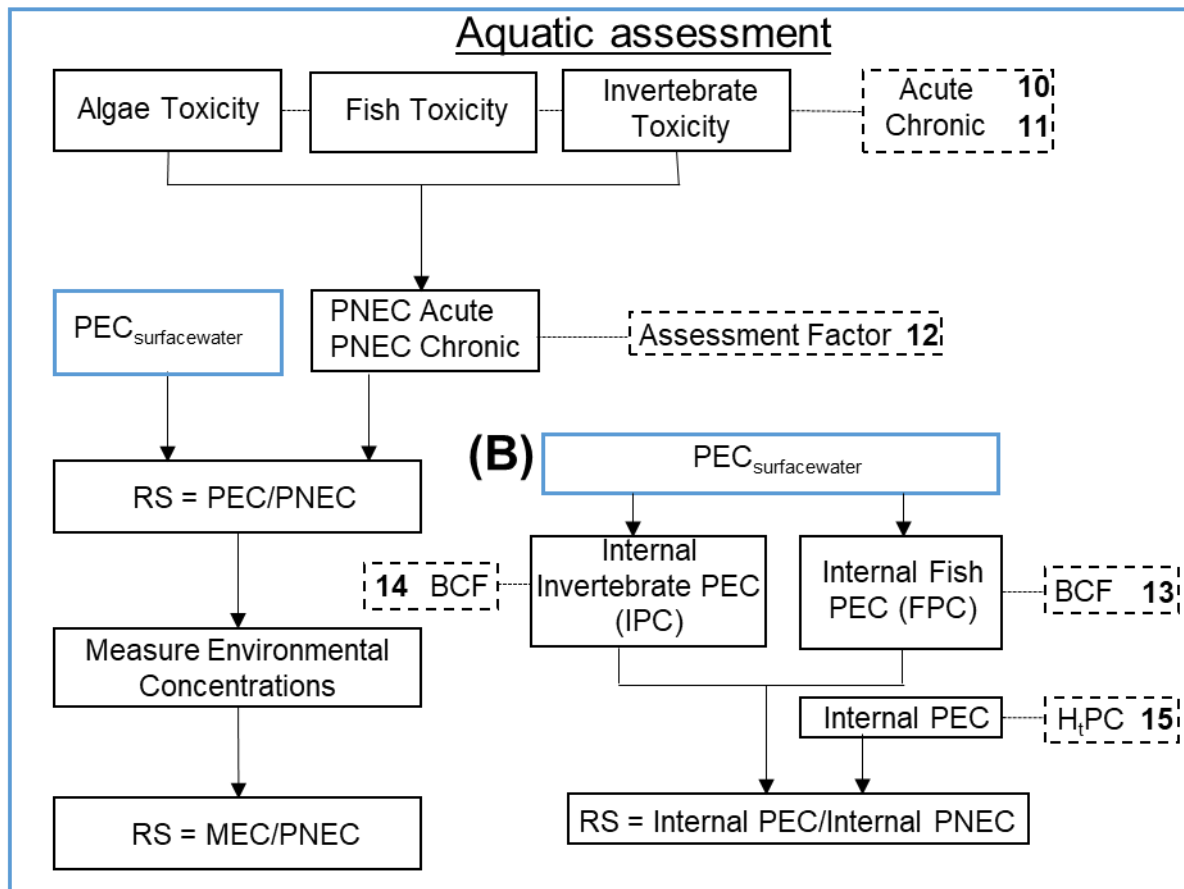


Figure 5. High level schematics demonstrating the prioritisation of risk posed to three trophic levels in aquatic, sediment and soil systems. Secondary approaches to prioritising risks to aquatic/sediment systems based on pharmaceutical uptake and internal concentrations compared to human therapeutic 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.

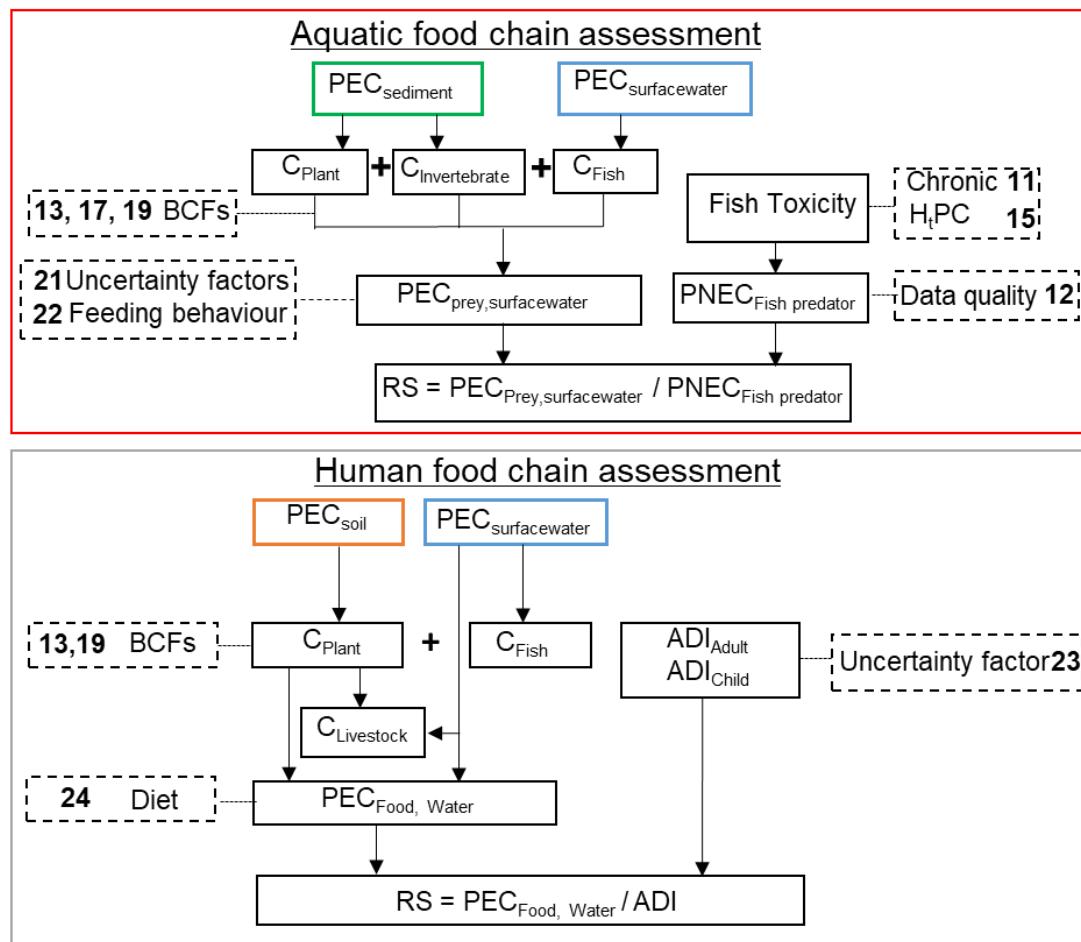


Figure 6. Prioritisation of pharmaceutical risks to humans considering both water intake or direct water exposure as well as other dietary sources such as plants and meat. Predatory wildlife food chain risk prioritisation which considers exposure to multiple prey/environmental sources (aquatic). Numbers 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 % Biodegradation % Sorption				
PEC _{surface water}	(5) Environmental dilution				
PEC _{sediment}	(6) Equilibrium partitioning Sediment (Kd)				
PEC _{soil}	(7) Degradation DT50 (sediment)				
	(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 _t PC				
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}	[Validated]	Acute	[Validated]
			Chronic	[Not designed]
Aquatic invertebrate	PEC _{surfacewater}	[Validated]	Acute	[Validated]
			Chronic	[Not designed]
Aquatic invertebrate	Invertebrate plasma concentration (IPC)	[None]	Read across	[None]
Aquatic wildlife (fish)	PEC _{sw}	[Validated]	Acute	[Validated]
			Chronic	[Not designed]
Aquatic wildlife (fish)	Fish plasma concentration (FPC)	[Lacks validation]	Read across	[Lacks validation]
Terrestrial plant	PEC _{soil}	[Lacks validation]	Acute	[None]
			Chronic	[None]
Terrestrial invertebrate	PEC _{soil}	[Not designed]	Acute	[Not designed]
			Chronic	[None]
Terrestrial invertebrate	PEC _{sediment}	[Not designed]	Acute	[Not designed]
			Chronic	[None]
Terrestrial invertebrate	Invertebrate plasma concentration (IPC)	[None]	Read across	[None]
Terrestrial wildlife (birds)	PEC _{diet}	[None]	Acute	[Not designed]
			Chronic	[None]
Terrestrial wildlife (birds)	PEC _{bird}	[Lacks validation]	Chronic	[None]
Human	PEC _{diet}	[None]	ADI	[Validated]
Human	PEC _{surfacewater}	[Validated]	ADI	[Validated]

[Validated]	Model exists and is validated for pharmaceuticals.
[Lacks validation]	Model exists and used for pharmaceuticals, but lacks validation.
[Not designed]	Model exists, but not designed for pharmaceuticals.
[None]	No model has been developed yet.

