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A RATIONAL APPROACH TO SELECTING AND RANKING SOME PHARMACEUTICALS OF CONCERN FOR THE AQUATIC ENVIRONMENT AND THEIR RELATIVE IMPORTANCE COMPARED WITH OTHER CHEMICALS

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Abstract: Aquatic organisms can be exposed to thousands of chemicals discharged by the human population. Many of these chemicals are considered disruptive to aquatic wildlife, and the literature on the impacts of these chemicals grows daily. However, because time and resources are not infinite, research must focus on the chemicals that represent the greatest threat. One group of chemicals of increasing concern is pharmaceuticals, for which the primary challenge is to identify which represent the greatest threat. In the present study, a list of 12 pharmaceuticals was compiled based on scoring the prevalence of different compounds from previous prioritization reviews. These included rankings based on prescription data, environmental concentrations, predicted environmental concentration/predicted no-effect concentration (PEC/PNEC) ratios, persistency/bioaccumulation/(eco)toxicity (PBT), and fish plasma model approaches. The most frequently cited were diclofenac, paracetamol, ibuprofen, carbamazepine, naproxen, atenolol, ethinyl estradiol, aspirin, fluoxetine, propranolol, metoprolol, and sulfamethoxazole. For each pharmaceutical, literature on effect concentrations was compiled and compared with river concentrations in the United Kingdom. The pharmaceuticals were ranked by degree of difference between the median effect and median river concentrations. Ethinyl estradiol was ranked as the highest concern, followed by fluoxetine, propranolol, and paracetamol. The relative risk of these pharmaceuticals was compared with those of metals and some persistent organic pollutants. Pharmaceuticals appear to be less of a threat to aquatic organisms than some metals (Cu, Al, Zn) and triclosan, using this ranking approach. *Environ Toxicol Chem* 2016;35:1021–1027.

Keywords: Pharmaceuticals Risk Environment Chemicals Identification

INTRODUCTION

Approximately 3000 pharmaceuticals are in general use today in the European Union. Many of these pharmaceuticals and/or their transformation products are found ubiquitously in rivers in the developed world, at concentrations from sub-ng/L to low μg/L [1]. Our scientific interest in pharmaceuticals and the effect they have on the aquatic environment has increased over the last 2 decades as our ability to detect them has increased [2]. The scale of the threat that aquatic organisms face with regard to the potential disruptive effect of these biologically active chemicals is unknown. Pharmaceuticals can enter surface waters via sewage effluent after use by humans, via runoff from farmland after the application of sewage sludge, directly from animals after veterinary pharmaceutical use, or directly following use in aquaculture. A possibly underestimated source could be pharmaceutical manufacturing sites, where concentrations in the local aquatic environment have been found in the mg/L range [3]. Pharmaceuticals as a class of chemicals have been designed to have biological activity and resist inactivation sufficiently before delivering the intended therapeutic effect. Therefore, we might expect their discharge to the environment to have some inadvertent effects on wildlife, particularly on vertebrates. The most notable problems reported have been the severe effect of diclofenac on vulture populations [4] and the disruptive effects of 17α-ethinyl estradiol (EE2) on fish at very low concentrations [5,6]. Various effects on fish, invertebrates, algae, and bacteria at varying concentrations have also been reported for other pharmaceuticals [7,8]. But where does this risk sit in relation to the threat posed by the other approximately 100 000 chemicals to which aquatic organisms are potentially exposed in rivers?

The awareness of the potential harmful effects of pharmaceuticals is starting to be reflected in policy; 3 pharmaceuticals are now on the European Union watch list—EE2, 17β-estradiol (E2), and diclofenac—and are candidates for future control under the Water Framework Directive of the European Community [9]. Nevertheless, our knowledge on their effects is still weak, especially with regard to chronic effect data. Pharmaceuticals have been measured in the aquatic environment [1,10]; but even with the improvement in analytical techniques to measure pharmaceuticals [3], very few measured environmental data are available. There is still no routine monitoring of pharmaceuticals to ascertain environmental concentrations [1], and there is concern about using predicted environmental data as an alternative [11]. It took more than 40 yr of research to gain a good knowledge of the discharges, fate, and effects of 24 heavy metals. How will we cope with doing the same job for 3000-plus pharmaceuticals? Where do pharmaceuticals sit as chemicals of concern compared with others, such as metals?

The present study describes an unbiased approach to selecting 12 pharmaceuticals from the current literature to be included in a wider study comparing the threat posed by different classes of chemicals to aquatic organisms in the United

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Kingdom [12]. Environmental and ecotoxicological data available in the literature for these 12 pharmaceuticals were used to conduct a preliminary risk ranking. Fitting with the wider study, the risks from these 12 pharmaceuticals were compared with 2 other organics (triclosan and lindane) and 12 metals (Ag, Al, As, Cd, Cr, Cu, Fe, Hg, Mn, Ni, Pb, and Zn). In terms of exposure of aquatic organisms to sewage effluent, the United Kingdom could be considered to be among the most exposed in Europe [13]; hence, if any chemical is harming aquatic wildlife, then it is very likely that harm will be occurring in the United Kingdom.

METHODOLOGY

Pharmaceutical selection

For the present study, 12 pharmaceuticals were selected as representatives of the class. Clearly, this is difficult, as many different pharmaceuticals prioritization methods have been suggested [14]. Each approach has its merits and weaknesses. The aim was to identify the pharmaceuticals considered by the scientific community as being of the greatest concern using a simple metric approach. Thus, the top 12 ranked pharmaceuticals only reflect our current thinking. Scientists working in the field have still examined only perhaps 100 out of 3000 different pharmaceuticals. A concern highlighted in 2014 by Daughton et al. [15] is the perception that perceived risk may be magnified because of the popularity of a chemical to researchers. This is represented by the number of papers and the data available per pharmaceutical and can often be driven by external factors such as fashion, media interest, and politics [15], something termed the *Matthew Effect*. Using the Web of Knowledge, keywords such as *pharmaceuticals*, *ranking*, *prioritization*, and reviews were used to locate papers from the literature.

Different pharmaceutical prioritization approaches used by environmental scientists

Sales and usage. The usage and sales data of pharmaceuticals can be obtained from annual prescriptions data, annual sales, and annual usage data. This approach does not take into account any ecological or toxicological data; it is based solely on the amount of pharmaceutical used [14,16–19].

Occurrence in the environment. This approach is based on the concentrations, either measured or predicted, of pharmaceuticals in the environment. It takes into account only environmental concentrations, not any ecotoxicology data [1,16,17,19].

Risk ratio. Typically, the risk ratio or quotient is calculated from either predicted or measured water concentrations and effect concentrations; the most common approach is to determine the risk ratio using the predicted environmental concentration/predicted no-effect concentration ratio (PEC/PNEC). Other risk ratio variations exist, such as the use of measured environmental concentrations [20] when these are available. This approach does take into consideration the toxicity of the chemical [14,17,21–23].

Multiple variables schemes. These approaches use multiple variables to derive a risk assessment. These schemes include persistency/bioaccumulation/(eco)toxicity (PBT), as well as other methods that incorporate toxicity data, water concentrations, annual prescription data, solubility, and case-by-case expert views [14,24–27].

Read-across theory

Fish plasma model. The fish plasma model calculates fish plasma steady-state concentrations and compares these with human therapeutic plasma concentrations for active pharmaceutical ingredients [28]. Where an environmentally plausible water concentration of a pharmaceutical is predicted to lead to a plasma concentration in a fish close to the human therapeutic concentration, that pharmaceutical is considered to be a high-risk chemical [14,29,30].

Critical environment concentration. The critical environmental concentration is the water concentration anticipated to produce in fish a plasma concentration similar to the human therapeutic concentration. Thus, the critical environmental concentration is expected to cause physiological effects and is obtained using literature data on human potencies together with a predicted bioconcentration factor for fish based on lipophilicity. It differs from the fish plasma model in that it is independent of the exposure/PEC [14,31].

From the 22 pharmaceutical prioritization papers identified, the lists of pharmaceuticals of potential concern were collated into a database (see Table 1 for references used and Supplemental Data, Table S1 for the complete database). The frequency of pharmaceuticals appearing on these lists was used to select the top 12. Thus, diclofenac, for example, ranked 1st, with 18 citations from the 22 papers (Table 2). This approach was chosen with the aim of providing as unbiased a selection of 12 pharmaceuticals as is currently possible. To state it another way, if pharmaceuticals are causing a problem in the aquatic environment, these are the pharmaceuticals that the scientific community considers mostly likely to be involved.

Risk ranking

The first-tier ranking methodology used in the present study has been described previously by Donnachie et al. [12]; a brief summary of the method is described in the following sections.

Gathering environmental toxicity information: An uncritical data collection process. A range of endpoints and effect concentrations for each of the selected pharmaceuticals is found in the literature, including lowest-observed-effect concentration, median effect concentration, and median lethal concentration, as well as acute toxicity and chronic toxicity concentrations. A wide range of species and endpoints was considered to ensure a representative spread of species and possible effects. The endpoints included mortality, growth inhibition, and changes in gene expression. In aquatic toxicological studies, bacteria, daphnids, and fish were the most commonly used test species. The data were collected from the literature during the summer of 2014 and may be seen as being representative of the research available up to that time.

Measured water concentrations. If possible, measured concentrations of pharmaceuticals in the United Kingdom were used. These were obtained from the literature; because few were found, however, the inclusion of predicted river values helps to give a representative range of concentrations likely to be encountered in UK rivers.

Predicted water concentrations. Predicted river concentrations start by using either reported UK effluent concentrations or consumption (UK)/excretion/sewage removal values before considering river dilutions. Based on the work done by the Centre for Ecology and Hydrology, the amount of dilution available in the different regions of England and Wales is known [32]. Also available was a range of dilution values for the River Thames at Reading and the River Soar at Leicester [33], which could be viewed as examples of likely river hot spots (urbanized, with a high proportion of sewage effluent). By using the dilution available from 90th percentile low-flow data for the

Table 1. Prioritization schemes used to generate the initial pharmaceuticals database

Scheme	Summary	Reference	Total references in each group
Sales and usage			
	Amount used in the United Kingdom (kg/yr)	[19]	5
	Top 25 pharmaceuticals used in Denmark in 1997 (Drug Distribution Data [DDD])	[16]	
	Swedish sales statistics (kg/yr)	[14,17]	
	Total amount consumed in Spain in 2003 (tonne/yr)	[18]	
Occurrence in the environment			
	Occurrence in the environment globally (Europe, North America, Asia)	[1]	4
	European Union PECs	[16]	
	PEC	[17,19]	
Risk ratio			
	Acute and chronic risk ratios	[21]	5
	PEC/PNEC	[14]	
	MEC/PNEC	[14]	
	Risk quotient	[17]	
	EC5/MC95	[22]	
	Risk ratio	[23]	
Multiple variable schemes			
	PBT	[14]	5
	Pharmaceuticals in the Environment, Information for Assessing Risk (PEIAR) database	[14,24]	
	QSAR model	[14]	
	Fish acute to chronic ratio	[25]	
	Three-tiered scheme	[26]	
	All species acute to chronic ratio	[27]	
Read-across theory			
	Fish plasma model	[14,30]	3
	Critical environment concentration	[14,31]	
Total			22

PEC = predicted environmental concentration; PNEC = predicted no-effect concentration; MEC = measured environmental concentration; EC5 = 5th percentile effect concentration; MC95 = 95th percentile measured concentration; PBT = persistency/bioaccumulation/(eco)toxicity; QSAR = quantitative structure–activity relationship.

Thames and Soar, this provides among the highest concentrations that fish might be exposed to in UK rivers. Reasonable agreement between predictions and river measurements of pharmaceutical concentrations has been demonstrated previously in the United Kingdom [32] and for Europe [34]. A benefit of using predicted data if river water concentrations are not available is that they can provide a wide range of concentrations that reflect different geographies and flow conditions. This provides a range of possible UK concentrations. At this stage, river attenuation was not included; therefore, it could be said that the predicted values are likely to represent a degree of overestimation and so represent a precautionary approach. The measured and predicted water concentrations have been combined and are referred to as water/environmental concentrations.

Risk analysis

In the present study, each chemical was considered based on water exposure, and hence the risk refers to that posed to aquatic species through the water (not food). All endpoints and species

Table 2. Frequency of pharmaceuticals of concern cited in the 22 risk-prioritizing papers in the literature

Frequency cited[a]	Pharmaceutical	Type	Use
18	Diclofenac (DCF)	Nonsteroidal anti-inflammatory	Relieving pain and reducing inflammation
17	Paracetamol (PAR)	Analgesic (pain reliever) and antipyretic (fever reducer)	Relieving headaches and other minor aches and pains
15	Ibuprofen (IBF)	Nonsteroidal anti-inflammatory	Relieving pain, alleviating fever, reducing inflammation
15	Carbamazepine (CBZ)	Anticonvulsant and mood-stabilizing	Treatment of seizure disorders and neuropathic pain (i.e., epilepsy)
15	Naproxen (NPX)	Nonsteroidal anti-inflammatory	Relieving pain, alleviating fever, reducing inflammation
11	Atenolol (ATN)	Beta-blocker	Cardiovascular diseases
11	Ethinyl estradiol (EE2)	Estrogen	Oral contraceptive pills
11	Aspirin (ASP)	Analgesic (pain reliever) and antipyretic (fever reducer)	Relief of headaches and other minor aches and pains
10	Fluoxetine (FLX)	Antidepressant	Depression
9	Propranolol (PRO)	Beta-blocker	Cardiovascular diseases
9	Metoprolol (MET)	Beta-blocker	Cardiovascular diseases
8	Sulfamethoxazole (SMX)	Antibiotic	Bacterial infections

[a]Out of the 22 prioritization articles examined in the literature.

were included, with no other moderating factors considered at this stage.

Ranking of chemicals based on exposure via the water. The approach gathers 2 subsets of data, the effects data and the environmental concentration data, with the proximity of these 2 datasets indicating the degree of concern posed by a chemical. For the risk ranking, it was necessary to select a single comparator to rank all of the chemicals. One possibility might have been to compare the proximity of the lowest effect concentration with the highest environmental concentration (similar to PEC/PNEC). However, there is the possibility that within both the effect and the environmental datasets there are outliers that may be misrepresentative for a number of reasons. These might include unrepeatable ecotoxicity results perhaps with ambiguous endpoints or high environmental concentrations from one-off localized polluted sites. Therefore, the median value was considered the most robust comparator between chemicals to indicate risk, as it is constructed from the whole body of the 2 data sets (Equation 1) [12]. The method is in effect trying to identify the chemical of greatest risk to the widest group of water bodies in the United Kingdom.

$$\text{Risk} = \frac{mW}{mT} \quad (1)$$

In Equation 1, mW is the median river water concentration (μg/L) and mT is the median effect concentration (μg/L). This value can be described as a risk ratio, which can be used to rank concern; the larger the value, the greater the concern.

Ranking of chemicals based on exposure via the water: A precautionary approach. The precautionary approach uses the 5th percentile ecotoxicity concentration (*5%ileT*; μg/L) and compares it with the median river water concentration (Equation 2). The 5th percentile ecotoxicity concentration was calculated (using Excel) directly from the effect data collected per chemical. Thus, this comparator gives greater weight to the most sensitive endpoints such as might arise from chronic ecotoxicity studies.

$$\text{Risk} = \frac{mW}{5\%ileT} \quad (2)$$

Summary

The approach was devised to rank all chemicals discharged by humans into the aquatic environment on the basis of environmental risk. Although related to harm, it was not designed to establish whether harm is in fact occurring. It was considered essential to maintain consistency by using the same method for data collection and analysis regardless of chemical. There is an argument that this approach is not fit for pharmaceuticals because chronic exposures causing nontoxic endpoints are arguably more relevant than acute toxic effects. Inclusion of acute effect data is likely to increase the median values, thereby decreasing the apparent degree of risk. To give greater weight to the chronic effects and sensitive endpoints, therefore, all chemicals were also ranked by taking the lowest 5th percentile effects concentration to compare with the median water concentration.

The method is limited by the quantity and quality of current data in the literature on these pharmaceuticals. It should be considered as an approach to reveal what we know now, and it is accepted that this knowledge will grow with time and that the rankings may alter in due course. It is intended that the influence that moderating factors might have on the ranking will be examined at a later stage. This might include a ranking whereby the severity of the effect is given precedence; for example, reproductive impacts might be ranked higher than some other physiological effects.

Ranking of chemicals based on species group. Although the overall objective of the present study was to compare chemicals on the basis of risk to wildlife as a whole, it is instructive to tease apart the wildlife data to review which species groups are more vulnerable: fish, invertebrates, or algae. Comparison of different groups of organisms can be based on the median effect concentration and median water concentration as well as on the 5th percentile effect concentration and median water concentration.

RESULTS AND DISCUSSION

Selection of pharmaceuticals

This subgroup of pharmaceuticals was selected and ranked based on different prioritization approaches found in the literature (Table 1). Although this may not be an exhaustive review, our objective was to provide a representative picture of some of the pharmaceuticals of current concern with respect to the environment. We are also aware that these are not the only pharmaceuticals of potential concern and that our selection may owe something to fashion and politics, rather than actual risk [15].

In the review of the pharmaceuticals prioritization literature, it was found that diclofenac and paracetamol received the highest citations. However, it was found that no 2 approaches gave the same top 5 pharmaceuticals of concern when comparing either different or similar approaches. It was for this reason that the frequency of occurrence was used to make the selection of the pharmaceuticals to investigate.

Risk ranking results

Ethinyl estradiol, fluoxetine, and propranolol were ranked of highest concern when the medians were compared (Figure 1). The pharmaceuticals for which the measured or predicted concentrations actually overlapped with some reported effect concentrations were EE2, fluoxetine, ibuprofen, carbamazepine, and diclofenac (Figure 1). For all pharmaceuticals studied, apart from EE2, the difference between the 2 median values

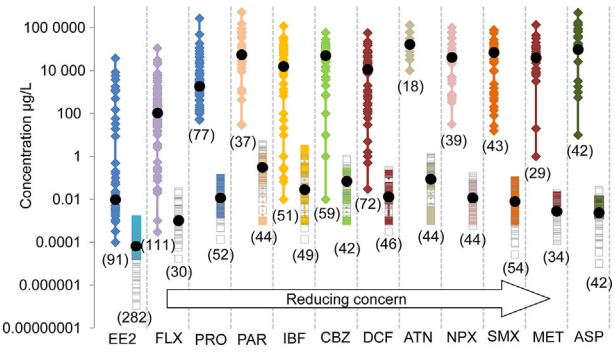

Figure 1. Comparison of literature effect concentrations (diamonds; left-hand column of each pair) with measured (closed squares) and predicted (open squares) UK river water concentrations (right-hand column of each pair) for aspirin (ASP), atenolol (ATN), carbamazepine (CBZ), diclofenac (DCF), ethinyl estradiol (EE2), fluoxetine (FLX), ibuprofen (IBF), metoprolol (MET), naproxen (NPX), paracetamol (PAR), propranolol (PRO), and sulfamethoxazole (SMX). The median values are plotted as black circles, and the arrow depicts the reduction in risk ratio. The numbers in parentheses represent the number of data points per data set.

was greater than 100 000-fold, giving a risk ratio of 0.00001 or less (Supplemental Data, Table S2). For EE2, the risk ratio was 0.0065, which was significantly higher than for the other pharmaceuticals reported in the present study. When the ranking was based on the difference between the 5th percentile effect concentration and the median river water concentrations, ibuprofen came 1st, with a risk ratio of 0.15, followed by EE2 (0.07), diclofenac (0.01), fluoxetine (0.01), and paracetamol (0.01) (Supplemental Data, Figure S1). The ranking of pharmaceuticals based on the 5th percentile effect data is a more precautionary approach to ranking, as the focus is on the most vulnerable species and the most sensitive endpoints. Even when using the precautionary approach, the risk ratio of all the pharmaceuticals was less than 1 (Supplemental Data, Table S2).

The reported effect concentration for EE2 ranged from 0.1 ng/L to 37.8×10^6 ng/L, with a median of 10 ng/L, whereas the environmental concentrations ranged between 1.13×10^{-4} and 1.07 ng/L, with a median value of 0.065 ng/L. The lowest reported effect concentration was 0.1 ng/L: a stimulatory effect was seen with an increase in the mean number of eggs spawned per pair in *Pimephales promelas* up to 1 ng/ L, but a decrease in egg production was observed at 3 ng/L [35]. Fluoxetine was ranked 2nd based on the comparison of median effect and river concentrations. The range of effect concentrations for fluoxetine was 0.0003 μg/L to 111 357 μg/L, with a median effect concentration of 106 μg/L. Antimicrobials may not have ranked very high in this group of pharmaceuticals, but we should be aware that there are other concerns with their use associated with the possible development of antimicrobial resistance [36].

Sensitivity of different species to pharmaceuticals

Pharmaceuticals have often been designed to target specific metabolic and molecular pathways common to vertebrates. Species with similar targets may be more likely to experience an effect as a result of the presence of pharmaceuticals in the environment, because they have a comparable pathway [37].

The risk to each category of species was assessed based on the risk ratio using the median effect value and the median river water concentration (Figure 2). It would appear from the selection of 12 that fish are the most sensitive species to pharmaceuticals. Given that fish appear to contain many of the same drug targets as humans, this is not surprising [29]. Considering the median data (Figure 2), EE2 is the pharmaceutical of most concern to fish, with a risk ratio of 0.013. It is a synthetic hormone that regulates reproductive functions in vertebrates. In contrast to fish, EE2 is ranked 11th and 12th for risk for algae and invertebrates, respectively, based on the median data. Within each species group, it is likely that there will be intraspecies sensitivity variation as well [7]. Paracetamol was ranked as the highest risk for invertebrates and fluoxetine the highest risk for algae, based on the median comparison. However, these species are 100 times less sensitive to these pharmaceuticals than fish are to EE2 (Figure 2).

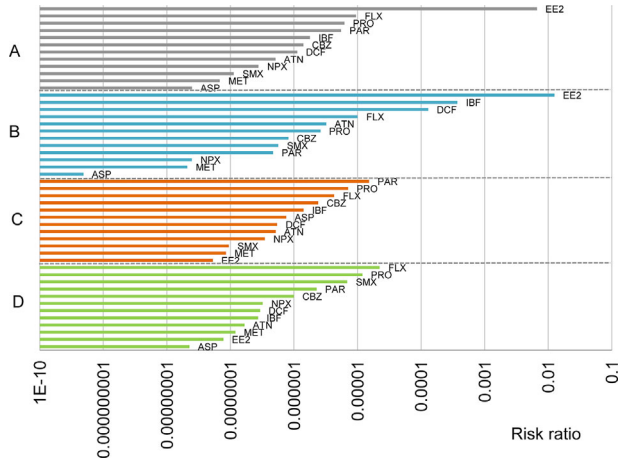

Figure 2. Ranking of pharmaceuticals—aspirin (ASP), atenolol (ATN), carbamazepine (CBZ), diclofenac (DCF), ethinyl estradiol (EE2), fluoxetine (FLX), ibuprofen (IBF), metoprolol (MET), naproxen (NPX), paracetamol (PAR), propranolol (PRO), and sulfamethoxazole (SMX)—by all species (**A**), fish (**B**), invertebrates (**C**), and algae (**D**). Rankings are based on a risk ratio comparing the median effect concentration and median river water concentration.

Fluoxetine is one of the more studied pharmaceuticals. It has been reported to be one of the most potentially disruptive human drugs to aquatic species [38], and in the present study was ranked 1st, 3rd, and 4th for its risk to algae, invertebrates, and fish, respectively. This suggested that fluoxetine is of concern to all species groups, with algae being the more sensitive species group. The median fluoxetine effect concentration for algae reported in the present study was 45 μg/L, with effects reported on the most sensitive algae at 24 μg/L, at which point fluoxetine effected the growth of *Pseudokirchneriella subcapitata* [39]. The median fluoxetine effect concentration for invertebrates identified in the present study was 174 μg/L, and the most sensitive species appeared to be mussels, for which biochemical effects have been reported at 0.0003 μg/L [40]. Sumpter and Margiotta-Casaluci 2014 have openly questioned some of the reports claiming that invertebrates are exquisitely sensitive to fluoxetine [41]. When the precautionary approach was taken (5th percentile effect concentration vs median river concentration), ibuprofen was ranked highest for both invertebrates and fish, and propranolol was ranked highest for algae (Supplemental Data, Figure S2).

Where do pharmaceuticals rank compared with other chemicals in water risk?

To put the potential risk of pharmaceuticals into perspective with other chemicals to which freshwater organisms are exposed via the water, the calculated risk of pharmaceuticals was compared with that of some other chemicals, using the same approach. The first-tier risk ranking of metals and the organics triclosan and lindane was reported in in 2014 in Donnachie et al. [12]; this is an extension of that comparison. Triclosan is an antimicrobial agent found in soaps, deodorants, skin creams, and plastics and has been used in homes since the 1960s. Lindane (γ- hexachlorocyclohexane) is a pesticide designed to act as a neurotoxin and has been banned from agricultural use around the world since 2009. From this comparison, several metals (Cu, Al, and Zn) are indicated as being of greater concern than the highest ranked pharmaceutical (EE2); triclosan and lindane are ranked 5th and 12th, respectively (Figure 3). This ranking is based on exposure via the water; accumulation of chemicals by the biota was not considered (whereby mercury would assume much higher importance).

CONCLUSIONS

We have limited resources to protect the aquatic environment. We should therefore focus these resources on the greatest threats, which may not even be chemicals [42]. Nevertheless, chemicals discharged from human activities are a threat that we are struggling to assess. From this preliminary assessment, pharmaceuticals do not appear to pose as great a risk to aquatic wildlife as do many metals and triclosan. With this approach,

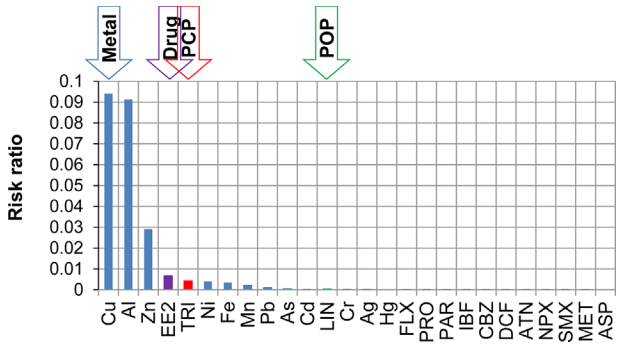

Figure 3. Risk ranking of 12 pharmaceuticals, 12 metals, lindane (LIN; a persistent organic pollutant [POP]) and triclosan (TRI; a personal care product [PCP]), based on the difference between the median effect concentration and the median river water concentration. The arrows highlight the highest-ranking chemical in each class.

there may be concerns about the nature and relevance of ecotoxicity effects unduly influencing the ranking one way or another, but there could also be potential issues with measurements that may be unduly dominated by high exposure/spill sites. No ranking system will ever be perfect. This review has considered only 12 out of a possible 3000-plus pharmaceuticals and hence represents an initial look at the impacts of an expanding class of chemical contaminants. What has been highlighted is that only a very small proportion of pharmaceuticals has been studied sufficiently (and to a reliable standard) to make even preliminary judgments on whether they pose a risk. The limitations of time and funding reinforce the need for intelligent approaches and predictive tools to gauge the environmental concentrations and the effects of pharmaceuticals on aquatic organisms. It is not going to be possible to measure, monitor, or conduct robust long-term studies of the effects of all pharmaceuticals, or probably even 10% of them, on aquatic organisms [43]. The prominence of EE2 in any risk ranking may be an indication that we should focus our efforts on hormonally acting pharmaceuticals [44].

Importantly, the occurrence of high concentrations of pharmaceuticals at specific sites [3] and the reports of effects occurring in the low ng/L range of some pharmaceuticals [45] suggest that possible effects as a result of the presence of pharmaceuticals in the environment do occur, notwithstanding their low ranking here. Classing pharmaceuticals as "not a problem" would be premature; but in comparison with other chemicals and based on the current state of the science, this preliminary risk assessment ranks them as less of a threat.

Supplemental Data—The Supplemental Data are available on the Wiley Online Library at DOI: 10.1002/etc.3165.

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Data availability—For data requests, please contact R. Donnachie (racdon@ceh.ac.uk).

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