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Ranking prescribed pharmaceuticals in terms of environmental risk: inclusion of hospital data and the importance of regular review

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Abstract:

A newly available dataset on pharmaceuticals used in Scottish hospitals enabled an Environmental Risk Assessment that includes hospital consumption of pharmaceuticals, as previous UK rankings have been based on community prescription only. As health and the environment are devolved issues for the Scottish government, it is in any case merited to consider a Scottish ranking separately; regional differentiation is particularly relevant in the spatial context of the Water Framework Directive.

Nine pharmaceuticals are identified as having a risk quotient (RQ) greater than 1. Four of these, the antibacterials piperacillin , tazobactam, flucloxacillin and ciprofloxacin, had high hospital contributions and had not been highlighted before in rankings based on community prescriptions. Some drugs with RQ < 0.1 are almost exclusively used in hospitals and could be more concentrated near effluents carrying hospital wastewater, where they may be of local concern. As separate treatment of hospital effluents is a policy option, specific inclusion of hospital consumption is important. Continually increasing availability of ecotoxicological data and trends in consumption further contribute to a substantially different prioritisation than in previous rankings. This leads us to conclude that regular review of risk is necessary.

Keywords: Pharmaceuticals, Prioritisation, Environment, Risk assessment, Hospital

BACKGROUND

Pharmaceutical micro-pollutants in aquatic environments and their environmental effects are receiving increasing attention from government institutions [1], academic researchers [e.g. 2, 3] and the popular press [4]. Recently, the European Commission placed 3 pharmaceuticals – the analgesic diclofenac and the hormones estrone (E1) and 17ß ethinyl estradiol (EE2) – on a "watch list" to gather monitoring data for the purpose of supporting the determination of appropriate measures to address the risk posed by those substances [1]. Pharmaceutical products are used ubiquitously in hospitals and in the community. Following human consumption, excreted residue enters the sewer either as the original parent compound or metabolite and is only partially removed in wastewater treatment works [5]. The continuous input of sewage effluent into surface waters leads to chronic exposure of aquatic organisms and toxic effects can occur at environmentally relevant concentrations [3, 6].

As thousands of different pharmaceutically active compounds are on the market - approximately 3000 are licensed in the UK [7] - screening is useful to gauge which pose the greatest environmental risk and might therefore warrant a more detailed risk assessment or environmental sampling and monitoring. In order to decide on approaches and strategies for the reduction of pharmaceuticals in the environment, an understanding of sources is vital. Advanced wastewater treatment technologies are available to remove some pharmaceutical residue [8], but can be expensive and energy intensive [9]. In some situations, point source treatment at hospitals could be merited [10]. Data on the range, relative amounts and toxicities of medicines used in hospitals and the community can inform decisions on whether and where advanced treatment is appropriate; these decisions will almost certainly need to be country- or region specific.

Prescription data can be used as a starting point for the identification of nationally relevant drugs, such as in Ayscough's screening exercise for the UK Environment Agency [7], but many

previous studies are limited by their adopted method or available datasets for ranking. The UK National Health Service (NHS) stores data on drugs dispensed in the community separately from data on drugs dispensed in hospitals. Previous studies on environmental risk from pharmaceuticals in the UK [11, 12, 13] were based on community prescription data only, excluding hospital consumption. Webb [14] included hospital consumption but limited his assessment to 60 compounds for which ecotoxicity data were available at the time. A further barrier to complete assessment of pharmaceutical consumption is, as remarked by Ayscough et al. [7] as well as Sebastine and Wakeman [12], that detailed data for over-the-counter (OTC) sales of drugs are not readily available for the UK.

Studies from elsewhere in the EU report that an estimated 20-25% (by total weight) of all human medicine is used in hospitals [15, 16], but the contribution from hospitals varies per drug. In Germany, the hospital contribution for total antibacterials does not exceed 25%, with cephalosporins and to a lesser extent penicillins showing a relatively high hospital contribution [17]. For iodinated contrast media (ICM) it is estimated to be approximately 50% [18]; hospital consumption of the cytostatics is also relatively high. Weissbrodt et al. [16] note that 70% of cytostatics and 50% of ICM consumed in hospitals are administered to outpatients and therefore likely to be excreted in the community. Drugs dispensed to inpatients may also be excreted after the patients are discharged from hospital.

Several studies have measured the contribution to pharmaceutical load made by hospitals. Ort et al. measured residues in WWTP and hospital wastewater and found low (<15%) hospital contributions for all drugs apart from trimethoprim and roxithromycin [19]. However, in rural areas with no large population centres, large hospitals with a full range of treatment facilities may be encountered in smaller towns, where they will serve a population much greater than that of the town where the hospital is located [9]. Other studies investigating hospital contributions at specific

wastewater treatment plants confirm that in some situations hospitals contribute very significantly to overall pharmaceutical load at WWTP: Escher et al.[20] show this using predictive data, Santos et al. [21] and Verlicchi et al.[22] using measured values. Santos et al. [21] found particularly high hospital contributions to loads for receptor antagonists, antibacterials and analgesics, whereas Verlicchi et al. [22] found high contributions for antibacterials, receptor antagonist and lipid regulators. Ort et al. [23] demonstrated that inadequate sampling regimes for hospital wastewater can pose significant uncertainties for the results; using a predictive approach such as in the present study can help identify such uncertainties, e.g. by enabling checks that expected compounds are captured by the sampling process. Predictive data, on the other hand, do not identify strong fluctuations and instead result in average values. As concentrations in hospital effluents are more likely to show such strong variations than community effluents, in the present study, some drugs are highlighted specifically because of their high hospital contribution, which points towards temporal fluctuations and an uneven spatial distribution with potential 'hotspots' of residue near effluents containing hospital wastewater.

Since Jones et al. [13] carried out their ranking exercise in 2002, a dataset for hospital consumption in Scotland has become available. Combined with a dataset on pharmaceuticals dispensed in the community, this enabled us - for the first time in the UK - to prioritise drugs by environmental risk, based on consumption data inclusive of pharmaceuticals used in hospitals. Because the hospital consumption data covered Scottish hospitals only, the screening exercise was carried out specifically for Scotland. The research methodology is suitable for application in other national or regional contexts.

METHODOLOGY

Data sources, calculation of total consumption and hospital contribution

Data on pharmaceutical use in the community were purchased from the Scottish National Health Service's Information Services Division (NHS ISD; data derived from the NHS Prescribing Information System) for the top 250 prescribed drug products by quantity (i.e. number of items dispensed) (NHS prescriptions only) for the period April 2010 – March 2011. Hospital consumption data were obtained for the same period of all medicines dispensed in hospitals in Scotland from the Hospital Medicines Utilisation Data (HMUD) database. X-ray contrast media were not included in the database. As for the community data, the active ingredients of the top 250 products by quantity used in hospitals were selected and summed by compound. In accordance with the 'Guideline on the Environmental Risk Assessment of Pharmaceutical Products for Human Use', published by the European Medicines Agency (EMEA) in 2006 [24], vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids, vaccines and herbal medicinal products were excluded from analysis. In addition, emollients and barrier preparations (section 13.2 of the British National Formulary, a joint publication by the Royal Pharmaceutical Society and the British Medical Association) were excluded; these are often prescribed in very large quantities and would have dominated the consumption data. Emollients and barrier preparations mostly consist of paraffin and other fatty substances, but can contain antimicrobials such as chlorhexidine gluconate. It is acknowledged that antimicrobials from community consumption are therefore underestimated by the present study; the exclusion was necessary for budgetary reasons and was thought to be preferable to overrepresentation of this group in the data. It is recommended that antimicrobials should be investigated elsewhere in full, taking also into account their extensive use in OTC products.

The current summation of the mass of active compounds in the top 250 products yielded total mass for 165 different compounds. 51 drugs only occurred in the community data, 41 only in the hospital data. Hospital contributions were calculated as

$$h_i = \frac{A_{i,h}}{A_{i,h}+A_{i,c}} \times 100 \qquad (1)$$

whereby

h_i = the percentage of total dispensed compound i which is dispensed in hospitals

$A_{i,h}$ = the total amount of compound i dispensed in hospitals

$A_{i,c}$ = the total amount of compound i dispensed in the community.

It was assumed that all dispensed pharmaceuticals are consumed. A recent survey by Healthcare Without Harm [25] indicated that most unwanted pharmaceuticals are disposed of via municipal solid waste, in which case our assumption would result in an overestimation of concentrations in WWTP effluent; however, where pharmaceuticals are disposed via the toilet or sink (or vomited up), the amount of active ingredient that enters the environment can be higher than when they are consumed. Specific data on disposal behaviours in hospitals vs. in the community could not be found.

Ranking of pharmaceuticals by risk to the aquatic environment in Scotland

The approach for risk assessment was developed with reference to the aforementioned EU Technical Guidance Document (EU TGD) on Environmental Risk Assessment Part II [26] and the EMEA guideline [24], which define the potential environmental risk of a substance as a Risk Quotient (RQ)

$$\mathrm{RQ} = \frac{\mathrm{PEC}}{\mathrm{PNEC}} \quad (2)$$

whereby

RQ = the Risk Quotient

PEC = the Predicted Environmental Concentration and

PNEC = the Predicted No Effect Concentration.

The predicted environmental concentration is calculated in the first instance as

$$\mathrm{PEC}_{(\mathrm{unrefined})\ \mathrm{w,i}} = \frac{\mathrm{A_{i,c}} + \mathrm{A_{i,h}}}{((365 * \mathrm{P} * \mathrm{V_c}) + \mathrm{V_h}) * \mathrm{D}} \quad (3)$$

whereby

$PEC_{w,i}$ = the expected concentration of compound *i* in surface water

$A_{i,c}$ = the amount of compound *i* used per year in the community;

$A_{i,c}$ = the amount of compound *i* used per year in hospitals;

P = the population under consideration;

V_c = the amount of wastewater produced by 1 person per day;

V_h = the total amount of hospital wastewater in 1 year in Scotland

D = a dilution factor in the environment;

Based on Scottish Government statistics [27] a population P of 5.222 million was assumed for Scotland for 2010, and water consumption per person per day V_c assumed as 150 litres. Water consumption in Scottish hospitals in the year April 2009- March 2010 was 5,163,989 $x10^3$ L [28]. A standard dilution factor of 10 is used, conform the Technical Guidance Document. It should be noted that under low flow conditions (Q95) such a dilution is not available everywhere. Available dilution under Q95 conditions was calculated for 15 Scottish WWTP in the Chemicals Investigation Programme carried out by UK Water Industries Research (UKWIR) and ranged from 1.9 to 590 [A. Zyndul, Scottish Water, Scotland, personal communication]. This does not affect the order of our ranking but again points to the need for spatial differentiation in risk assessments. The number of locations where concentrations exceed targets is of crucial importance to the affordability of strategies to address such exceedances.

The EMEA guideline stipulates that if $PEC_{unrefined}$ is below 0.01 µg/l, and no other environmental concerns are apparent, the product is unlikely to represent a risk to the environment [24]. After our initial assessment, 31 compounds with $PEC_{(unrefined)w,i}$ < 0.01 µg/l were omitted from further quantitative analysis. Levonorgestrel and ethinyl estradiol were found to have a PEC < 0.01 µg/l, but as very low PNECs (< 0.0001 µg/l) are known for these compounds, they were therefore taken forward to the initial risk assessment, in accordance with the EMEA guideline [24].

PNEC values were sought for all compounds with a $PEC_{unrefined}$ > 0.01 µg/l and levonorgestrel and ethinyl estradiol either directly from literature, or by calculation from experimental data in literature, or by modelling using the Structure-Activity Relationship modelling software ECOSAR. In the case of 4 drugs, PNEC data were taken from Kümmerer and Henningen's study on 'Promoting resistance by the emission of antibacterials from hospitals and households into effluent' [29]. In the study, PNECs are calculated as Minimum Inhibitory Concentration (MIC_{50}) divided by 10, which the authors state is a somewhat arbitrary but good compromise for risk assessment. It is acknowledged that these different derivations of PNEC introduce an element of uncertainty in the resulting ranking and where further experimental data become available in the future they should replace ECOSAR values.

For compounds with $\frac{PEC_{(unrefined)w,i}}{PNEC}$ > 0.1, $PEC_{(unrefined)\ w,i}$ was refined by including data on excretion and removal in wastewater treatment with activated sludge:

$$PEC_{w,i} = \frac{(A_{i,c}+A_{i,h})*\eta\left(1-\frac{R}{100}\right)}{365*P*V*D} \quad (4)$$

whereby

R = the removal efficiency in wastewater treatment (R in %)

η = percentage excreted as unchanged parent compound (0 < η < 1).

Data on percentage excreted as parent compound were mostly taken from Ashley and Currie [30]. The body of research into removal of pharmaceuticals was reviewed and presented in several studies, most comprehensively in Verlicchi et al. [5]. Removal efficiencies are not available for all compounds and, where they are, there is considerable variation in the values reported. It should be noted that combined sewers are common in Scotland and that therefore sewage may enter the environment untreated via Combined Sewer Overflows (CSO) during heavy rain.

RESULTS

Hospital contributions

Based on the available data, for 43 drugs the hospital contribution was 100% (note that this indicates that the compound was not present in the top 250 community prescribed products, rather than that it is used exclusively in hospitals (although this may be the case), and vice versa). Of these, 24 had a $PEC_{unrefined}$ > 0.01 µg/l and were therefore investigated further. High (> 20%) hospital contributions were found in particular for antibacterials: piperacillin (4.5 tonnes (t) prescribed in hospitals; 100% hospital contribution) and tazobactam (0.5 t; 100%), which are normally administered together, metronidazole (0.3 t; 100%), clarithromycin (0.1 t; 100%), ciprofloxacin (3.4 t; 26%), flucloxacillin (1.4 t; 22%), and several others in smaller quantities. In other therapeutic groups, hyperkalaemia drug calcium polystyrene sulphonate (0.7 t; 100%), cancer drugs capecitabine (0.5 t; 100%) and hydroxycarbamide (0.3 t; 100%), antipsychotic medicine clozapine (0.4 t; 100%), angina medication glyceryl trinitrate (0.3 t; 100%), enzyme inhibitor clavulanic acid (used in the combination drug co-amoxiclav) (0.2 t;100%), hepatitis C drug ribavirin (0.2 t; 100%), antivirals aciclovir (0.2 t; 100%), and lopinavir (0.1 t; 100%), gastric ulcer medicine sucralfate (0.1 t; 100% and schizophrenia drug amisulpride (0.1 t; 100%), sleeping tablet trazodone (0.5 t; 66%), asthma drug salbutamol (0.3 t; 33%) and a number of others used in smaller quantities also have high hospital contributions.

Attention is also drawn to 2 antiseptic substances: the surgical scrub povidone-iodine and chlorhexidine gluconate, used amongst other things in mouthwash, as well as dimeticone, used in headlice shampoo. None of these have received much attention in the literature from an environmental risk perspective; these compounds are perhaps not strictly speaking medicines but disinfectant and pesticide compounds. All three are available under a General Sales License and, in addition to the amount prescribed, are therefore sold over the counter. The data suggest that the amount consumed in hospitals alone merits further analysis. It should be noted that the hospital contribution of chlorhexidine gluconate could not be calculated accurately due to the exclusion from

the community data (as mentioned in the methodology) and that its total consumption is underestimated.

Ranking by mass

Of the considered compounds, paracetamol is prescribed in the highest amount overall, with over 328 t prescribed in 2010. Three other analgesics, ibuprofen, aspirin and codeine, are also all in the top 10 prescribed compounds. Very high consumption is also reported for lactulose (201 t), a synthetic laxative, and for metformin hydrochloride (67 t), a diabetes medicine. The most consumed antibacterial is amoxicillin (13 t), followed by flucloxacillin (6 t).

Overall risk assessment

For the 131 with $PEC_{unrefined}$ > 0.01 µg/l as well as ethinyl estradiol and levonorgestrel all data are given in the Supplementary Information (S.I.). Robust experimental-based PNEC values were found for 82 compounds. A further 41 values were obtained using EcoSAR modelling (or taken from literature referring to modelling). No PNEC, and therefore no RQ, could be found or calculated for 15 compounds: these are, in order of descending PEC: mesalazine, chlorhexidine gluconate, ferrous fumarate, calcium polystyrene, esomeprazole, dimeticone, glyceryl trinitrate, hydroxicarbamide, sodium feredetate, sucralfate, hyoscine butylbromide, montelukast, chlorphenamine, isotrenitoin, solifenacin, and tolterodine.

It should be noted that the PEC values, and consequently all calculated RQ values, are based on the assumption of standard dilution of 10. Where less dilution is available, RQ values for individual compounds may be higher and vice versa. Not yet accounting for excretion and removal, 53 pharmaceuticals were found to have a $PEC_{unrefined}$/PNEC greater than or equal to 0.1. Removal efficiency data was available for just under half of these 53 compounds. For the remaining compounds, a removal efficiency of 0% was assumed as a precautionary approach. This does of

course present an uncertainty in the ranking and lack of data is indicated in Table 1 and the S.I.

Similarly, for 1 compound no excretion rate was found and excretion was assumed to be 100%.

Table 1 Top pharmaceuticals by Environmental Risk for Scotland, with indication of hospital contribution

	Total consumption (kg)	Hospital contribution (%)	Removal (%)[a]	Excretion (%)[a]	$PEC_{refined}$ (µg/l)	PNEC (µg/l)[a,b]	RQ = $PEC_{refined}$/PNEC	RQ in Jones et al., 2002 (assumptions: no metabolism, no removal)	Compounds highlighted as of potential concern in Hilton et al., 2003	RQ in Webb, 2000
Amoxicillin	13,277	12	96	80	0.15	0.0037	39	588.02		
Piperacillin	4,475	100	0[c]	80	1.2	0.06	21			
Flucloxacillin	6,278	22	0[c]	40	0.86	0.3	2.9			
Phenoxymethyl penicillin (Penicillin V)	3,406	10	60	60	0.28	0.1	2.8	0.004		
Tazobactam	559	100	0[c]	80	0.15	0.06	2.6			
Erythromycin	2,086	0	26	8	0.042	0.02	2.1	0.04	x	<0.17
Ketoconazole	180	0	0[c]	100[d]	0.062	0.05	1.2			
Ciprofloxacin	1,319	26	70	40	0.054	0.05	1.1			
Oxytetracycline	3,212	0	44	35	0.22	0.207	1.0	3.6		26.8
Propranolol	1,020	0	39	2	0.0043	0.005	0.85		x	1.16
Clotrimazole	52	11	31	95	0.012	0.014	0.84		x	
Naproxen	4,671	0	73	94	0.41	0.64	0.64	0.01		0.09
Amlodipine	467	1	0c	8	0.013	0.28	0.57			
Venlafaxine	323	0	0[c]	5	0.0056	0.013	0.43			
Metformin	67,132	1	0[c]	100	23	60	0.38	0.01		0.19
Ethinyl estradiol	1	6	78	9	9.8×10^{-6}	0.00003	0.33			<0.01
Povidone-Iodine	3,255	100	0[c]	50	0.56	1.84	0.30			

Ferrous sulphate	4,697	9	0[c]	100[d]	1.6	7.1	0.23	0.16		
Allopurinol	3,123	0	0[c]	8	0.086	0.45	0.19	0.01		
Fluoxetine	683	1	56	8	0.0083	0.05	0.17		x	14.19
Clopidogrel	1,173	7	0[c]	50	0.20	1.6	0.13			
Clarithromycin	98	100	0[c]	20	0.0067	0.07	0.096			
Gentamicin	40	100	0[c]	90	0.012	0.15	0.083			
Carbamazepine	4,909	0	18	2	0.028	0.42	0.066	0.19		
Ezetimibe	96	0	0[c]	20	0.0066	0.13	0.051			
Ranitidine	4,645	5	52	38	0.29	6.2	0.047			0.02

a) A full dataset including all references for removal efficiency, excretion and PNEC are given in the Supplementary Information

b) The number of decimals given is determined by the source publication

c) Indicates no removal data; no removal assumed

d) Indicates no excretion data; 100% excretion assumed

Thus refined, 9 drugs had an RQ > 1 (Table 1) and pose a significant risk to the environment; all but 1 of these are antibacterials. Ketoconazole (RQ 1.24) is an antifungal compound. RQ is highest for amoxicillin at 39, despite a removal efficiency of 96%. This is due to a combination of high consumption and a low PNEC value. No removal efficiency was found for the hospital antibacterial piperacillin so that no removal in WWTP was assumed. As a result, the overall RQ value of 21 is likely to be an overestimation, but as this drug is likely to be unevenly distributed even a high degree of removal could locally give an RQ > 1. It must be noted that for piperacillin, flucloxacillin, phenoxymethylpenicillin and tazobactam, PNEC values, taken from Kümmerer and Henninger [29], were based on MIC values rather than experimental PNECs. In several other publications [e.g. 5, 32] such values are used alongside ecotoxicity data, but as described in section 2.2.2, their derivation is different and further research on the correlation between ecotoxicity data and MIC values is recommended.

In the range 0.1 < RQ < 1, a wider range of therapeutic groups feature; the highest ranking drug other than antibacterials is the beta-blocker propranolol at 0.85, which is toxic at very low concentrations. The antifungal clotrimazole has an RQ of 0.84 but, as it is also available over the counter, consumption may be higher. However, as this compound is often used in a cream, it is also possible that unfinished tubes are disposed of with solid waste and do not enter the wastewater. Again, further research is recommended. Other featured compounds are the painkiller naproxen, the diabetes medicine metformin, the contraceptive hormone ethinyl estradiol, the anti-gout medication allopurinol, 2 antidepressants, an anti-thrombotic drug, 2 more antibacterials, an anti-convulsant, a cholesterol absorption inhibitor, an antacid and a calcium channel blocker.

A number of drugs with a calculated 0.001 < RQ < 0.1 have very high hospital concentrations. It may be prudent to pay some attention to these. Capecitabine (RQ 0.03), metronidazole (RQ 0.02), lopinavir (RQ 0.02), clindamycin (RQ 0.01), amisulpride (RQ 0.0035),

clozapine (RQ 0.0017) and fluticasone (RQ 0.0001) all have hospital contributions of 100% (based on the available data). Depending on the therapeutic group, these may be used in specific hospital types only; for example, amisulpride and clozapine arise mostly from the 22 mental hospitals in Scotland and will be concentrated around these localities. This could result in locally much higher risks than suggested by the overall RQ; it is suggested that for hospital drugs a different type of risk indicator may be required. This should be the subject of further research.

DISCUSSION

Comparison with measured values

To validate predictions, we were able to compare the results of the UK Water Industries (UKWIR)'s Chemicals Investigation Programme (CIP) [31], in which 8 pharmaceuticals were monitored at 150 WWTP throughout the UK, with concentrations in effluent as predicted by the present study. For 7 out of 8 compounds, the 50^{th} percentile values of measured concentrations in CIP are within a factor 5 of predictions. Four of these are above and 3 are below predicted values. Only the 50^{th} percentile value for oxytetracycline is 12 times lower than the predicted value. Overestimation may be due to the assumption that all pharmaceuticals are consumed. Underestimation may be due to the fact that predictions were based on the assumption of removal in activated sludge, whereas at some facilities less efficient processes such as trickling filters are used for secondary treatment.

Comparison with previous studies

Where possible, results for RQ are compared with those presented in Jones et al. [13], who ranked the top 25 pharmaceuticals (by mass) in England by environmental risk, and Webb [14], also noting the compounds with 'top 10' PEC/PNEC ratios in Hilton et al.'s prioritisation for monitoring for the Environment Agency [11]. In the latter, numerical values are not given although the authors state that only lofepramine, dextropropoxyphene and procyclidine had an RQ > 1.

Four of the drugs with RQ > 1, piperacillin, flucloxacillin, tazobactam and ciprofloxacin, have a hospital contribution greater than 20%; none of these was identified as of concern by Webb [14], Jones et al. [13], or Hilton et al. [11]. Penicillin V and erythromycin were previously listed as having a much lower RQ (below 0.1) by Jones et al. [13]. Amoxicillin was listed by Jones et al. [13] with an RQ of 588; this can be explained by the fact he assumed no metabolism or removal in sewage treatment works. Oxytetracycline had a higher RQ in rankings by Jones et al. [13] and Webb [14] than was found in the present study.

Of the compounds with 0.1 < RQ < 1, propranolol, naproxen, metformin, and fluoxetine, were all previously identified as having an RQ > 0.1 by Webb [14], in accordance with our findings; Hilton et al. [11] previously identified propranolol, clotrimazole, and fluoxetine as of concern. Of the antimicrobials, apart from erythromycin, Hilton et al. highlighted trimethoprim and sulfamethoxazole [11]. The latter two are – according to the data at hand – not the ones posing the greatest risk in Scotland in terms of RQ. Comparison of the PNEC values given in Hilton's study with those found for the ranking in the present study reveals that in the last decade, new toxicity data have become available for nearly all, resulting in higher risk quotients. An RQ > 0.1 for carbamazepine (0.07 in the present study) and ferrous sulphate (0.23 in the present study) had previously been identified by Jones et al. [13]. The authors also considered naproxen, allopurinol, and metformin but found RQ values much lower than found in the present study, as with increasing toxicity data the reported PNEC values have decreased by 2 orders of magnitude for most of these compounds. Venlafaxine, povidone-iodine, clopidogrel, clarithromycin, gentamicin, amlodipine and ezetimibe had not been identified by the studies we used for comparison. Of these, povidone-iodine, clarithromycin and gentamycin have very high hospital contributions, which would explain why they were not included by Jones et al. [13] or Hilton et al. [11] (although povidone-iodine may have been deliberately excluded by the authors as a disinfectant).

Comparison with other national studies

Few other national studies were identified that considered both community and hospital consumption. Huschek et al. [33] assessed environmental risks for pharmaceuticals in Germany in 2004. Compounds with RQ > 1 were ciprofloxacin, clarithromycin, ethinylestradiol, acetylsalicylic acid (aspirin), paracetamol and povidone-iodine, whilst ibuprofen, metformin and bezafibrate had 0.1 < RQ < 1. Several others, e.g. propranolol and carbamazepine, are listed as having lower RQs but would have had RQ > 1 if the PNECs found in the present study had been available. Apart from bezafibrate, all of these identified by Huschek et al. were also identified with RQ > 0.1 in the present study. Huschek et al. did not identify some of our highest ranking compounds, e.g. piperacillin and flucloxacin, possibly because available toxicity data were limited or possibly because they fell below an initial cut-off point of sales in excess of 5000 kg/a. A study instigated by the Nordic Council of Ministers [34] investigated environmental risk from pharmaceuticals in the Nordic Countries. In Denmark, the following substances were identified: those with 0.01 < RQ < 0.1 were prednisolone, citalopram, metoprolol, tramadol and losartan; those with 0.1 < RQ < 1 were atorvastatin, norethisterone, felodipine, metformin, amlodipine, diazepam, and those with RQ > 1 sertraline, diclofenac, ibuprofen, and aspirin. There is a notable lack of antibacterial drugs on this list; this may be because the study only considered the top 40 most sold substances. Furthermore, the study uses 'defined daily doses' (DDD) as defined by WHO for the calculation of the amount sold, which can be problematic in the case of combination drugs, such as co-amoxiclav or co-codamol, for which no DDD are issued. Hospital contributions in Denmark were much lower than those calculated in the present study; only prednisolone has a hospital contribution over 5%. In Finland, 65 compounds were considered, of which amlodipine, atorvastatin, and aspirin have 0.1 < RQ < 1. Metformin, paracetamol, ibuprofen, naproxen, and several sex hormones have RQ > 1. As in Denmark, no antibacterials were identified as having high risk quotients.

The comparison with these studies suggests that it is important to include a large number of substances for initial consideration, as some very low PNEC values can result in high risk even for compounds lower on a ranking by mass. There are a lot of similarities between the high ranking compounds in Huschek's study and those in the present study; differences appear to be in some cases due to different PNEC data rather than actual different risks.

Trends in consumption

Changing consumption patterns are likely to affect risk assessment: the total number of antidepressant prescriptions in Scotland rose from 1.2M in 2003 to over 5M in 2012, whilst in the UK, gout, for which allopurinol can be prescribed, is reported to have risen by 64% between 1997 and 2012 [35]. The prevalence of diabetes in Scotland, often treated with metformin, nearly doubled between 2003 and 2008 [36]. The use of antibacterial drugs continues to receive international attention because of concerns about resistance. The Scottish Antibacterial Prescribing Group (SAPG), established in 2008, has developed prescribing policies intending to influence the choice of antibacterial use towards narrower spectrum antibacterials, with a particular focus on co-amoxiclav, clindamycin, fluoroquinolones (mainly ciprofloxacin) and cephalosporins ('the four C's') [37] and reports some interesting trends. In primary care (excluding dental), the use of broad spectrum penicillins (which include co-amoxiclav) and fluoroquinolones (which include ciprofloxacin) decreased by 6% and a dramatic 29%, respectively. In secondary care however, there was a 26% increase in the use of co-amoxiclav over the same period, whilst use of fluoroquinolones decreased by 8%. Use of the piperacillin-tazobactam combination increased by 30%. Use of macrolide antibacterials, which include erythromycin and clarithromycin, was relatively stable in both primary and secondary care (based on DDDs/1000/d). A drug not highlighted by the present study, nitrofurantoin, saw a doubling in use from 45.7 to 96.0 DDDs/1000/d. It is possible that where reduced use of certain antibacterials is encouraged, use of other antibacterials may increase as a result. Based on these trends, we may expect the hospital contributions for amoxicillin and for

ciprofloxacin to have increased, the RQ for ciprofloxacin and amoxicillin to have reduced slightly, and the RQ for piperacillin and tazobactam to have increased substantially since the data for the present study were collected. Given the ecotoxicological importance of antibacterial drugs, it would be highly interesting to investigate the environmental consequences of the rapidly developing antimicrobial resistance agenda more fully in a further study.

Implications for mitigation

Half of the pharmaceuticals with RQ > 1 have high hospital contributions, whilst a number of compounds with lower RQ may be locally concentrated WWTP serving hospitals and pose a local risk. In such situations, point source treatment of hospital effluent could be an effective strategy for the reduction of environmental risk as a large fraction of the pollutant load could be removed by treating a relatively small amount of wastewater. However, some pollutants of key concern, such as erythromycin and propranolol, would not be effectively targeted by point source treatment as they are predominantly used in the community. To enable informed decision making on treatment options, spatially differentiated risk assessment may be required to prioritise locations and select appropriate mitigation. The marked reduction in use in primary care of the four C's indicates that where the necessary drivers are in place, pharmaceutical use can to some extent be influenced by prescribing policy, implying that such policies could be considered as a preventative measure to reduce environmental risk from pharmaceuticals. Other studies [25] indicate that disposal of waste pharmaceuticals via the sewer is still common despite collection facilities at pharmacies, so that awareness raising may be a useful intervention. No single obvious solution presents itself and it may be that a range of stakeholders and policies have a role to play in the reduction of environmental risk.

CONCLUSIONS AND RECOMMENATIONS

Attention is drawn to a number of drugs not previously highlighted as of concern for the UK. As expected, for some compounds this is likely due to the inclusion of the hospital consumption data; indeed 4 of these compounds – all with an RQ > 1 - have hospital contributions over 20%. However, several drugs not previously identified as of concern are predominantly used in the community. Three probable explanations are proposed. Firstly, in the past decade much more experimental ecotoxicity data have become available, in particular for antibacterials, which means lower PNEC values have been established. Based on the available datasets, antimicrobials now have the highest RQs. Secondly, compounds may previously have been excluded from research programmes due to the lack of analytical methods or due to other deliberate exclusions. Thirdly, for yet others a marked increase in consumption is thought to have led to an increased risk to the aquatic environment. The changes from previous prioritisations highlight the importance of regular review.

As hospital drug usage and thus release into the environment is likely to have an uneven spatial distribution, risk quotients for hospital drugs may be locally higher than reported here. Geographical refinement of the risk assessment is recommended and should take account of any hospitals as well as local dilution rates. Although the available data on consumption, toxicity and removal are improving, gaps remain. For the newly highlighted drugs, it is recommended that further study on removal efficiencies as well as environmental studies are carried out. In order to make a complete, holistic risk assessment of the pharmaceuticals we consume, research is further required on the prevalence, fate and effect of active metabolites and the fate and effect of sorbed pharmaceutical residue and metabolites applied to land via sludge. Furthermore, as in previous studies, the datasets acquired were limited by both availability and price and required extensive and laborious manipulation before they could be used. Whilst the present study was able to identify a number of compounds over a range of treatment groups that carry a moderate or high

environmental risk for Scotland, it cannot exclude the possibility that others should also be of concern. As awareness of the issue of pharmaceuticals in the environment is growing and more regularly updated research is clearly required, it would be beneficial if data gathering and storage systems by NHS and other agencies were better suited also to the environmental types of analyses required. Interdisciplinary, multi-agency and international collaboration would be required to improve this situation.

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References

1. European Parliament. 2013. Surface waters: 12 new controlled chemicals, three pharmaceuticals on watch list. 20130701IPR14760. Press Release Plenary Sessions. EU.

2. Kümmerer K (Editor). 2008. *Pharmaceuticals in the environment: sources, fate, effects and risks*. 3rd ed, Springer-verlag, Berlin Heidelberg, Germany.

3. Parolini M, Binelli A, Cogni D, Riva C, Provini A. 2009. An in vitro biomarker approach for the evaluation of the ecotoxicity of non-steroidal anti-inflammatory drugs (NSAIDs). *Toxicol in vitro* 23:935-942

4. Ravilious K. 2010. Prozac pollution making shrimp reckless. *National Geographic Daily News* 16 July 2010. National Geographic Society. [cited 29 March 2014]. Available from: http://news.nationalgeographic.com/news/2010/07/100715-shrimp-prozac-antidepressants-environment-science/?source=email_gg

5. Verlicchi P, Al Aukidy M, Zambello E. 2012. Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment — a review. *Sci Total Environ* 429:123-155.

6. Mehinto AC, Hill EM, Tyler CR. 2010. Uptake and Biological Effects of Environmentally Relevant Concentrations of the Nonsteroidal Anti-inflammatory Pharmaceutical Diclofenac in Rainbow Trout (*Oncorhynchus mykiss*). *Environ Sci Technol* 44:2176-2182.

7. Ayscough NJ, Fawell J, Franklin G, Young W. 2000. Review of pharmaceuticals in the environment. R&D Technical Report P390, Environment Agency, Bristol, UK.

8. Huber MM, Göbel A, Joss A, Hermann N, Löffler D, McArdell CS, Ried A, Siegrist H, Ternes TA,Von Gunten U 2005. Oxidation of Pharmaceuticals during Ozonation of Municipal Wastewater Effluents: A Pilot Study. *Environ Sci Technol* 39:4290 - 4299.

9. Lyko S, Nafo I, Evenblij H, Benetto E, Cornelissen A, Igos E, Klepiszewski K, Venditti S, Kovalova L, McArdell C, Helwig K, Hunter C, Jiang J, MacLachlan J, McNaughtan M, Pahl O, Roberts J, Barraud O, Casellas M, Dagot C, Maftah C, Ploy M, Stalder T. 2012. Pharmaceutical Input and Elimination from Local Sources: Final report of the European co-operation project PILLS. PILLS, Gelsenkirchen, Germany

10. Lienert J, Koller M, Konrad J, McArdell CS, Schuwirth N. 2011. Multiple-criteria decision analysis reveals high stakeholder preference to remove pharmaceuticals from hospital wastewater. *Environ Sci Technol* 45:3848-3857

11. Hilton MJ, Thomas KV, Ashton D. 2003. Targeted Monitoring Programme for Pharmaceuticals in the Aquatic Environment. R&D Technical Report P6-012/06/TR. Environment Agency, Bristol, UK.

12. Sebastine IM, Wakeman RJ. 2003. Consumption and Environmental Hazards of Pharmaceutical Substances in the UK. *Process Saf and Environ* 81:229-235.

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

14. Webb S. 2000. Risk Assessment Approaches for Pharmaceuticals. *Proceedings,* International Seminar on Pharmaceuticals in the Environment. Brussels, Belgium, 9 March 2000.

15. Schuster A, Hädrich C & Kümmerer K. 2008. Flows of Active Pharmaceutical Ingredients Originating from Health Care Practices on a Local, Regional, and Nationwide Level in Germany—Is Hospital Effluent Treatment an Effective Approach for Risk Reduction? *Water, Air Soil Poll* 8:457-571.

16. Weissbrodt D, Kovalova L, Ort C, Pazhepurackel V, Moser R, Hollender J, Siegrist H, McArdell CS 2009. Mass Flows of X-ray Contrast Media and Cytostatics in Hospital Wastewater. *Environ Sci Technol* 43:4810-4817.

17. Kümmerer K. 2008. Antibiotics in the environment. In Kümmerer K. (ed) 2008, *Pharmaceuticals in the environment: sources, fate, effects and risks,* 3rd ed, Springer-verlag, Berlin Heidelberg, Germany, pp. 75-93.

18. Kümmerer K, Schuster A, 2008. Substance Flows Associated with Medical Care – Significance of Different Sources. In Kümmerer K. (ed) 2008, *Pharmaceuticals in the environment: sources, fate, effects and risks*, 3rd ed, Springer-verlag, Berlin Heidelberg. Germany, pp.43-59.

19. Ort C, Lawrence MG, Reungoat J, Eaglesham G, Carter S, Keller J. 2010. Determining the fraction of pharmaceutical residues in wastewater originating from a hospital. *Water Res* 44:605-615.

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

21. Santos LHMLM, Gros M, Rodriguez-Mozaz S, Delerue-Matos C, Pena A, Barceló D, Montenegro MCBSM. 2013. Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals. *Sci Total Environ* 461-462:302-316.

22. Verlicchi P, Al Aukidy M, Galletti A, Petrovic M, Barceló D. 2012. Hospital effluent: investigation of the concentrations and distribution of pharmaceuticals and environmental risk assessment. *Sci Total Environ* 430:109–118

23. Ort C, Lawrence MG, Rieckermann J, Joss A. 2010. Sampling for Pharmaceuticals and Personal Care Products (PPCPs) and Illicit Drugs in Wastewater Systems: Are Your Conclusions Valid? A Critical Review. *Environ Sci Technol* 44:6024-6035.

24. European Medicines Agency. 2006. Guideline on the environmental risk assessment of medicinal products for human use. EMEA/CHMP/SWP/4447/00. European Medicines Agency, London, UK.

25. Amaral MJ, Fop L, 2013. Unused Pharmaceuticals - Where Do They End Up? A Snapshot of European Collection Schemes. Healthcare Without Harm, Brussels, Belgium.

26. EC .2003. Technical Guidance Document (TGD) in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and the Council concerning the placing of biocidal products on the market. Edition 2. EUR 20418 EN/2. European Commission Joint Research Centre, Ispra, Italy. EU.

27. Scottish Government 2011. Scotland's population 2011 - The Registrar General's Annual Review of Demographic Trends: General Register Office For Scotland. [cited 02 May 2013] Available from: http://www.gro-scotland.gov.uk/statistics/at-a-glance/annrev/2011/all-figures.html

28. National Health Service Scotland. 2010. Water Efficiency Audits. SUP002-002. NHSS, Edinburgh, UK.

29. Kümmerer K, Henninger A. 2003. Promoting resistance by the emission of antibiotics from hospitals and households into effluent. *Clinical Microbiol Infec* 9:1203-1214.

30. Ashley C, Currie A (Editors) 2009. The Renal Drug Handbook, 3rd edn, Radcliffe, Oxford, UK.

31. Gardner A, Jones V, Thornton A. 2013. Chemical Investigations Programme: Volume 1 – Main Report. 13/EQ/01/6. UKWIR, London, UK.

32. De Souza SML, de Vasconcelos EC, Dziedzic M, de Oliveira CMR 2009. Environmental risk assessment of antibiotics: An intensive care unit analysis. *Chemosphere* 77:962-967

33. Huschek G, Hansen PD, Maurer HH, Krengel D, Kayser A. 2004. Environmental Risk Assessment of MedicinalProducts for Human Use According to European Commission Recommendations. *Environ toxicol* 19:226-240

34. Woldegiorgis A, Wiklund P, Moe M. 2009. Retrospective environmental risk assessment of human pharmaceuticals in the Nordic countries 1997-2007. TemaNord 2009:587. Nordic Council of Ministers. Copenhagen, Denmark.

35. Kuo C, Grainge MJ, Mallen C, Zhang W, Doherty M. 2013. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 74:661-667.

36. Hamer M, Kengne AP, Batty GD, Cooke D, Stamatakis E. 2011. Temporal trends in diabetes prevalence and key diabetes risk factors in Scotland, 2003-2008. *Diabetic Med* 28:595-598.

37. NHS 2015. Antimicrobial Use and Resistance in Humans. 2013 Publication Report, ISD Scotland Statistics, Edinburgh, UK.

Ranking prescribed pharmaceuticals in terms of environmental risk: inclusion of hospital data and the importance of regular review

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SUPPLEMENTAL DATA

Pharmaceutical	Total cons. [kg]	Hosp. contr. [%]	PEC [u] [µg/l]	PNEC [µg/l]	Ref. #	Remov. [%]	Ref. #**	Excr. [%]	Ref. #	PEC refined [µg/l]	RQ	Reference RQs		
												Jones	Hilton	Webb
Mesalazine	6760	0	2.32	nd		0	*	100	*	2.32	nd	0		
Ferrous fumarate	3540	6	1.22	nd		0	*	100	*	1.22	nd			
Calcium polystyrene sulphonate	737	100	0.26	nd		0	*	100	1	0.26	nd			
Esomeprazole	360	0	0.12	nd		0	*	0	2	0.00	nd			
Dimeticone	354	24	0.12	nd		0	*	100	†	0.12	nd			
Glyceryl trinitrate	331	100	0.12	nd		0	*	1	2	0.00	nd			
Hydroxicarbamide	275	100	0.10	nd		0	*	50	2	0.05	nd			
Sodium feredetate	225	9	0.08	nd		0	*	100	*	0.08	nd			
Sucralfate	125	100	0.04	nd		0	*	4	2	0.00	nd			
Hyoscine butylbromide	104	6	0.04	nd		0	*	2	2	0.00	nd			
Montelukast	57.5	0	0.02	nd		0	*	0	2	0.00	nd			
Chlorphenamine	35.5	9	0.01	nd		0	*	22	2	0.00	nd		x	
Isotrenitoin	23.9	100	0.01	nd		0	*	0	2	0.00	nd			
Solifenacin	21.8	0	0.01	nd		0	*	7	3	0.00	nd			
Tolterodine	16.6	0	0.01	nd		0	*	1	2	0.00	nd			
Amoxicillin	13300	12	4.56	0.0037	4	96	4	80	5	0.15	3.9E+01	588.02		
Piperacillin	4480	100	1.54	0.06	5	0	*	80	5	1.23	2.1E+01			
Flucloxacillin	6280	22	2.16	0.3	5	0	*	40	5	0.86	2.9E+00			
Phenoxymethyl penicillin (PCN V)	3410	10	1.17	0.1	5	60	4	60	5	0.28	2.8E+00	0.004		
Tazobactam	559	100	0.19	0.06	6	0	*	80	1	0.15	2.6E+00			
Erythromycin	2090	0	0.72	0.02	4	26	4	8	5	0.04	2.1E+00	0.04	x	<0.17
Ketoconazole	180	0	0.06	0.05	6	0	*	100	1	0.06	1.2E+00			
Ciprofloxacin	1320	26	0.45	0.05	7	70	4	40	5	0.05	1.1E+00			
Oxytetracycline	3210	0	1.10	0.207	4	44	4	35	2	0.22	1.0E+00	3.6		26.8
Propranolol	1020	0	0.35	0.005	9	39	4	2	10	0.00	8.5E-01		x	1.16
Clotrimazole	52.5	11	0.02	0.014	11	31	4	95	1	0.01	8.4E-01		x	
Naproxen	4670	0	1.60	0.64	12	73	4	94	13	0.41	6.4E-01	0.01		0.09
Amlodipine	467	1	0.16	0.28	14	0	*	8	10	0.01	5.7E-01			
Venlafaxine	323	0	0.11	0.013	15	0	*	5	16	0.01	4.3E-01			
Metformin	67100	1	23.06	60	17	0	*	100	18	23.06	3.8E-01	0.01		0.19
Ethinyl estradiol	1.44	6	0.00	0.00003	19	78	4	9	10	0.00	3.3E-01			<0.01
Povidone-Iodine	3260	100	1.12	1.84	17	0	*	50	††	0.56	3.0E-01			
Ferrous sulphate	4700	9	1.61	7.1	20	0	*	100	*	1.61	2.3E-01	0.16		
Allopurinol	3120	0	1.07	0.45	12	0	*	8	10	0.09	1.9E-01	0.01		
Fluoxetine	683	1	0.23	0.05	4	56	4	8	10	0.01	1.7E-01		x	14.19
Clopidogrel	1170	7	0.40	1.6	11	0	*	50	2	0.20	1.3E-01			
Clarithromycin	97.9	100	0.03	0.07	4	0	*	20	5	0.01	9.6E-02			
Gentamicin	40.2	100	0.01	0.15	5	0	*	90	5	0.01	8.3E-02			
Carbamazepine	4910	0	1.69	0.42	21	18	4	2	22	0.03	6.6E-02	0.19		
Ezetimibe	96.0	0	0.03	0.13	12	0	*	20	1	0.01	5.1E-02			
Ranitidine	4650	5	1.60	6.2	9	52	4	38	10	0.29	4.7E-02			0.02
Trimethoprim	1060	12	0.37	3	23	40	4	60	5	0.13	4.4E-02		x	
Paracetamol	328000	6	112.85	9.2	9	93	4	5	1	0.39	4.3E-02	1.29	x	
Ibuprofen	16300	9	5.60	1.65	4	87	4	7	10	0.05	3.1E-02	0.99	x	
Sulfasalazine	9760	0	3.35	30.3	E.	-80	24	15	1	0.91	3.0E-02	0.04		
Quinine	4210	0	1.44	10.1	25	0	*	20	1	0.29	2.9E-02	0.53		0.54
Capecitabine	504	100	0.17	0.2	9	0	*	3	1	0.01	2.6E-02			
Furosemide	2080	4	0.71	14.9	9	51	4	98	1	0.34	2.3E-02		x	

Pharmaceutical	Total cons. [kg]	Hosp. contr. [%]	PEC [u] [µg/l]	PNEC [µg/l]	Ref. #	Removv. [%]	Ref. #**	Excr. [%]	Ref. #	PEC refined [µg/l]	RQ	Reference RQs		
												Jones	Hilton	Webb
Betahistine dihydrochloride	165	0	0.06	2.3	E.	0	*	90	2	0.05	2.2E-02			
Metronidazole	301	100	0.10	1.25	5	38	4	40	5	0.03	2.0E-02			0.23
Lopinavir	133	100	0.05	0.05	11	0	*	2	1	0.00	1.8E-02			
Phenytoin	456	1	0.16	0.5	E.	5	26	5	2	0.01	1.5E-02			
Clindamycin	55.5	100	0.02	0.5	5	0	*	35	5	0.01	1.3E-02			
Sertraline	791	0	0.27	0.056	12	0	*	0	1	0.00	9.7E-03			
Atenolol	3640	0	1.25	30	4	38	4	37	10	0.29	9.6E-03	0.01	x	
Simvastatin	4610	2	1.58	9.6	9	57	4	13	2	0.09	9.2E-03			
Losartan	1150	0	0.40	1.9	E.	0	*	4	1	0.02	8.3E-03			<0.01
Orlistat	1110	0	0.38	1.92	9	0	*	4	2	0.02	7.9E-03			
Prednisolone	145	11	0.05	<2.3	27	0	*	30	1	0.01	6.5E-03			
Citalopram	988	1	0.34	6.5	E.	0	*	12	1	0.04	6.3E-03			
Tramadol	4820	4	1.65	64	25	23	4	30	28	0.38	6.0E-03		x	<0.01
Methadone	637	1	0.22	10.6	11	0	*	28	29	0.06	5.8E-03			
Gliclazide	3050	2	1.05	2	E.	0	*	1	1	0.01	5.2E-03			
Glipizide	28.7	0	0.01	0.24	E.	0	*	10	1	0.00	4.1E-03			
Lymecycline	2160	0	0.74	45.4	12	0	*	25	2	0.19	4.1E-03			
Amisulpride	109	100	0.04	5.4	E.	0	*	50	2	0.02	3.5E-03			
Hydroxychloroquine sulphate	887	0	0.30	2.72	12	0	*	3	2	0.01	3.4E-03			
Benzydamine hydrochloride	20.8	23	0.01	2.3	E.	0	*	100	†	0.01	3.1E-03			
Pravastatin	188	0	0.06	1.8	4	57	4	20	1	0.01	3.1E-03			
Magnesium hydroxide	931	16	0.32	100	30	0	*	100	*	0.32	3.0E-03			
Omeprazole	2530	3	0.87	3	E.	9	4	1	2	0.01	2.6E-03			<0.01
Metoclopramide	88.9	8	0.03	3.8	E.	0	*	30	2	0.01	2.4E-03			
Felodipine	30.6	0	0.01	0.05	9	0	*	1	1	0.00	2.1E-03			
Dihydrocodeine tartrate	2740	3	0.94	108.9	E.	0	*	22	2	0.21	1.9E-03			
Clozapine	355	100	0.12	0.71	9	0	*	1	1	0.00	1.7E-03			
Mirtazapine	147	0	0.05	32	9	0	*	75	2	0.04	1.2E-03			
Fluticasone	72.1	100	0.02	0.48	25	0	*	2	31	0.00	1.0E-03			0.01
Bisoprolol fumarate	169	1	0.06	35.6	9	0	*	55	10	0.03	9.0E-04			
Diclofenac	3180	4	1.09	9.7	4	29	4	1	10	0.01	8.0E-04	0.01	x	
Diazepam	171	3	0.06	2	4	14	4	3	10	0.00	7.6E-04			0.04
Nicotine	42.0	0	0.01	2.4	E.	0	*	12	10	0.00	7.2E-04			
Rosuvastatin	66.2	0	0.02	1.8	9	0	*	5	2	0.00	6.3E-04			
Sodium valproate	3960	2	1.36	160	9	0	*	7	2	0.10	6.0E-04	0		
Loratadine	76.9	0	0.03	0.382	9	15	4	1	1	0.00	5.9E-04			
Doxazosin	69.9	0	0.02	2.3	9	0	*	5	2	0.00	5.2E-04			
Aspirin	11100	3	3.80	61	32	90	4	8	10	0.03	5.0E-04	0.01		1
Baclofen	103	5	0.04	53.3	E.	0	*	70	2	0.02	4.6E-04			
Quetiapine	194	8	0.07	10	9	0	*	5	2	0.00	3.3E-04			
Salbutamol	814	34	0.28	240	19	61	4	64	2	0.07	2.9E-04			
Zopiclone	85.6	3	0.03	5.1	E.	0	*	5	2	0.00	2.9E-04			
Piroxicam	38.4	0	0.01	2.6	E.	0	*	5	2	0.00	2.5E-04			
Lansoprazole	1320	2	0.45	18	25	0	*	1	33	0.00	2.5E-04			<0.01
Trazodone	835	66	0.29	14.2	E.	0	*	1	1	0.00	2.0E-04			
Chlorhexidine gluconate	1490	83	0.51	2622	E.	0	*	100	†	0.51	1.9E-04			
Dipyridamole	3830	5	1.32	356	E.	0	*	5	2	0.07	1.9E-04			
Cetirizine	211	0	0.07	278	34	0	*	60	2	0.04	1.6E-04			<0.01
Amitriptyline	1350	0	0.47	2.5	9	96	4	2	1	0.00	1.5E-04			1.29

Pharmaceutical	Total cons. [kg]	Hosp. contr. [%]	PEC [u] [µg/l]	PNEC [µg/l]	Ref. #	Remov. [%]	Ref. #**	Excr. [%]	Ref. #	PEC refined [µg/l]	RQ	Reference RQs Jones	Hilton	Webb
Candesartan cilexetil	157	0	0.05	100	9	0	*	26	2	0.01	1.4E-04			
Betamethasone	15.1	0	0.01	1.9	9	0	*	5	2	0.00	1.4E-04			
Morphine	114	12	0.04	32	12	0	*	10	2	0.00	1.2E-04			
Bendroflumethiazide	234	1	0.08	26	E.	91	4	30	2	0.00	8.4E-05		x	
Clavulanic acid	202	100	0.07	332.7	E.	0	*	40	2	0.03	8.4E-05			
Prochlorperazine	48.3	0	0.02	2.4	E.	0	*	1	2	0.00	6.9E-05			
Cyclizine	44.1	100	0.02	2.5	E.	0	*	1	2	0.00	6.1E-05			
Ramipril	424	0	0.15	53	E.	0	*	2	2	0.00	5.5E-05			
Nitrazepam	27.4	0	0.01	9.5	E.	0	*	5	2	0.00	5.0E-05			
Lisinopril	617	0	0.21	4577	E.	0	*	90	2	0.19	4.2E-05			
Paroxetine	109	0	0.04	<2.5	9	91	4	2	1	0.00	3.6E-05			0.13
Temazepam	84.2	5	0.03	17.4	E.	0	*	2	2	0.00	3.3E-05			
Azathioprine	286	0	0.10	59.3	E.	0	*	2	2	0.00	3.3E-05			
Nicorandil	343	2	0.12	56	E.	0	*	1	2	0.00	2.1E-05			
Loperamide hydrochloride	21.4	4	0.01	52.3	9	0	*	10	2	0.00	1.4E-05			
Lamuvidine	72.4	100	0.02	320	9	>76	35	70	2	0.00	1.3E-05			
Enalapril maleate	207	0	0.07	346	19	69	4	20	10	0.00	1.3E-05			
Ribavirin	196	100	0.07	72	9	97	35	40	2	0.00	1.1E-05			
Lidocaine	66.4	100	0.02	106	9	0	*	5	10	0.00	1.1E-05			
Gabapentin	10800	4	3.70	24347.1	E.	93	4	100	2	0.26	1.1E-05			<0.01
Perindopril	122	0	0.04	>990	34	0	*	12	2	0.01	5.1E-06			<0.01
Aciclovir	151	100	0.05	200	9	97	35	5	36	0.00	3.9E-07			
Finasteride	42.8	0	0.01	20	34	0	*	0	2	0.00	3.7E-07			<0.01
Carbocisteine	4320	8	1.48	1008474	E.	0	*	23	37	0.34	3.4E-07			
Lactulose	202000	12	69.23	6564894	E.	0	*	3	2	2.08	3.2E-07			
Hydrocortisone	51.6	0	0.02	565	E.	0	*	1	10	0.00	3.1E-07			
Isosorbide mononitrate	707	0	0.24	75474	E.	0	*	2	2	0.00	6.4E-08			
Domperidone	209	13	0.07	12000	38	0	*	1	2	0.00	6.0E-08			
Aluminium hydroxide	1080	20	0.37	∞	30	0	*	100	*	0.37	0.0E+00			
Codeine	7440	4	2.56	0.06	E.	68	4	0	2	0.00	0.0E+00		x	
Mebeverine hydrochloride	2500	0	0.86	27	E.	0	*	0	1	0.00	0.0E+00	0.74	x	
Levonorgestrel	3.51	9	0.00	<0.00008	39	0	*	0	1	0.00	0.0E+00			
Warfarin	98.8	2	0.03	12	19	0	*	0	2	0.00	0.0E+00			<0.01
Norethisterone	23.1	0	0.01	0.6	19	0	*	0	1	0.00	0.0E+00		x	
Atorvastatin	1860	0	0.64	0.13	12	0	*	0	2	0.00	0.0E+00			
Budesonide	25.7	100	0.01	8.6	9	0	*	0	2	0.00	0.0E+00			<0.19

* Indicates lack of data, precautionary value used; ** From [4], mean values were used; † Not ingested; †† Author's estimate; [u] unrefined; E. Ecosar; RQ = PEC/PNEC*Ecr*(1-R); RQs from Jones *et al.* (2002), Hilton (2003) and Webb (2000)

1. eMC: Datapharm Communications Ltd., electronic Medicines Compendium [Cited 17 Feb 2014]. Available from: www.medicines.org.uk
2. Ashley C, Currie A (Editors) 2009. The Renal Drug Handbook, 3rd edn, Radcliffe, Oxford, UK
3. Doroshyenko O, Fuhr U. 2009. Clinical pharmacokinetics and pharmacodynamics of solifenacin. *Clin Pharmacokinet* 48:281-302
4. Verlicchi P, Al Aukidy M, Zambello E. 2012. Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment—A review. *Sci Total Environ* 429:123-155
5. Kümmerer K, Henninger A. 2003. Promoting resistance by the emission of antibiotics from hospitals and households into effluent. *Clin Microbiol Infec* 9:1203-1214.
6. Woldegiorgis A, Wiklund P, Moe M. 2009. Retrospective environmental risk assessment of human pharmaceuticals in the Nordic countries 1997-2007. TemaNord 2009:587. Nordic Council of Ministers. Copenhagen, Denmark.
7. Halling-Sørensen B, Holten-Lützhøft H-C, Andersen HR and Ingerslev F. 2000. Environmental risk assessment of antibiotics: comparison of mecillinam, trimethoprim and ciprofloxacin. *J Antimicrob Chemother* 46:53S-58S.
8. De Souza SML, de Vasconcelos EC, Dziedzic M, de Oliveira CMR. 2009. Environmental risk assessment of antibiotics: An intensive care unit analysis. *Chemosphere* 77:962-967.
9. FASS Allmänhet. 2013. [Cited 17 Feb 2014]. Available from: http://www.fass.se/LIF/startpage?5

10. Lienert J, Güdel K, Escher B. 2007. Screening Method for Ecotoxicological Hazard Assessment of 42 Pharmaceuticals Considering Human Metabolism and Excretory Routes. *Environ Sci Technol* 41:4471-4478.
11. Escher BI, Baumgartner R, Koller M, Treyer K, Lienert J, McArdell CS. 2011. Environmental toxicology and risk assessment of pharmaceuticals from hospital wastewater. *Water Res* 45:75-92.
12. Grung M, Heimstad ES, Moe M, Schlabach M, Svenson A, Thomas K, Woldegiorgis A. 2007. Human and Veterinary Pharmaceuticals, Narcotics, and Personal Care Products in the Environment. TA-2325/2007. Norwegian Pollution Control Authority, Oslo, Norway
13. Runkel R, Chaplin M, Boost G, Segre E, Forchielli E. 1972. Absorption, distribution, metabolism, and excretion of naproxen in various laboratory animals and human subjects. *J Pharm Sci* 61:703-708.
14. Huber S, Remberger M, Goetsch A, Davanger K, Lennart K, Herze D, Schlabach M, Jörundsdóttir H, Vester J, Arnórsson M, Mortensen I, Schwartson R, Dam M. 2013. Pharmaceuticals and additives in personal care products as environmental pollutants: Faroe Islands, Iceland and Greenland. TemaNord 2013:541. Nordic Council of Ministers. Copenhagen, Denmark.
15. Valcárcel Y, Alfonso SG, Rodríguez-Gil JL, Gil A, Catalá M. 2011. Detection of pharmaceutically active compounds in the rivers and tap water of the Madrid Region (Spain) and potential ecotoxicological risk. *Chemosphere* 84:1336-1348.
16. Jain RT, Panda J, Srivastava A. 2011. Two formulations of Venlafaxin are bioequivalent when administered as open capsule mixed with applesauce to healthy subjects. Indian *Indian J Pharm Sc*i 73:510-516.
17. Huschek G, Hansen PD, Maurer HH, Krengel D, Kayser A. 2004. Environmental risk assessment of medicinal products for human use according to European Commission recommendations. *Environ Toxicol* 19:226-240.
18. Pentikäinen P, Neuvonen P, Penttilä A. 1979.Pharmacokinetics of metformin after intravenous and oral administration to man. *Eur J Clin Pharmacol* 16:195-202.
19. Carlsson C, Johansson A, Alvan G, Bergman K, Kühler T. 2006. Are pharmaceuticals potent environmental pollutants? Part I: Environmental risk assessments of selected active pharmaceutical ingredients. *Sci Total Environ* 364:67-87.
20. Jones OAH, Voulvoulis N, Lester JN. 2002. Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. *Water Res* 36:5013–5022.
21. Ferrari B, Paxéus N, Giudice RL, Pollio A, Garric J. 2003. Ecotoxicological impact of pharmaceuticals found in treated wastewaters: study of carbamazepine, clofibric acid, and diclofenac. *Ecotoxicol Environ Saf* 55:359-370.
22. McArdell CS, Kovalova L, Siegrist HR. 2011. Input and Elimination of Pharmaceuticals and Disinfectants from Hospital Wastewater. Final Report. EAWAG, Zürich, Switzerland.
23. Hembrock-Heger A, Bergmann A. 2007. Eintrag von Arzneimittel und deren Verhalb und Verbleib in der Umwelt. Fachbericht 2. Landesamt für Natur, Umwelt und Verbraucherschutz, Nordrhein-Westfalen, Recklinghausen, Germany.
24. Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ. 2009.The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. *Water Res* 43:363-380.
25. Webb S. 2000. Risk Assessment Approaches for Pharmaceuticals. *Proceedings*, International Seminar on Pharmaceuticals in the Environment. Brussels, Belgium, 9 March 2000.
26. Rimmer EM, Richens A. 1989. Interaction between Vigabatrin and Phenytoin. *Brit J Clin Pharmaco* 27:27S-33S.
27. DellaGreca M, Fiorentino A, Isidori M, Lavorgna M, Previtera L, Rubino M, Temussi F. 2004. Toxicity of prednisolone, dexamethasone and their photochemical derivatives on aquatic organisms. *Chemospere* 54:629-637.
28. Lintz W, Erlaçin S, Frankus E, Uragg H. 1981. Biotransformation of tramadol in man and animal (author's transl.) *Arznei-forschung* 31:1932-1943.
29. Lai FY, Ort C, Gartner C, Carter S, Prichard J, Kirkbride P, Bruno R, Hall W, Eaglesham G, Mueller JF. 2011. Refining the estimation of illicit drug consumptions from wastewater analysis: Co-analysis of prescription pharmaceuticals and uncertainty assessment. *Water Res* 45:4437-4448.
30. European Chemicals Agency. 2015. Registered Substances. Helsinki (Finland): ECHA. [cited 2015 September 24]. Available from: http://echa.europa.eu/information-on-chemicals/registered-substances.
31. Unbound Medicine 2000-2015. Davis' Drug Guide. [Cited 23 Feb 2015]. Available from: http://www.drugguide.com/ddo/view/Davis-Drug-Guide/109875/all/fluticasone_vilanterol__inhalation_ .
32. Stuer-Lauridsen F, Birkveda M, Hansen LP, Holten-Lützhøft HC, Halling-Sørensen B. 2000. Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. *Chemosphere* 40:783-793.
33. Delhotal Landes B, Petite J P, Flouvat B. 1995.Clinical Pharmacokinetics of Lansoprazole. *Clin Pharmacokinet* 28:458-470.
34. Prasse C, Schlüsener MP, Schulz R and Ternes T. 2010. Antiviral Drugs in Wastewater and Surface Waters: A New Pharmaceutical Class of Environmental Relevance? *Environ Sci Technol* 44:1728–1735.
35. Webb SE. ERA of Human Pharmaceuticals II - Aquatic Risk Characterisation. In: Kümmerer K (Editor). 2004. *Pharmaceuticals in the environment: sources, fate, effects and risks*. 1st ed, Springer-verlag, Berlin Heidelberg, Germany.
36. Jjemba PK. 2006. Excretion and ecotoxicity of pharmaceutical and personal care products in the environment. *Ecotoxicol Environ Saf* 63:113-130.
37. Gregory WL, James OF, Turner I, Meese CO, Idle JR. 1993. Re-evaluation of the metabolism of carbocisteine in a British white population. *Pharmacogenetics* 3:270-274.
38. Van de Steene J, Stove C P, Lambert WE. 2010. A field study on 8 pharmaceuticals and 1 pesticide in Belgium: Removal rates in waste water treatment plants and occurrence in surface water. *Sci Total Environ* 408:3448-3453.
39. Zeilinger J, Steger-Hartmann T, Maser E, Goller S, Vonk R, Länge R. 2009. Effects of Synthetic Gestagens on Fish Reproduction. *Environ Toxicol Chem* 28:2663-2670.