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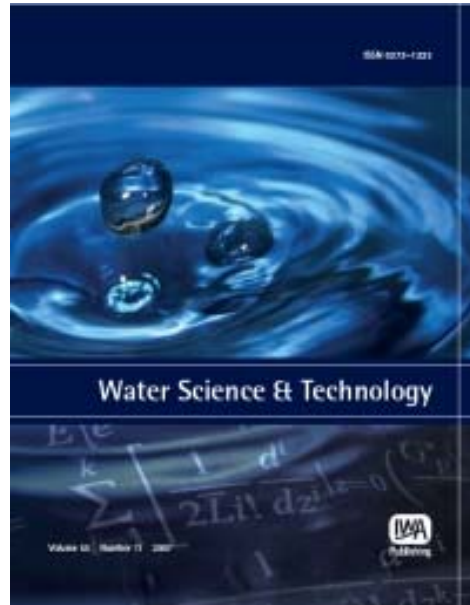
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Development of a common priority list of pharmaceuticals relevant for the water cycle

P. de Voogt, M.-L. Janex-Habibi, F. Sacher, L. Puijker and M. Mons

ABSTRACT

Pharmaceutically active compounds (PhACs), including prescription drugs, over-the-counter medications, drugs used in hospitals and veterinary drugs, have been found throughout the water cycle. A desk study was initiated by the Global Water Research Coalition to consolidate a uniform selection of such compounds in order to judge risks of PhACs for the water cycle. By identifying major existing prioritization efforts and evaluating the criteria they use, this study yields a representative and qualitative profile ('umbrella view') of priority pharmaceuticals based on an extensive set of criteria. This can then be used for further studies on analytical methods, occurrence, treatability and potential risks associated with exposure to PhACs in water supply, identifying compounds most likely to be encountered and that may have significant impact on human health. For practical reasons, the present study excludes veterinary drugs. The pragmatic approach adopted provides an efficient tool to manage risks related to pharmaceuticals and provides assistance for selecting compounds for future studies.

Key words | pharmaceuticals, priority setting

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INTRODUCTION

Pharmaceutically active compounds (PhACs) are a family of compounds that includes prescription drugs, over-the-counter medications, drugs used in hospitals and veterinary drugs. Numerous studies in Europe and the United States have shown that a wide variety of pharmaceuticals are present in wastewater effluents, surface waters, and ground-water (GWRC 2004). The large number of compounds reported in the literature makes it difficult to evaluate the credibility of findings and to assess the impact of all PhACs on the water cycle.

Several prioritization setting exercises for pharmaceutically active compounds have been and are currently being undertaken by regulatory bodies and research institutions in various countries. The criteria used in each of these efforts depend on the objectives of the body conducting the exercise.

The present desk study has been initiated by the Global Water Research Coalition (GWRC) to consolidate a

uniform selection of compounds in order to judge risks of PhACs for the water cycle. The approach used, rather than embarking upon a new priority setting effort, was to identify some major existing prioritization efforts in North America, Europe, Australia and East Asia, and evaluate criteria used in those prioritization exercises. The study will thus yield a representative and qualitative profile ('umbrella view') of priority pharmaceuticals based on an extensive set of criteria. The list of representative priority PhACs can be used for further studies on analytical methods, occurrence, treatability, and potential risks associated with exposure to PhACs in the water supply. The list will identify compounds that are most likely to be encountered in water supplies and that may have significant impact on human health. For practical reasons, the present study excludes veterinary drugs. Once the draft final list has been established, its use within the GWRC membership will ensure that research findings are reliable and comparable.

METHODOLOGY

Documentation from ongoing pharmaceuticals-prioritization activities were collected and additional information was submitted by a so called e-mail support group of experts related to the GWRC. It should be noted that the present study did not involve any new individual scoring of pharmaceuticals on particular criteria, as it made use of existing ranking documents only. Additional key references from the scientific literature were selected and screened for further underpinning of poorly represented criteria in the prioritization exercises. A total of 25 reports and references were used which had the prioritization of pharmaceuticals as key subject. The number of appearances of pharmaceuticals in the 25 base documents was scored.

Furthermore a list of criteria was established that gathered the criteria applied in the 25 base documents for selection or prioritization of pharmaceuticals. In total 17 different criteria were identified, most of them being used in several documents. The criteria employed in the base documents were subjected to expert judgement and evaluation by the project team members. Based on this judgement, seven criteria were regarded as being of special relevance for the GWRC members and selected as a basis for drawing up a second priority list. Subsequently, the initial list of pharmaceuticals (which was established by applying all criteria) was re-evaluated based on the selected seven criteria. Documents from the base set that did not use any of the final set of criteria were omitted and pharmaceuticals that did not score on these final criteria were deleted from the initial list. Finally the chemicals were

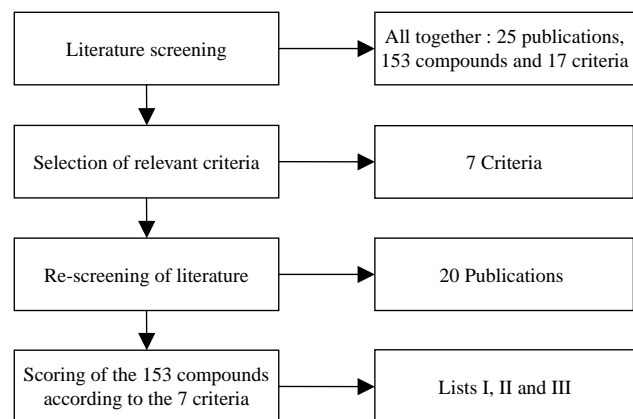


Figure 1 | Schematic representation of approach used.

ranked based on the number of fulfilled criteria. The approach is illustrated in Figure 1.

RESULTS AND CONCLUSIONS

Base documents

Twenty-five documents served as the base documents for this study. The documents are presented in the list of references. By using these twenty-five documents it was tried to cover the different approaches used in various countries (with special emphasis on countries represented within the GWRC) and by groups with different objectives and background. Although this set of base documents is not exhaustive, it represents an ‘average’ of approaches used in various countries and provides a good overview of criteria used in priority setting of pharmaceuticals.

A total of 153 pharmaceuticals were listed in the base documents. Twenty-four of these occurred in two priority lists, 16 pharmaceuticals appeared in 3 to 5 lists, and 19 appeared in more than 5 lists.

Rationale for criteria selection

The criteria used in the base documents are tabulated in Table 1. In total 17 criteria were mentioned in all base documents together. From these, seven criteria were selected for use in a second step (see Figure 1). Only scientific considerations were used for selection of criteria and especially those criteria were selected that were regarded as being of particular relevance for the GWRC members. The rationale for selection of criteria is also given in Table 1. Apart from the criteria used in the base documents, public interest and media coverage were discussed as other possible criteria (e.g. referring to HIV treatment, hard drugs, Viagra). From a scientific point of view, these criteria were judged as of less importance than the seven selected and thus no longer used for further evaluation. No further prioritization of the criteria selected was made, i.e. all seven criteria were considered as being equally important.

In addition to the selection of pharmaceuticals from the initial list according to the seven criteria, the antibacterial triclosan and the natural hormones 17 β -estradiol and

Table 1 | Criteria used in the base documents and rationale for priority setting of pharmaceuticals

Criteria used in the base documents	Criterion Nr.*	Criterion selected by expert judgement?	Reasoning
Regulation	1	Yes	Wastewater utilities and drinking water suppliers are obliged to fulfil any regulation and thus pharmaceuticals that are listed in any environmental Directive are of special relevance
Consumption/sales	2	Yes	Numbers on production and use are directly related to the probability of occurrence in the environment (as long as no special mechanism of elimination is active)
Therapeutic dose		No	The therapeutic dose was mentioned as a way of approaching PNEC, therefore it can be considered as redundant
Representativity of drug group/pharmacological target		No	From a scientific point of view there is no need for all different classes of pharmaceutical to be represented in the final priority list
Long term use forecast		No	For evaluation of the current situation long term use is not a helpful criterion. Furthermore, most of the forecast data exhibit rather high uncertainties and are thus not regarded to be a good criterion
Physicochemical properties	3	Yes	Physico-chemical properties (such as polarity, water solubility, chemical reactivity) determine the behaviour of pharmaceuticals in the environment as well as during wastewater treatment and drinking water treatment (sorption, degradation) and thus have a major impact on the relevance of a compound
Analytical feasibility		No	Analytical feasibility as such is not regarded as being a criterion for selection or prioritization. A pharmaceutical is not relevant because an analytical method is available. If a pharmaceutical is regarded as being relevant according to other criteria, analytical methods have to be developed in order to monitor its occurrence in the water cycle
Metabolism/excretion		No	For most of the compounds occurrence data give much better information about the relevance of a compound and thus the behaviour of a pharmaceutical in the human body is not regarded as a primary criterion
Degradability/persistence	6	Yes	Degradation of a compound during wastewater treatment or in the environment can significantly decrease the environmental relevance of a compound and thus this criterion is regarded as being relevant
Ability to build stable metabolites		No	The ability to build stable metabolites as such is not regarded as relevant criterion for selection of a pharmaceutical. If stable metabolites are formed, they might be selected if they fulfil other criteria
Resistance to treatment	7	Yes	Pharmaceuticals that are difficult to remove during treatment are of high relevance and thus resistance to (wastewater and drinking water) treatment is an important criterion
Toxicity (human)	4	Yes (combined with ecotoxicity)	Protection of the health of humans and wildlife is one of the major objectives of all GWRC members and consequently toxic compounds are of special relevance. At this stage it was decided not to distinguish between human and eco toxicity
Ecotoxicity	4	Yes (combined with human toxicity)	See above

Table 1 (continued)

Table 1 | (continued)

Criteria used in the base documents	Criterion Nr.*	Criterion selected by expert judgement?	Reasoning
Predicted environmental concentration (PEC)		No	The PEC is not selected because the information is already included in other criteria such as production/ consumption data and persistence. Furthermore, in most cases measured environmental concentrations give a more reliable description of the situation (if available)
Relative risk approach (PEC/PNEC)		No	The PEC/PNEC ratio was not selected because information about PEC values as well as PNEC data are already covered by other criteria
Occurrence in surface waters, groundwater, drinking water	5	Yes	Occurrence of a compound in the environment is one of the key criteria for its selection because if a compound is found in the environment there is a need for further activities (e.g. evaluation of its relevance or behaviour during treatment). At this stage, the different types of waters (wastewater, surface water, groundwater, drinking water,...) will not be weighted. However, if a compound is only found in the influent of a wastewater treatment plant but not in the effluent and not in other types of waters it will be regarded as less relevant
Occurrence in wastewater	5	Yes	see above

* The numbers do not correspond to any priority ranking.

estrone were deleted because the list should cover pharmaceuticals (and metabolites of pharmaceuticals) only.

As a consequence of the selection of criteria, several of the initial base documents could be omitted, viz. those that in their prioritization either had not used any of the seven criteria selected, or had not specified which criteria had been used. From the 25 base documents, five were thus omitted (California DHS 2006; Besse & Garric 2007; Grung *et al.* 2007; US EPA 2007; Kostich & Lazorchak 2008). The citations in the remaining documents were again evaluated. For each pharmaceutical the number of base documents where this particular pharmaceutical is selected was scored. In addition, for each pharmaceutical, the number of criteria (from a maximum set of seven) that had been used in the twenty remaining documents in which it was prioritized was then scored. The results are shown in Table 2.

Obviously, the more a pharmaceutical is cited in priority lists, the more likely it will have been evaluated on a larger number of criteria. However, compounds that have been prioritized in a single document that evaluated many of the seven criteria do show up occasionally. Examples of the latter are atorvastatin, risperidone, and simvastatin. Yet it is clear that a large overlap exists between the pharmaceuticals selected according to both scoring methods. Although a further weighting of the individual criteria may change the individual ranking, it appears that in further studies on pharmaceutically active compounds in relation to water supply (monitoring studies, treatment options) the focus should be given to those compounds that result from these two scorings.

It is perhaps important to realize that the 153 PhAC cited in the base documents do not include a single medication drug approved for fighting HIV. Apparently this group of PhAC has not been part of recent investigations or prioritization exercises yet, despite their increasing use in certain parts of the world.

Classification

Based on the scorings outlined above, different lists can be made, categorizing the pharmaceuticals in several classes:

Table 2 | Alphabetical list of PhACs with criteria met for each PhAC

Compound	Class	Regulation	Consumption	Physchem properties	Toxicity	Occurrence	Persistence	Resistance to treatment
Acetyl salicylic acid	II		x		x	x	x	
Amidotrizoic acid	II	x	x			x		
Amoxicillin	II		x		x	x	x	
Atenolol	I		x		x	x	x	x
Bezafibrate	I		x	x	x	x	x	
Carbamazepin	I	x	x	x	x	x	x	x
Cefalexin	III		x			x	x	
Cimetidine	III		x			x		x
Ciprofloxacin	I		x		x	x	x	x
Clarithromycin	II		x		x	x		
Clofibric acid	II		x	x		x	x	
Clotrimazole	III	x	x		x			
Codeine	II		x		x	x		x
Cyclophosphamide	II		x		x	x	x	
Diazepam	II		x	x	x	x		x
Diclofenac	I	x	x	x	x	x	x	x
Dilantin	III		x		x	x		x
Diltiazem	III		x			x		x
Doxycycline	III		x		x	x	x	
Enalapril	III		x		x	x		x
Erythromycin	I		x		x	x	x	x
Fluoxetine	III		x		x	x		x
Furosemide	II		x		x	x	x	
Gemfibrozil	I		x		x	x	x	x
Hydrochlorothiazide	II		x		x	x	x	
Ibuprofen	I		x	x	x	x	x	x
Iomeprol	III		x			x		
Iopamidol	III	x				x		
Iopromide	II		x	x		x		x
Lincomycin	II		x		x	x	x	x
Metformin	III		x		x			
Metoprolol	II		x			x	x	x
Naproxen	I		x		x	x	x	x
Norfluoxetine	III		x		x	x		x
Ofloxacin	II		x		x	x	x	
Oxazepam	III		x		x	x		x
Paracetamol	II		x		x	x	x	
Ranitidine	II		x		x	x	x	
Salbutamol	III		x		x	x	x	
Simvastatin β -hydroxy-acid	III		x		x	x		x
Sotalol	II		x		x	x		
Sulfamethoxazole	I	x	x	x	x	x	x	x
Trimethoprim	II		x		x	x		x
Valproic acid	III		x			x	x	

Class 1: high priority pharmaceuticals

Pharmaceuticals that are mentioned in five or more of the base documents cited, and that fulfil more than four of the seven criteria

Class 2: priority pharmaceuticals

Pharmaceuticals that are mentioned in more than two of the base documents cited, and that fulfil more than two criteria.

Table 3 | Class 1: High priority pharmaceuticals (10 pharmaceuticals)

Name	Number of occurrences on lists	Type of criterion*	Number of criteria	Classification
Carbamazepin	15	1,2,3,4,5,6,7	7	Class I
Sulfamethoxazole	13	1,2,3,4,5,6,7	7	
Diclofenac	12	1,2,3,4,5,6,7	7	
Ibuprofen	11	2,3,4,5,6,7	6	
Naproxen	8	2,4,5,6,7	5	
Bezafibrate	7	2,3,4,5,6	5	
Atenolol	6	2,4,5,6,7	5	
Ciprofloxacin	6	2,4,5,6,7	5	
Erythromycin	6	2,4,5,6,7	5	
Gemfibrozil	5	2,4,5,6,7	5	

*Numbering according to Table 1, see also Table 2

Table 4 | Class 2: Priority pharmaceuticals (18 pharmaceuticals)

Name	Number of occurrences on lists	Type of criterion*	Number of criteria	Classification
Paracetamol	7	2,4,5,6	4	Class II
Acetyl salicylic acid	5	2,4,5,6	4	
Clofibric acid	5	2,3,5,6	4	
Cyclophosphamide	5	2,4,5,6	4	
Furosemide	5	2,4,5,6	4	
Iopromide	5	2,3,5,7	4	
Amidotrizoic acid	5	1,2,5	3	
Diazepam	4	2,3,4,5,7	5	
Lincomycin	4	2,4,5,6,7	5	
Amoxicillin	4	2,4,5,6	4	
(hydro)chlorothiazide	4	2,4,5,6	4	
Metoprolol	4	2,5,6,7	4	
Ranitidine	4	2,4,5,6	4	
Trimethoprim	4	2,4,5,7	4	
Sotalol	4	2,4,5	3	
Codeine	3	2,4,5,7	4	
Ofloxacin	3	2,4,5,6	4	
Clarithromycin	3	2,4,5	3	

*Numbering according to Table 1, see also Table 2

Table 5 | Class 3: Lower priority pharmaceuticals (16 pharmaceuticals)

Name	Number of occurrences on lists	Type of criterion*	Number of criteria	Classification
Iomeprol	3	2,5	2	Class III
Iopamidol	3	1,5	2	
Metformin	3	2,4	2	
Dilantin	2	2,4,5,7	4	
Doxycycline	2	2,4,5,6	4	
Enalapril	2	2,4,5,7	4	
Fluoxetine	2	2,4,5,7	4	
Norfluoxetin	2	2,4,5,7	4	
Oxazepam	2	2,4,5,7	4	
Salbutamol	2	2,4,5,6	4	
Simvastatin β -hydroxy-acid	2	2,4,5,7	4	
Cefalexin	2	2,5,6	3	
Cimetidine	2	2,5,7	3	
Clotrimazole	2	1,2,4	3	
Diltiazem	2	2,5,7	3	
Valproic acid	2	2,5,6	3	

*Numbering according to Table 1, see also Table 2

Class 3: lower priority pharmaceuticals

Pharmaceuticals that are mentioned in two documents of the base documents cited, and fulfil two or more criteria

The three classes are presented in Tables 3, 4 and 5, respectively, together with the citation frequencies and number and type of criteria relevant.

CONCLUSIONS

A short list of 10 compounds was extracted from the literature review work on prioritisation. These compounds represent the *minimum* that should be considered in any study on pharmaceuticals in water management. Lists II and III represent secondary targets, but nevertheless include several pharmaceuticals that are well known from many monitoring studies. Which lists are to be used in further research, will depend on the goal of the individual research projects.

The lists derived in this study are only based on compounds already mentioned in the literature. As a consequence they will be time related. This means that

this list will need to be updated depending on the outcomes of future studies (especially given the increasing occurrence dataset). Attention for 'new' compounds therefore will remain relevant.

In the current study equal weight was given to all criteria selected. It can be discussed whether certain criteria should have more weight or not. This might result in small changes between the lists, but it is expected that the current lists still give a good view of the relevant compounds.

Despite those limitations, which are inherent to this type of exercise, the pragmatic approach that has been adopted in this work provides an efficient tool to manage the risks related to pharmaceuticals in the drinking water industry.

This report provides assistance for selecting pharmaceuticals for future studies. It will enable harmonization of the selection of compounds to be studied and thereby contribute to comparability of results worldwide.

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