Global Water Research Coalition

Development of an International Priority List of Pharmaceuticals Relevant for the Water Cycle

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Global Water Research Coalition

Global cooperation for the generation of water knowledge

GWRC is a non-profit organization that serves as a collaborative mechanism for water research. The benefits that the GWRC offers its members are water research information and knowledge. The Coalition focuses on water supply and wastewater issues and renewable water resources: the urban water cycle.

The members of the GWRC are: the Awwa Research Foundation (US), CRC Water Quality and Treatment (Australia), EAWAG (Switzerland), Kiwa Water Research (Netherlands), PUB (Singapore), Suez Environment – CIRSEE (France), Stowa - Foundation for Applied Water Research (Netherlands), DVGW-TZW Water Technology Center (Germany), UK Water Industry Research (UK), Veolia- Anjou Recherché (France), Water Environment Research Foundation (US), Water Research Commission (South Africa), WaterReuse Foundation (US), and the Water Services Association of Australia.

These organizations have national research programs addressing different parts of the water cycle. They provide the impetus, credibility, and funding for the GWRC. Each member brings a unique set of skills and knowledge to the Coalition. Through its member organizations GWRC represents the interests and needs of 500 million consumers.

GWRC was officially formed in April 2002 with the signing of a partnership agreement at the International Water Association 3rd World Water Congress in Melbourne. A partnership agreement was signed with the U.S. Environmental Protection Agency in July 2003. GWRC is affiliated with the International Water Association (IWA).

Disclaimer

This study was jointly funded by GWRC members. GWRC and its members assume no responsibility for the content of the research study reported in this publication or for the opinion or statements of fact expressed in the report. The mention of trade names for commercial products does not represent or imply the approval or endorsement of GWRC and its members. This report is presented solely for informational purposes.

Preface

The issue of pharmaceuticals in the water cycle is part of the research agenda of most of the members of the Global Water Research Coalition (GWRC). It is on the priority list of the GWRC.
In December 2003 a Research Strategy Workshop was held in Nieuwegein, the Netherlands (GWRC, 2004b). During this workshop the members of the Global Water Research Coalition agreed that the first step of the research agenda should be to consolidate a list of compounds that can be used to judge risks for the water cycle (i.e. environmental and health risks) and to be able to compare results.

This report was prepared by Pim de Voogt (Kiwa Water Research), Frank Sacher (TZW), Marie-Laure Janex-Habibi, Auguste Bruchet (both CIRSEE), Leo Puijker and Margreet Mons (both Kiwa Water Research).
Quality assurance was conducted by the members of the GWRC project steering group : Janet Khiari, Gordon Wheale and Frans Schulting.
Valuable information was received from the e-mail support group consisting of Joshua Dickinson (WRF), Susan Glassmeyer (EPA), Francine Manciot (Anjou), Annatjie Moolman (WRC), Gayle Newcombe (CRC WQT), Bert Palsma (STOWA), Aik Num Puah (PUB), Mitchell Kostich (US EPA), Margaret Stewart (WERF), John Fawell (Fawell Consult) and Shane Snyder (Southern Nevada Water Authority).

Summary

Numerous studies have shown that a wide variety of pharmaceutically active compounds (PhACs) are present in wastewater effluents, surface waters, and ground waters (GWRC, 2004a). The large number of compounds reported makes it difficult to evaluate the impact of all PhACs on the water cycle. The Global Water Research Coalition identified that the first step of the research agenda should be to consolidate a list of compounds that can be used to judge risks for the water cycle. The objective of this desk study was to develop a list of representative priority PhACs that can be used for further studies on analytical methods, occurrence, treatability, and potential risks associated with exposure to PhACs in the water supply.

Major existing prioritization efforts in USA, Europe, Australia and East Asia were identified and criteria used in those prioritization exercises evaluated. A total of 25 reports were used which had the prioritization of PhACs as key subject. The total number of pharmaceuticals thus reviewed was 153 compounds. The number of appearances of PhACs in the 25 base documents was scored. In total 17 different criteria were identified. These were subjected to expert judgement and evaluation. Seven criteria were regarded as being of special relevance and selected for drawing up a priority list.

The number of criteria relevant for a chemical was scored, and a ranking based on number of fulfilled criteria was made. The ranked PhACs are grouped in three classes:

- Class I (high priority) involves PhACs that are mentioned in five or more of the base documents cited, and that fulfil more than four of the seven criteria.
- Class II (medium) contains PhACs that are mentioned in more than two of the base documents cited, and that fulfil more than two criteria.
- Finally, Class III (low) PhACs are mentioned in two documents of the base documents cited, and fulfil two or more of the criteria selected.

The final result of the classification of the reviewed pharmaceuticals into these three classes is: 10 (high), 18 (medium) and 16 (low) priority PhACs.

Contents

1 Introduction

Pharmaceutically active compounds (PhACs) are a family of compounds that includes prescription drugs, over-the-counter medications, drugs used in hospitals (such as X-ray contrast chemicals) 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 waters (GWRC, 2004a). The very large number of compounds reported in the literature makes it difficult to interpret findings and to assess the impact of all PhACs on the water cycle. During a GWRC Research Strategy Workshop the members of the Global Water Research Coalition agreed that the first step of the research agenda should be to consolidate a list of compounds that can be used to judge risks for the water cycle (i.e. environmental and health risks) and to be able to compare results (GWRC, 2004b).

Therefore a project was started, the objective of which is to develop a GWRC list of representative priority PhACs that can be used for further studies on analytical methods, occurrence in the aquatic environment and water resources used for drinking water production, treatability, and potential risks associated with exposure to PhACs in the water supply. The list will identify compounds that are most likely found in water supplies and that may have significant impacts on human and environmental health. The use of such a list within the GWRC membership will ensure that future research findings are reliable and comparable. The list will help guide the membership in follow up studies that relate to monitoring, development of analytical methods, toxicity screening, identifying hot spots of emissions, and evaluation of treatment processes.

2 Approach

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 approach used in the present study, 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. 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.

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

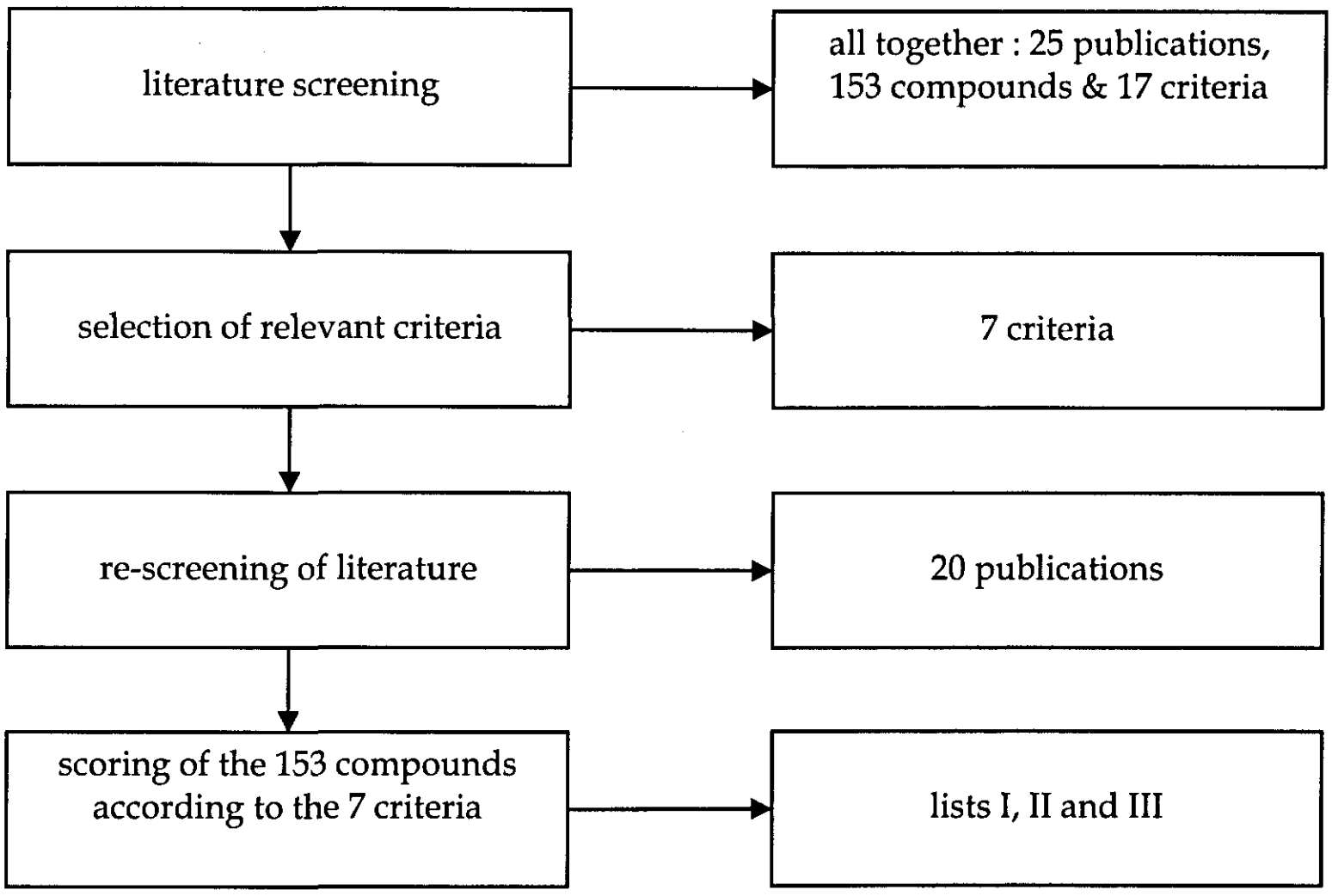

Figure 1. Schematic representation of approach used

3 Results and discussion

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 (see Annex 1). 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. The pharmaceuticals cited in two or more priority documents are presented in Table 1.

Rationale for criteria selection
The criteria used in the base documents are tabulated in Table 2. 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 details for selection of criteria are also given in Table 2.

In addition to 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 17ß-estradiol and 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 (Besse and Garric, 2007; California DHS, 2005; US EPA, 2007; Grung et al. 2007; Kostich and Lazorchak, 2007). The citations in the remaining documents were again evaluated. Figure 2 shows the corresponding ranking of pharmaceuticals. For each pharmaceutical the number of publications where this particular pharmaceutical is selected is presented (pharmaceuticals cited twice or more shown).

Table 1. Pharmaceuticals cited twice or more in the 25 base documents

Category	>5x cited	3-5 x cited	2 x cited
Antibiotics	Sulfamethoxazole Erythromycin Ciprofloxacin Amoxycillin Trimethoprim	Lincomycin Clarithomycin Ofloxacin	Tetracycline Doxycycline Cefalexin Salbutamol
Analgesics	Acetyl salicylic acid Diclofenac Ibuprofen Naproxen Paracetamol	Ketoprofen Codeine	Mefenamic acid
X-ray contrast media	Iopromide	Amidotrizoic acid Iomeprol	Iohexol Iopamidol Ioxitalamic acid
Lipid regulators	Bezafibrate Clofibric acid Gemfibrozil	Atorvastatin	Simvastatin
Anti epileptics	Carbamazepin		Valproic acid Primidon Dilantin
Anticonceptiva	Ethinyl-estradiol		
Beta blockers	Atenolol	Metoprolol Sotalol Propranolol	
Chemotherapy/anticancer	Cyclophosphamide		Fluorouracil Ifosfamide
Anti hypertension			Diltiazem Naftidrofuryl Enalapril
Tranquilizer Antidepressant		Diazepam Fluoxetine	Oxazepam Sertraline
Antifungal			Clotrimazole
Stimulant		Caffeine	
Diuretic	Furosemide	Chlorothiazide	
Ulcer treatment		Ranitidine	Cimetidine
Anti diabetic		Metformin	
Metabolites			Fenofibric acid Norfluoxetin β-hydroxy-acid derivative of simvastatin
Antihypertonic agent			Verapamil
Total number	19	17	25

Table 2. Criteria used in the base documents for priority setting of pharmaceuticals

Criteria used in the base documents	Criterion Nr.[a]	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.

Table 2 (*continued*) **Criteria used in the base documents**	**Criterion Nr.**[a]	**Criterion selected by expert judgement?**	**Reasoning**
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.
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

[a] *the numbers do not correspond to any priority ranking*

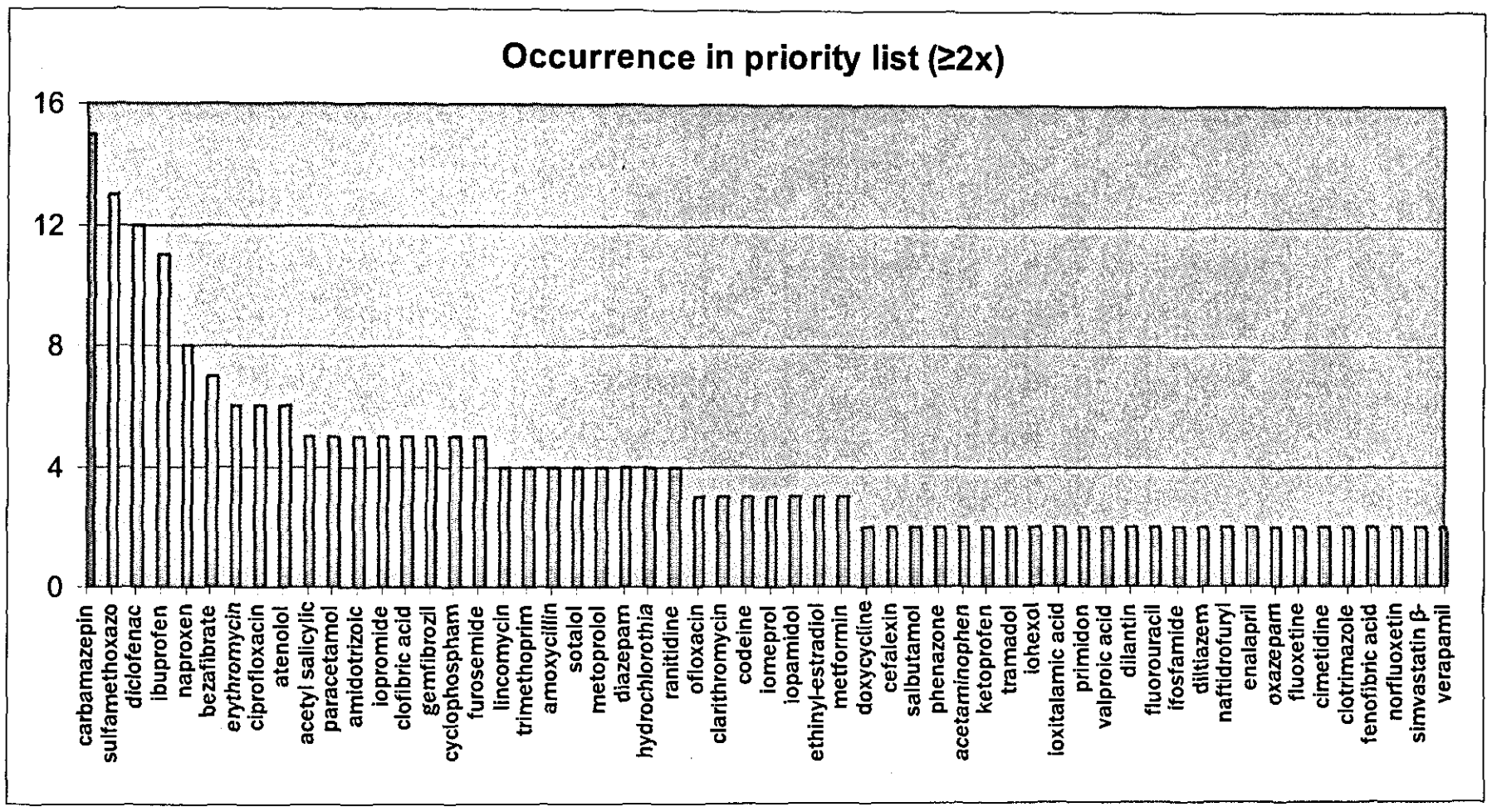

Figure 2. *Ranking of pharmaceuticals based on number of citations in prioritization documents that included the seven criteria selected*

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 when equal weighting of criteria is applied are shown in Figure 3.

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 may show up in Figure 3, whereas they may not appear in Figure 2. Examples of the latter are atorvastatin, risperidone, and simvastatin. Yet it is clear that a large overlap exists between the pharmaceuticals in Figures 2 and 3, respectively. 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 mentioned in these two figures.

It is perhaps important to realize that the 153 PhAC listed in Annex 1 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.

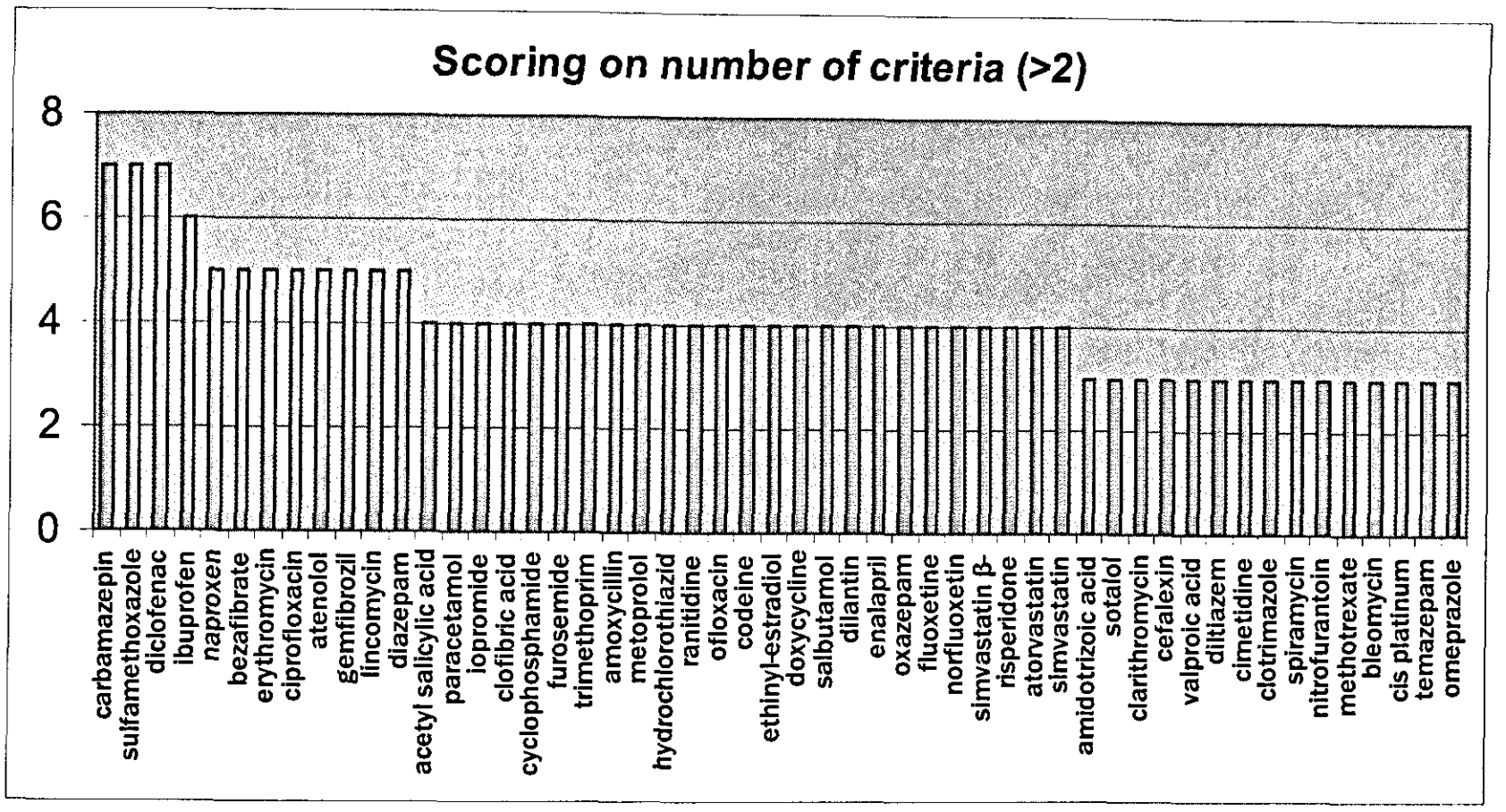

Figure 3. *Pharmaceuticals ranked according to number of criteria applied for their prioritization*

Classification

Based on Figures 2 and 3, different lists can be made, categorizing the pharmaceuticals in several classes.

Class I: 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 II: Priority pharmaceuticals

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

Class III: Lower priority pharmaceuticals

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

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

Table 3. Class I: high priority pharmaceuticals (10 pharmaceuticals)

Name	Number of occurrences on lists	Type of criterion[1]	Number of criteria	Classification
carbamazepin	15	1,2,3,4,5,6,7	7	
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	Class I
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	

[1] numbering according to Table 2, see also Annex 2

Table 4. Class II: priority pharmaceuticals (18 pharmaceuticals)

Name	Number of occurrences on lists	Type of criterion[1]	Number of criteria	Classification
paracetamol	7	2,4,5,6	4	
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	Class II
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	

[1] numbering according to Table 2, see also Annex 2

Table 5. Class III: Lower priority pharmaceuticals (16 pharmaceuticals)

Name	Number of occurrences on lists	Type of criterion[1]	Number of criteria	Classification
iomeprol	3	2,5	2	
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	Class III
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	

[1] numbering according to Table 2, see also Annex 2

4 Conclusions

A short list of 10 compounds (list I) was extracted from the literature review work on prioritisation (see also table 6). 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 results 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.

Table 6. Pharmaceuticals cited twice or more in the 25 base documents and their categorisation in classes.

Category	>5x cited	3-5 x cited	2 x cited
Antibiotics	Sulfamethoxazole	Lincomycin	Tetracycline
	Erythromycin	Clarithomycin	Doxycycline
	Ciprofloxacin	Ofloxacin	Cefalexin
	Amoxicillin		Salbutamol
	Trimethoprim		
Analgesics	Acetyl salicylic acid	Ketoprofen	Mefenamic acid
	Diclofenac	Codeine	
	Ibuprofen		
	Naproxen		
	Paracetamol		
X-ray contrast media	Iopromide	Amidotrizoic acid	Iohexol
		Iomeprol	Iopamidol
			Ioxitalamic acid
Lipid regulators	Bezafibrate	Atorvastatin	Simvastatin
	Clofibric acid		
	Gemfibrozil		
Antiepileptics	Carbamazepin		Valproic acid
			Primidon
			Dilantin
Anti-conceptiva	Ethinyl-estradiol		
Beta blockers	Atenolol	Metoprolol	
		Sotalol	
		Propranolol	
Chemotherapy/anticancer	Cyclophosphamide		Fluorouracil
			Ifosfamide
Anti hypertension			Diltiazem
			Naftidrofuryl
			Enalapril
Tranquilizer		Diazepam	Oxazepam
Antidepressant		Fluoxetine	Sertraline
Antifungal			Clotrimazole
Stimulant		Caffeine	
Diuretic	Furosemide		
		Chlorothiazide	
Ulcer treatment		Ranitidine	Cimetidine
Anti diabetic		Metformin	
Metabolites			Fenofibric acid
			Norfluoxetin
			β-hydroxy-acid derivative of simvastatin
Antihypertonic agent			Verapamil
Total number	19	17	25

red = class I, orange = class II, yellow = class III

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ANNEX 1. Alphabetical list of pharmaceuticals evaluated in this study

acetaminophen
acetyl salicylic acid
acetylsulfamethoxazole
allopurinol
amidotrizoic acid
aminophylline
amiodarone
amitriptyline
amoxycillin
atenolol
atorvastatin (lipitor)
azithromycin
beclometasone
bendroflumethiazide
bezafibrate
bleomycin
caffein
carbamazepin
carboxy-ibuprofen
cefaclor
cefalexin
cefuroxim
chlormadinone
chlorothiazide
chlorphenamine
cimetidine
ciprofloxacin
cis platinum
clarithromycin
clavulanic acid
clofibric acid
clotrimazole
codeine
cotinine
cyamemazine
cyclophosphamide
demethyltramadol
desmethylvenlafaxine
dextropropoxyphene
diazepam
diclofenac
dihydro-nifedipine
dilantin
diltiazem
diosmetin
diphenhydramine
doxycycline
enalapril
erythromycin
estradiol
estrone
ethinyl-estradiol
etoposide
fenofibrate
fenofibric acid
flucloxacillin
fluorouracil
fluoxetine
fosfomycine
furosemide
gemfibrozil
gliclazide
hydrocortisone
2-hydroxy-atorvastatin
4-hydroxy-atorvastatin
hydroxycarbamide
14-hydroxyclarithromycine
hydroxy-ibuprofen
hydroxy-metronidazole
β-hydroxy-acid derivative of simvastatin
ibuprofen
ifosfamide
imatinib
indometacin
iodinated contast media
iodixanol
iohexol
iomeprol
iopamidol
iopromide
iotalamic acid
ioxitalamic acid
ketoprofen
lactulose
lidocaine
lincomycin
lofepramine
losartan
mebeverine
meclobemide
mefenamic acid
meprobamate
metamizol
metformin
methadon
methotrexate
methyldopa
metoprolol
metronidazol
morphine
naftidrofuryl
naproxen
nitrofurantoin
norethindrone
norethisterone
norfloxacin
norfluoxetin
norfluoxetine
ofloxacin
omeprazole
oxazepam
oxytetracycline
paracetamol =acetaminophen
pentaerythrityltetra nitrate
pentoxifyllin
perindoprilate
phenazone
phenoxymethyl penicillin
phenytoin
pravastatin
prednisolone
prilocain
primidon
pristinamycin
procyclidine
promethazine
propranolol
propyphenazon
quinine
ranitidine
risperidone
roxithromycin
salbutamol
sertraline
simvastatin
sotalol
spiramycin
sulfadimethoxine
sulfamethazine
sulfamethoxazole
sulfathiazole
sulphasalazine
tamoxifen
temazepam
terbinafine
tetracycline
theophylline
thioridazine
tramadol
triclosan
trimethoprim
valproic acid
verapamil

ANNEX 2. Alphabetical list of PhACs from Classes I-III and 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		
amoxycillin	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
norfluoxetin	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	