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Programme

KNAPPE

Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters

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The deliverable authors are responsible for the content

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1. Introduction

For several years the presence of pharmaceutical products (PPs) has been investigated in various aqueous matrices such as raw sewage (STPi), sewage treatment plant effluents (STPe) [59, 89, 109], surface water (SW) [31], bank filtrate (BF) [46] groundwater (GW), drinking water (TW) [25] and marine water (MW)[20, 23]. Recent reports have shown the presence of a large variety of PPs in the effluent from STP's and surface waters, with concentrations up to several $\mu\text{g/L}$ [16]. More than 150 PPs have been detected in various environmental matrices [89]. This is due to the development and the continuous improvement of analytical techniques. The majority of the pharmaceuticals enters municipal STP's via domestic and hospital sewages or through industrial discharges. The compounds most frequently detected in STP's are antibiotics, antiepileptics, antiphogistics, X-ray contrast media, lipid regulators betablockers and tranquillizers [VI]. These compounds vary strongly in their chemical structure and their physico-chemical properties [VI]. Considerable effort is being made in the development of analytical techniques for the determination of PPs in complex matrices (including wastewaters and sludge) and in the assessment of their environmental behaviour (sorption, biodegradability).

The aim of this study is to evaluate and to interconnect results from several data base(s) and current knowledge (scientific papers, national and international project, reports from national water management organisations ...), in order to establish a list of PPs most relevant in terms of exposure in the aquatic environment.

This list will then be used, together with output from WP2 and WP4, to develop a classification system, to prioritize the environmental risks of PPs, thus supporting water managers, health authorities and especially panels involved in the establishment of river basin management plans and strategies to minimize point and diffuse pollutions of water.

The environmental relevance of PPs found in rivers and streams is another open question. The establishment of a list of main PPs detected in European surface water ("exposure") will be used together with ecotoxicity evaluation (WP4) to extract those PPs and metabolites with the highest potential do pose risks to the environment. Thus, it is foreseen to identify PPs of most concern (from WP4), which should be integrated in future monitoring programs.

2. Revision of literature on PPs

The first major task within WP 1 and subject of this deliverable was the preparation of a list with PPs which are administered and sold in European countries in high quantities, are detected in the aquatic environment or might be known to cause a high ecotoxic risk. Therefore, national and international literature regarding these topics were evaluated and crucial results were summarised in an excel data file. The data file contains data on consumption, physico-chemical properties, pharmacokinetic properties and environmental fate of PPs. In order to facilitate the PP occurrence, data was included as mean, maximum, median, 90-percentiles for STP influents, STP effluents, surface water, bank filtrates, groundwater, tap water and marine/coastal waters.

Until now, the content evaluation of several databases were considered (e.g. SciFinder Scholar [I], Clarke's Analysis of Drugs and Poisons; [II], Hazardous Substances Data Bank (HSDB) of the Toxicology data network [III], McGraw-Hill AccessMedicine [IV]). Additionally, more than 2500 international scientific papers were reviewed concerning keywords such as: pharmaceuticals, environment, water, bank filtrate, groundwater and sewage treatment plant from the years 1998 to 2007. Primarily the list is based on the annual consumption data of pharmaceuticals in the EU, and their occurrence in scientific communication and national databases. Data on occurrence was extracted from a total of 112 scientific papers and national report (Annex).

All data on pharmaceutical residues found in the reviewed literature concerning consumption data or measurements in the aquatic environment were included into the list. National consumption data was contributed by the project partners from the respective countries.

Some pharmaceutical products were excluded, e.g. caffeine and quinine. These substances are widely used as additives in soft drinks, as for quinine in concentrations of up to 85 mg/L in "Tonic-Water". Their impact on the aquatic environment due to their application in pharmaceutical products can be neglected. As well theophyllin is used in soft-drinks and occurs also naturally at low concentrations in tea and chocolate. Same consideration counts holds true for theophyllin as for the exclusion of caffeine and quinine from the list, but this PP is not used in a similar amount in soft-drinks. The impacts of theophyllin as PP in the environment can not be estimated in the moment. Therefore, theophyllin was initially included into the list and might be excluded later if more data about consumption as PP and food additive is available. Natural hormones were also excluded from the list since these substances are naturally excreted by mammals (e.g. humans). Elimination data from STPs for

17 α -ethinylestradiol (EE2) with concentrations in STP influent and effluents are covered by the work within WP 2. Since most today's analytical methods for the determination of EE2 in other aqueous matrices (e.g. surface water, bank filtrate, groundwater, tap water and marine/coastal water) do not prove to be reliable at the very low environmental pg/L-levels, EE2 was totally excluded from the data list. It has to be stated, that the availability of occurrence data for pharmaceutical products in drinking water is very limited. In part, this applies also for marine waters. In general, for tap water and marine water analytical procedure have to be improved or developed to enhance the determination of to PPs in the picogramm per liter range.

Consumption data

The consumption data are based mainly on published data for Germany [104], France and UK [111, 112], since for many of the countries no data are available. French data was provided from the AFFSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé); for 2004 the AFFSPAPS data (top 100 products most consumed, sales numbers) were recalculated to obtain kg/year by Besse and Garric 2007 [VII].

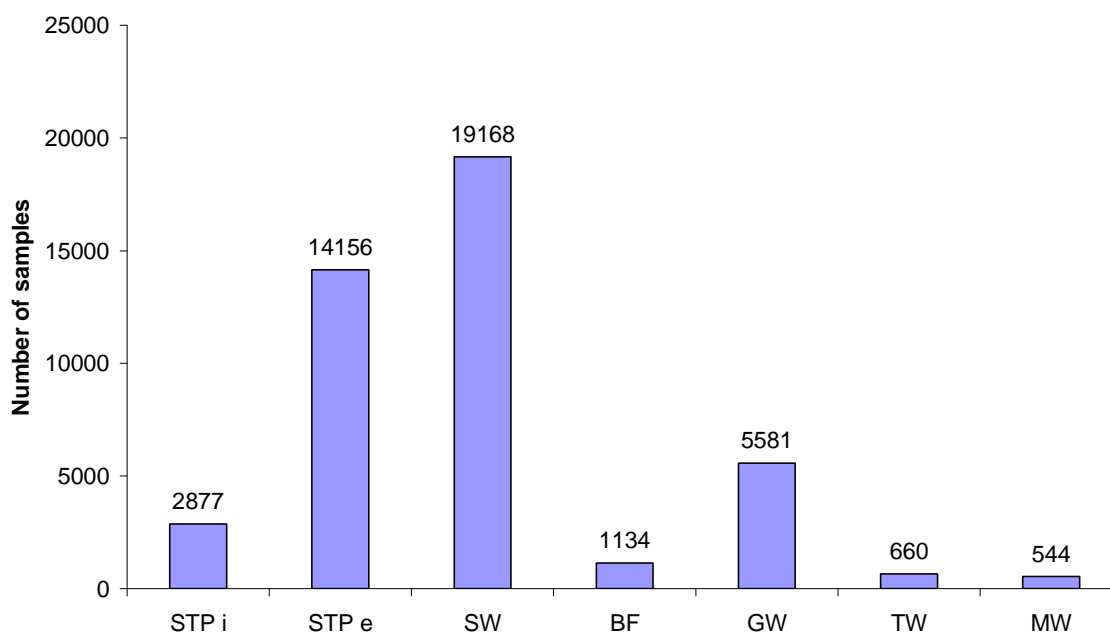
No consumption data in relation to the quantity of the active compounds were available for Poland and Spain. Only the numbers of sold packages/containers were available for these countries. Therefore, consumption were predicted by the following calculation. We used a simple approach by multiplying the quantity of the pharmaceutical with number of pills in the smallest available package and the number of packages sold. As an example for Poland 38,687,702 packages of paracetamol were sold in 2006. The smallest package contains 10 pills with each 500 mg of the active compound. The result of 193,439 kg of paracetamol in 2006 is comparable with other European countries on an annual per capita basis (5 g / capita Poland, 8 g / capita Germany, 4 g / capita Spain, 7 g / capita UK). The other PPs behave similar to this approach. However, the consumption of Paracetamol in France is different to the other EU-countries (54 g /capita per year).

Table 2 shows the evaluated list of 135 pharmaceutical products and metabolites which were detected in the aquatic environment. A total of 44120 records of environmental measurements were included from the reviewed literature. For 14 pharmaceuticals with a high consumption of up to 510 tons per year no measurement data from the aquatic environment were found. Hence, those compounds are candidates for future research.

3. Results and Discussion

This data list presents the state of the our work at September 1st, 2007. From all data included, STP effluent and surface water samples represent 75% of all measurements (Figure 1). Most frequently measured were antibiotics followed by the anti-inflammatory drugs (Figure 2). STP influent samples seems under-represented, as probably not all analytical groups were able or willing to measure in highly matrix loaded STP influents. This might be due to the fact, that analytical methods for surface water or groundwater frequently have to be improved to be applicable for raw sewage.

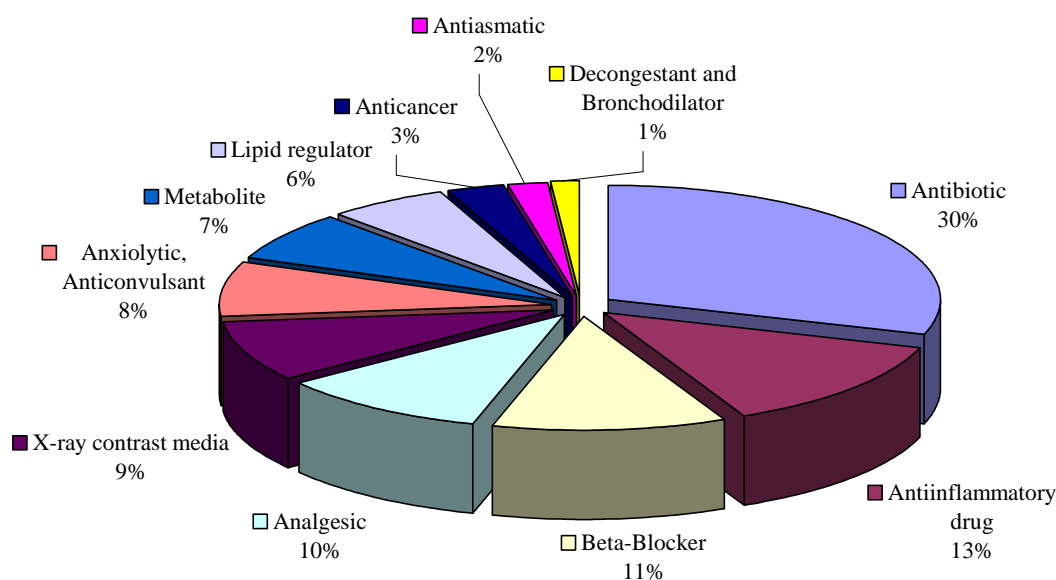
Figure 1: Sum about the quantity of samples of all pharmaceuticals products in influents sewage treatment plants (STP i), effluents of sewage treatment plants (STP e), surface water (SW), bank filtrate (BF), groundwater (GW), tap water (TP) and marine water (MW)



Known metabolites, excreted by humans, and iodinated X-ray contrast medias were frequently quantified in relatively high concentrations in the aquatic environment [33, 91]. As a consequence, further work should be concentrated on the detection and quantification of metabolites and environmental transformation products in environmental water compartments.

Figure 2 shows the distribution of studied samples according to therapeutic classes of PPs. Antibiotics are the first in the rank, followed by antiinflammatories (anti-inflammatory drugs) and betablockers

Figure 2: Partitioning of all quantified samples based on their pharmaceutical sub-class



In addition, as indicated in Table 2, fourteen pharmaceuticals were not measured in the aquatic environment in spite of high consumption with up to 510 tons per year in Germany. However, based on the POSEIDON approach [VI] a PEC^1 in raw sewage could be calculated for Germany (Table 1).

Table 1: Calculated PEC values for fourteen non measured pharmaceuticals. PEC in raw waste water is based on the approach of the EU-project Poseidon for Germany [VI].

Name	Annual consumption of the active compound in Germany[kg]	Renal excretion of parent compound	PEC in raw waste water [µg/L]
Captopril	31565	50%	2.0
Allopurinol	131821	12%	2.0
Theophylline	146431	18%	3.4
Sulfasalazine	46420	15%	0.9
Ioversol	43581	100%	5.6
Carbocisteine	31565	29%	1.2
Piracetam	134048	66%	11.4
Troxerutin	146131	9%	1.6
Povidone-Iodine	508694	0%	
Zopiclone	1948	0%	
Diosmin	373543	0%	
Valproic acid	112162	0%	
Mesalazine	56947	0%	
Lactiol	22967	0%	

metabolites expected

¹ PEC: (Predicted Environmental Concentration is an indication of the expected concentration of a material in the environment, taking into account the amount initially present (or added to) the environment, its distribution, and the probable methods and rates of environmental degradation and removal, either forced or natural)

4. Conclusions

This data list presents the state of the work at September 1st, 2007. Three-quarters of the exposure data stems from measurements of STP effluents and surface water. The substances most frequently measured were antibiotics followed by the anti-inflammatory drugs. Due to a lack of analytical methods, most of the human metabolites of PPs have not been measured in the aquatic environment yet. Hence, further work should be concentrated on the detection and quantification of metabolites and environmental transformation products in environmental water compartments.

The next step in WP 1 is to develop a classification system, together with output from WP 2 and WP 4, to prioritize the environmental risks of PPs, thus supporting water managers, health authorities and especially panels involved in the establishment of river basin management plans and strategies to minimize point and diffuse pollutions of water.

Furthermore, a prediction system of PPs in different aquatic environmental matrices will be established based on the consumption, excretion data, physicochemical chemistry and measured concentration in the environment. From the data collection a first outcome was the identification of data gaps for 14 PPs for which no occurrence data was found despite a high consumption. A PEC based on the POSEIDON approach was already calculated for these 14 compounds and will be provided for all others in each water compartment and compared with MEC data.

The established list of PPs detected in European surface water (“exposure”) will be used together with ecotoxicity evaluation (WP 4) to extract those PPs and metabolites with the highest potential do pose risks to the environment. Thus, it is foreseen to identify PPs of most concern (from WP 4), which should be integrated in future monitoring programs (WP 5).

5. List of abbreviations and acronyms

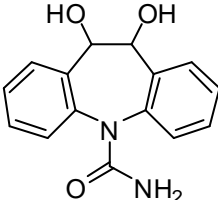
BF	Bank filtrate
EE2	17α-Ethinylestradiol
GW	Ground water
MEC	Measured Environmental Concentration
MW	Marine water
PEC	Predicted Environmental Concentration
STP e	Sewage treatment plants effluents
STP i	Sewage treatment plants influent
SW	Surface water
TW	Tap water

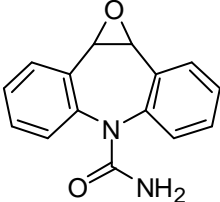
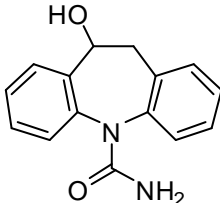
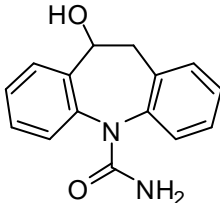
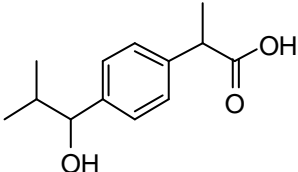
6. References

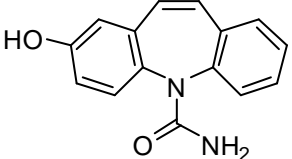
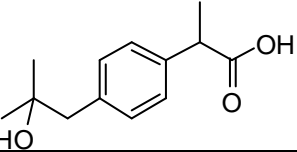
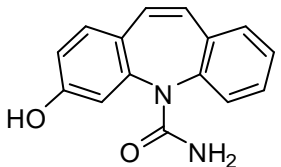
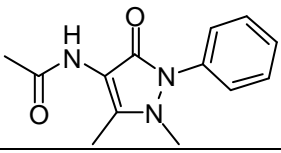
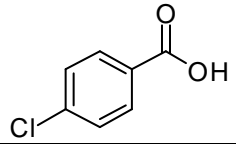
- [I] SciFinder Scholar includes the databases of: CAPLUS, CASREACT, CHEMLIST, CHEMCATS, REGISTRY: all Copyright © 2007 American Chemical Society and MEDLINE: Produced by the U.S. National Library of Medicine
- [II] Clarke's Analysis of Drugs and Poisons; Moffat, A. C., Osselton, M. D., Widdop, B., Eds; Pharmaceutical Press 2004; London, UK
- [III] Hazardous Substances Data Bank (HSDB) of the Toxicology data network (Toxnet) <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB> , U.S. National Library of Medicine
- [IV] McGraw-Hill AccessMedicine, <http://www.accessmedicine.com/> Copyright ©2007 The McGraw-Hill Companies. All rights reserved
- [V] IMS Health AG, European Intercontinental Marketing Service Health: PharmaScope National Service, <http://www.imshealth.de/sixcms/detail.php/237>
- [VI] Human Pharmaceuticals, Hormones and Fragrances - The challenge of micropollutants in urban water management, Ternes, T. A.; Joss, A. ed. ;IWA Publishing 2006, London, UK
- [VII] JP Besse and J Garric, Médicaments à usage humain : risque d'exposition et effets sur les milieux récepteurs, rapport AE RM&C, 2007, 238 p

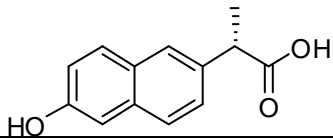
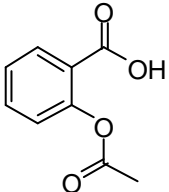
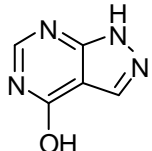
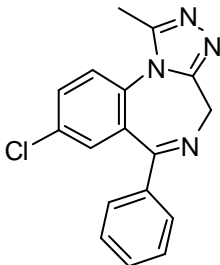
7. List of relevant PPs

Table 2: List of pharmaceutical products and metabolites with name and chemical structure including the annular consumption, CAS number, molecular weight and number occurrence in influents sewage treatment plants (STP i), effluents of sewage treatment plants (STP e), surface water (SW), bank filtrate (BF), groundwater (GW), tap water (TP) and marine water (MW)

Name Structure	Consumption in an European country [kg/a] Molecular weight [g/mol]	Sub-Class CAS-No.	STP i	STP e	SW	BF	GW	TW	MW
10,11-Dihydro-10,11-dihydroxycarbamazepine 	- 270.2833	Metabolite 35079-97-1	14	15	6	0	0	0	0

<p>10,11-Dihydro-10,11-epoxycarbamazepine</p> 	- 252.268	Metabolite -	3	3	3	0	0	0	0
<p>10,11-Dihydro-10-hydroxycarbamazepine</p> 	- 254.2839	Metabolite 29331-92-8	3	3	3	0	0	0	0
<p>10,11-Dihydrocarbamazepine</p> 	- 238.2845	Metabolite 3564-73-6	1	1	3	0	0	0	0
<p>1-Hydroxyibuprofen</p> 	- 222.2802	Metabolite -	2	5	27	0	2	0	20

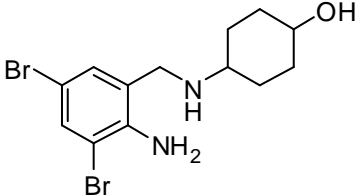
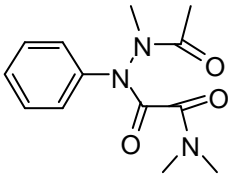
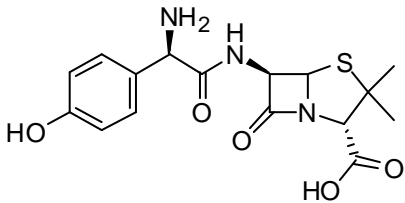
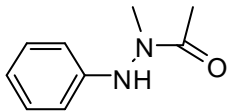
2-Hydroxycarbamazepine 	- 252.268	Metabolite 68011-66-5	3	3	3	0	0	0	0
2-Hydroxyibuprofen 	- 222.2802	Metabolite -	0	10	27	0	2	0	8
3-Hydroxycarbamazepine.wmf 	- 252.268	Metabolite -	3	3	3	0	0	0	0
4-Acetoamidoantipyrine 	- 245.2804	Metabolite 83-15-8	12	12	20	0	0	0	0
4-Chlorobenzoic acid 	- 156.5683	Metabolite 74-11-3	0	0	27	0	2	0	8

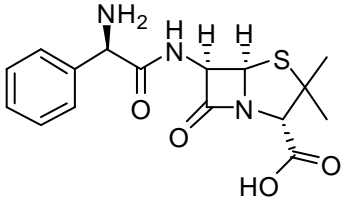
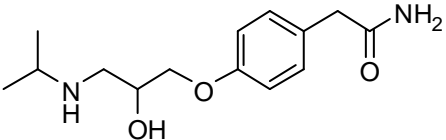
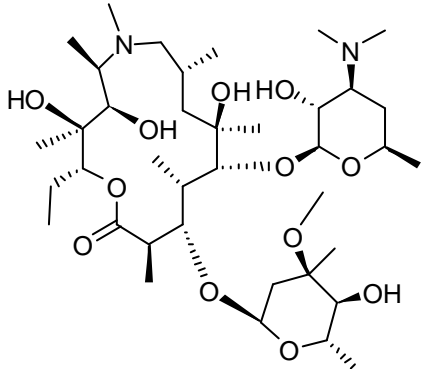
<p>6-o-desmethyl naproxen</p> 	<p>39000 (F)</p> <p>216.2326</p>	<p>Metabolite</p> <p>60756-73-2</p>	0	0	27	0	2	0	8
<p>Acetylsalicylic acid</p> 	<p>902272 (D)</p> <p>180.1598</p>	<p>Anti-inflammatory</p> <p>50-78-2</p>	45	145	119	0	0	55	0
<p>Allopurinol</p> 	<p>131821 (D)</p> <p>136.1128</p>	<p>Antigout</p> <p>315-30-0</p>	0	0	0	0	0	0	0
<p>Alprazolam</p> 	<p>-</p> <p>308.7695</p>	<p>Sedative</p> <p>28981-97-7</p>	0	0	27	0	2	0	8

KNAPPE

 Knowledge and Need Assessment on Pharmaceutical
 Products in Environmental Waters

D1.1: List of relevant PPs

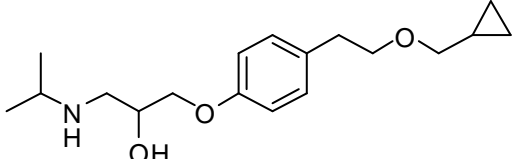
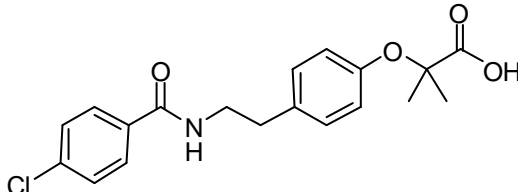
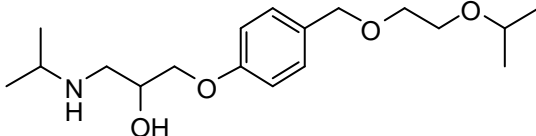
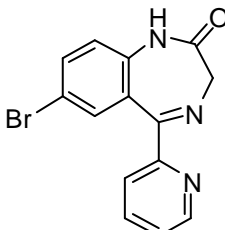
Ambroxol 	14472 (D) 378.106	Mucolytic 18683-91-5	0	3	22	4	0	0	0
AMDOPH 	- 263.2924	Metabolite 519-65-3	12	12	21	0	0	0	0
Amoxicillin 	333223 (F) 365.4032	Antibiotic 61336-70-7	19	86	58	0	16	0	0
AMPH 	- 164.2044	Metabolite 38604-70-5	12	22	5	0	0	0	0

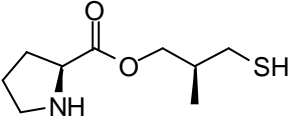
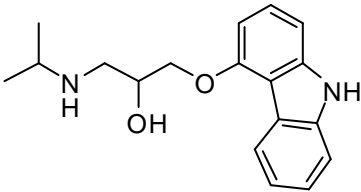
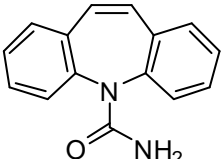
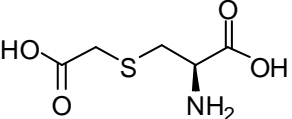
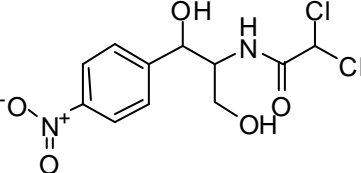
<p style="text-align: center;">Ampicillin</p>  <p>The chemical structure of Ampicillin is shown, featuring a phenylacetamido group attached to a penicillin nucleus. The penicillin nucleus consists of a four-membered beta-lactam ring fused to a five-membered thiazolidine ring, which has a methyl group and a carboxylic acid group attached.</p>	<p>13419 (D) 349.4038</p>	<p>Antibiotic 69-53-4</p>	<p>0</p>	<p>70</p>	<p>42</p>	<p>0</p>	<p>10</p>	<p>0</p>	<p>0</p>
<p style="text-align: center;">Atenolol</p>  <p>The chemical structure of Atenolol is shown, consisting of a 1-propanolamine chain with an isopropyl group on the nitrogen, a hydroxyl group on the second carbon, and a 4-(2-aminophenyl)ethoxy group on the third carbon.</p>	<p>18336 (F) 266.3394</p>	<p>Beta-Blocker 29122-68-7</p>	<p>35</p>	<p>171</p>	<p>288</p>	<p>32</p>	<p>81</p>	<p>0</p>	<p>8</p>
<p style="text-align: center;">Azithromycin</p>  <p>The chemical structure of Azithromycin is shown, a complex macrolide antibiotic. It features a 14-membered macrolide ring with a nitrogen atom at the 14-position, and several side chains including methyl, hydroxyl, and a 2,6-dimethyl-3,5-dihydroxy-4-pyridinyl group.</p>	<p>4073 (F) 748.993</p>	<p>Antibiotic 83905-01-5</p>	<p>14</p>	<p>90</p>	<p>45</p>	<p>0</p>	<p>10</p>	<p>0</p>	<p>0</p>

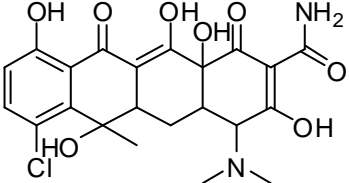
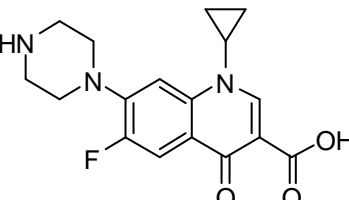
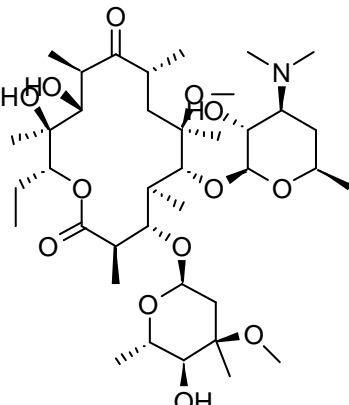
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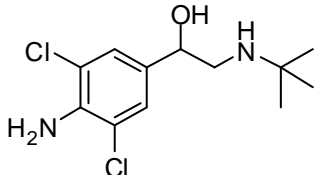
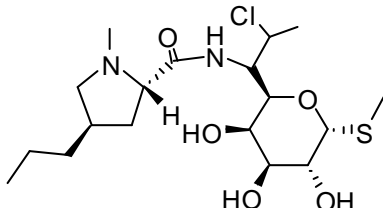
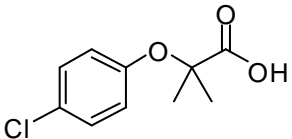
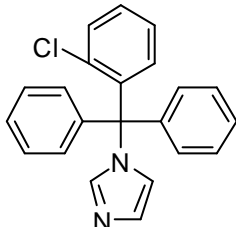
Knowledge and Need Assessment on Pharmaceutical
Products in Environmental Waters

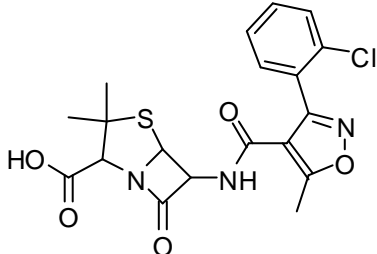
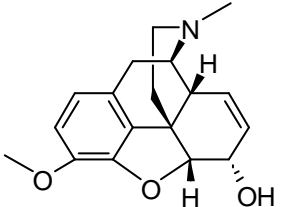
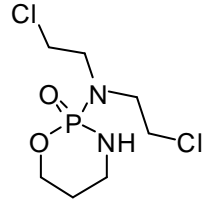
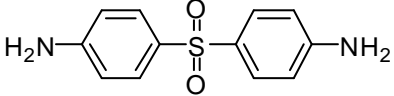
D1.1: List of relevant PPs

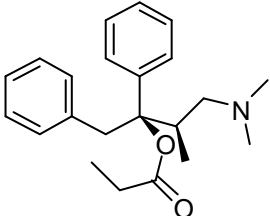
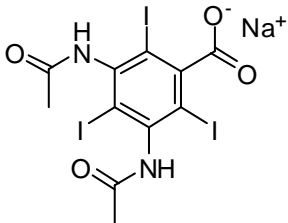
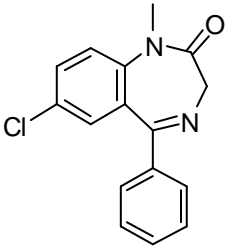
<p>Betaxolol</p> 	<p>437 (D) 307.432</p>	<p>Beta-Blocker 63659-18-7</p>	0	164	177	0	29	0	0
<p>Bezafibrate</p> 	<p>39073 (D) 361.8243</p>	<p>Lipid regulator 41859-67-0</p>	55	396	461	49	277	55	8
<p>Bisoprolol</p> 	<p>2957 (D) 325.4472</p>	<p>Beta-Blocker 66722-44-9</p>	15	283	413	32	117	0	0
<p>Bromazepam</p> 	<p>2603 (F) 316.1565</p>	<p>Sedative, Anxiolytic 1812-30-2</p>	0	0	27	0	2	0	8

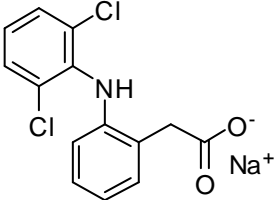
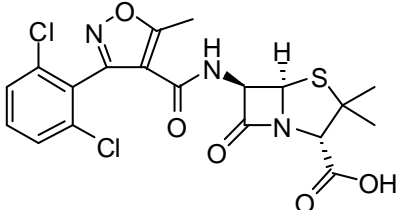
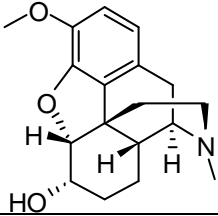
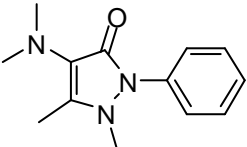
<p>Captopril</p> 	31565 (D) 203.3018	Antihyperten sion 62571-86-2	0	0	0	0	0	0	0
<p>Carazolol</p> 	2 (D) 298.384	Beta-Blocker 57775-29-8	0	112	121	0	23	0	0
<p>Carbamazepine</p> 	87605 (D) 236.2726	Anticonvulsa nt 298-46-4	120	495	786	70	531	12	34
<p>Carbocisteine</p> 	232308 (F) 179.1904	Mucolytic 2387-59-9	0	0	0	0	0	0	0
<p>Chloramphenicol</p> 	437 (D) 323.1322	Antibiotic 56-75-7	24	107	320	11	98	1	0

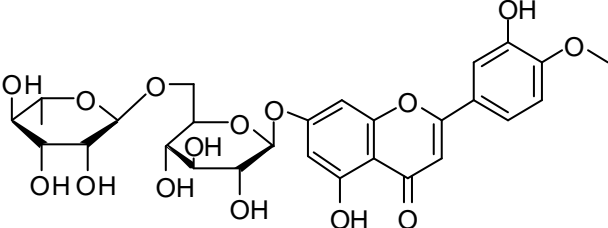
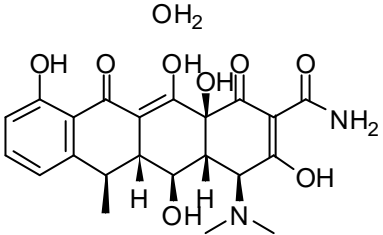
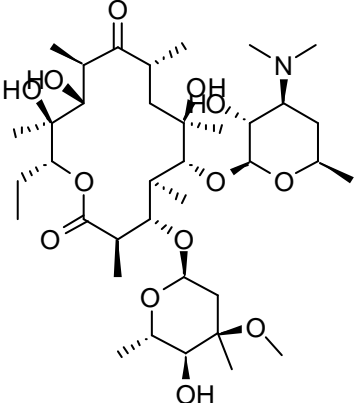
<p>Chlortetracycline</p>  <p>The chemical structure of Chlortetracycline is a tetracycline derivative. It features a central tetracycline core with a chlorine atom at the 7-position, a methyl group at the 8-position, and a dimethylamino group at the 4-position. The core includes a dimethylamino group at the 4-position, a methyl group at the 8-position, and a chlorine atom at the 7-position. The core also has a dimethylamino group at the 4-position, a methyl group at the 8-position, and a chlorine atom at the 7-position.</p>	<p>140 (D) 478.8853</p>	<p>Antibiotic 57-62-5</p>	3	83	262	0	58	0	0
<p>Ciprofloxacin</p>  <p>The chemical structure of Ciprofloxacin is a fluoroquinolone. It features a central quinolone core with a piperazine ring at the 7-position, a cyclopropyl group at the 8-position, a fluorine atom at the 6-position, and a carboxylic acid group at the 4-position.</p>	<p>17973 (D) 331.3459</p>	<p>Antibiotic 85721-33-1</p>	44	138	196	0	10	0	0
<p>Clarithromycin</p>  <p>The chemical structure of Clarithromycin is a macrolide. It features a 14-membered macrolide ring with a dimethylamino group at the 13-position, a methyl group at the 14-position, and a hydroxyl group at the 15-position. The ring also has a dimethylamino group at the 13-position, a methyl group at the 14-position, and a hydroxyl group at the 15-position.</p>	<p>15104 (F) 747.962</p>	<p>Antibiotic 81103-11-9</p>	125	326	360	13	128	1	0

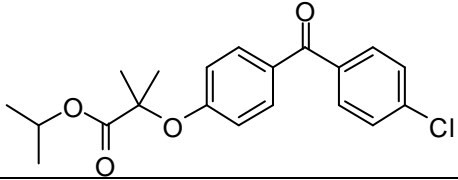
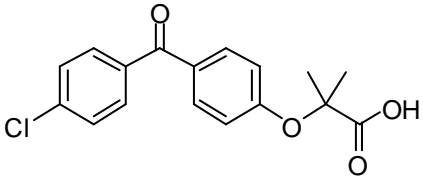
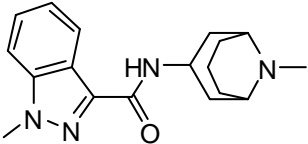
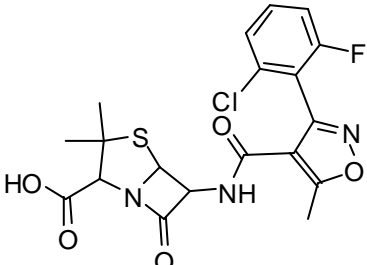
<p>Clenbuterol</p> 	<p>1 (D) 277.193</p>	<p>Decongestant and Bronchodilat or 37148-27-9</p>	14	237	200	32	87	0	0
<p>Clindamycin</p> 	<p>16081 (D) 424.9821</p>	<p>Antibiotic 18323-44-9</p>	19	98	41	0	0	0	0
<p>Clofibric acid</p> 	<p>- 214.6455</p>	<p>Metabolite 882-09-7</p>	62	452	535	66	383	90	30
<p>Clotrimazole</p> 	<p>8324 (D) 344.8427</p>	<p>Antifungal 23593-75-1</p>	3	3	46	0	2	0	8

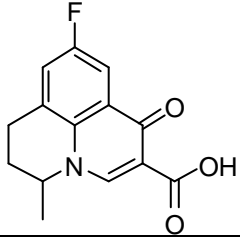
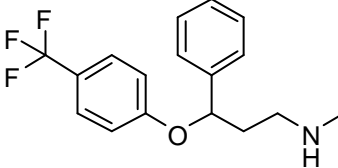
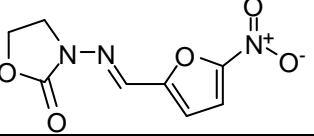
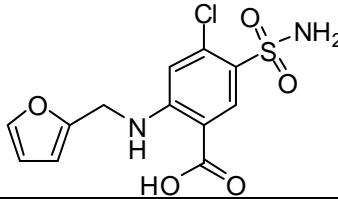
<p>Cloxacillin</p> 	- 435.8813	Antibiotic 61-72-3	0	11	34	0	37	0	0
<p>Codeine</p> 	26600 (UK) 299.3688	Analgesic, Antitussive and Antidiarrheal 76-57-3	16	48	90	0	2	0	27
<p>Cyclophosphamide</p> 	430 (D) 261.0875	Anticancer 50-18-0	52	190	272	32	85	12	0
<p>Dapsone</p> 	76 (D) 248.299	Antibacterial 80-08-0	0	0	14	0	6	0	0

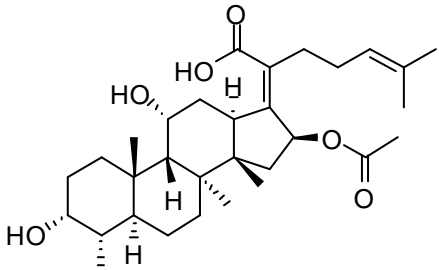
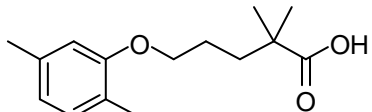
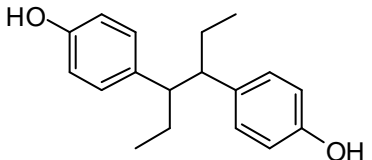
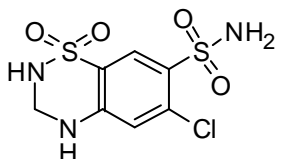
<p>Dextropropoxyphene</p> 	<p>51962 (F) 339.4766</p>	<p>Analgesic 469-62-5</p>	<p>3</p>	<p>6</p>	<p>42</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>
<p>Diatrizoate sodium</p> 	<p>60687 (D) 635.8985</p>	<p>X-ray contrast media 737-31-5</p>	<p>7</p>	<p>106</p>	<p>135</p>	<p>30</p>	<p>47</p>	<p>10</p>	<p>0</p>
<p>Diazepam</p> 	<p>1184 (D) 284.7445</p>	<p>Anxiolytic, Anticonvulsant, Sedative 439-14-5</p>	<p>37</p>	<p>279</p>	<p>437</p>	<p>32</p>	<p>90</p>	<p>12</p>	<p>8</p>

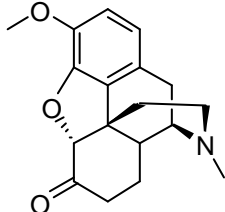
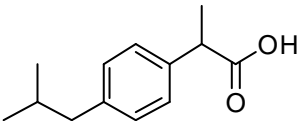
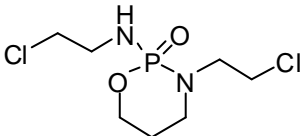
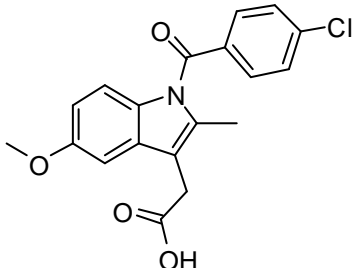
<p>Diclofenac</p> 	<p>85801 (D) 318.1343</p>	<p>Analgesic and Antiinflamm 15307-86-5</p>	93	591	820	74	459	56	8
<p>Dicloxacillin</p> 	<p>125 (D) 470.3264</p>	<p>Antibiotic 3116-76-5</p>	0	70	77	0	53	0	0
<p>Dihydrocodeine</p> 	<p>6830 (UK) 301.3846</p>	<p>Antitussive 125-28-0</p>	6	38	36	0	2	0	0
<p>Dimethylaminophenazone</p> 	<p>218 231.2968</p>	<p>Analgesic 58-15-1</p>	25	106	179	0	33	2	0

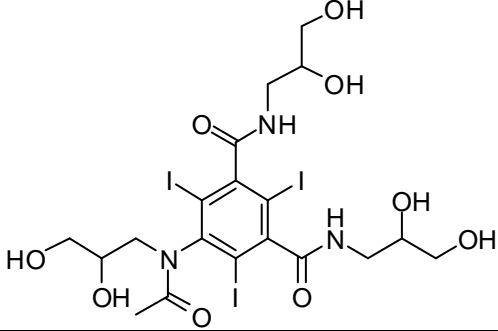
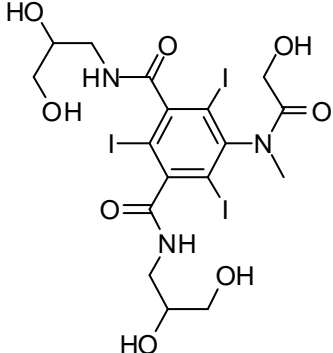
<p style="text-align: center;">Diosmin</p> 	<p>373543 (F) 608.5518</p>	<p>Phlebotropic 520-27-4</p>	0	0	0	0	0	0	0
<p style="text-align: center;">Doxycycline</p> 	<p>14056 (D) 462.4554</p>	<p>Antibiotic 564-25-0</p>	32	104	170	0	37	0	0
<p style="text-align: center;">Erythromycin</p> 	<p>27042 733.9352</p>	<p>Antibiotic 114-07-8</p>	123	348	559	13	128	1	0

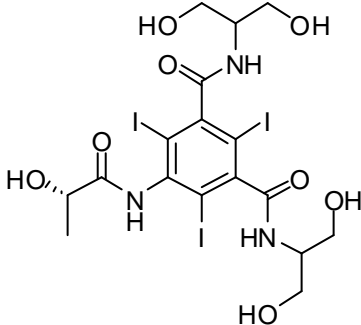
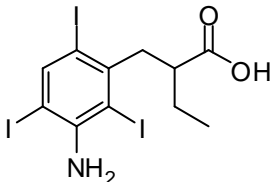
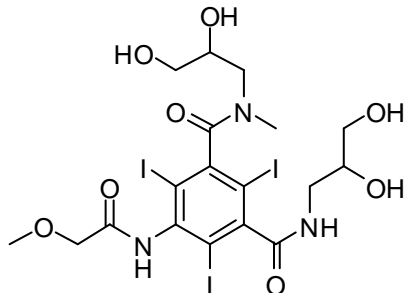
<p>Fenofibrate</p> 	<p>85669 (F) 360.8365</p>	<p>Lipid regulator 49562-28-9</p>	5	55	190	17	28	12	35
<p>Fenofibric acid</p> 	<p>- 318.7516</p>	<p>Metabolite 42017-89-0</p>	0	258	258	0	20	55	8
<p>Fenoterol</p> 	<p>170 (D) 312.4138</p>	<p>Antiasmthic 13392-18-2</p>	0	112	121	0	3	0	0
<p>Flucloxacillin</p> 	<p>23380 (UK) 453.8718</p>	<p>Antibiotic 5250-39-5</p>	0	54	6	0	0	0	0

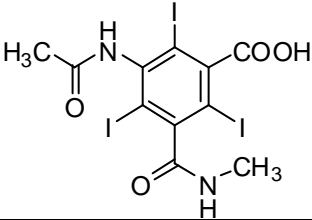
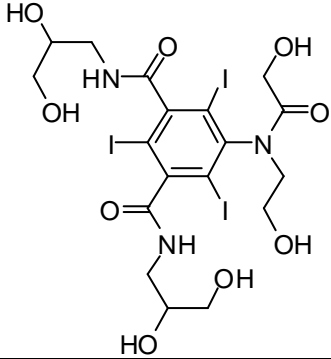
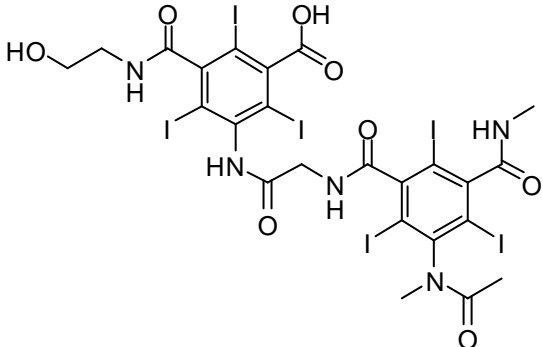
<p>Flumequine</p> 	- 261.2521	Antibiotic 42835-25-6	19	19	0	0	0	0	0
<p>Fluoxetine</p> 	3740 (F) 309.3305	Antidepressant 54910-89-3	18	28	50	0	2	5	27
<p>Furazolidone</p> 	17 (D) 225.1604	Antibiotic 67-45-8	0	0	14	0	6	0	0
<p>Furosemide</p> 	32189 (D) 330.7423	Diuretic 54-31-9	9	8	34	0	2	0	8

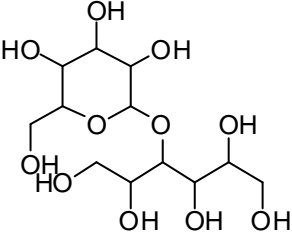
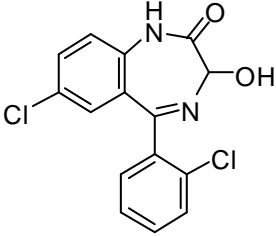
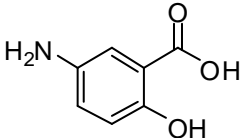
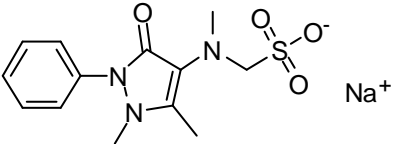
<p>Fusidine</p> 	- 516.7166	Antibiotic 6990-06-3	19	19	0	0	0	0	0
<p>Gemfibrozil</p> 	8908 (D) 250.337	Lipid regulator 25812-30-0	31	283	485	0	17	55	8
<p>Hexestrol</p> 	- 270.3706	Contraceptive 5635-50-7	0	0	14	0	2	0	0
<p>Hydrochlorothiazide</p> 	26722 (D) 297.7309	Diuretic 58-93-5	9	8	15	0	0	0	0

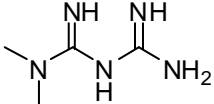
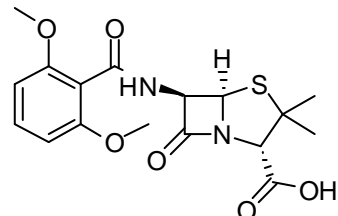
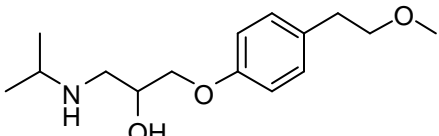
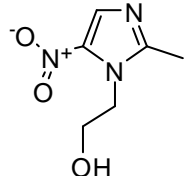
<p>Hydrocodone</p> 	<p>9 (D) 299.3688</p>	<p>Analgesic and Antitussive 125-29-1</p>	7	40	43	0	2	0	26
<p>Ibuprofen</p> 	<p>344884 (D) 206.284</p>	<p>Anti-inflammatory 15687-27-1</p>	86	516	773	47	79	60	22
<p>Ifosamide</p> 	<p>204 (D) 261.0875</p>	<p>Anticancer 3778-73-2</p>	30	156	250	32	85	12	0
<p>Indometacin</p> 	<p>4436 (D) 357.7927</p>	<p>Antiinflammatory 53-86-1</p>	18	312	496	49	81	55	0

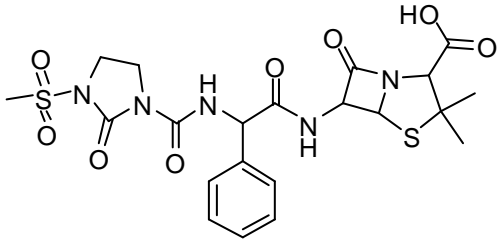
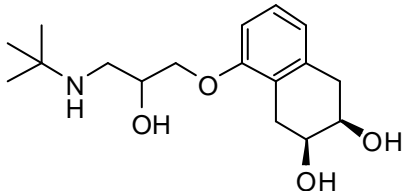
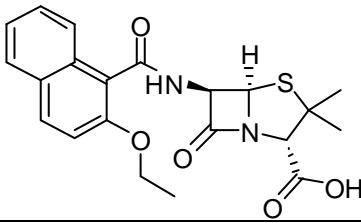
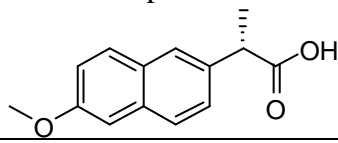
<p style="text-align: center;">Iohexol</p> 	<p>8053 (D) 821.1426</p>	<p>X-ray contrast media 66108-95-0</p>	<p>130</p>	<p>366</p>	<p>12</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>
<p style="text-align: center;">Iomeprol</p> 	<p>83370 (D) 777.0896</p>	<p>X-ray contrast media 78649-41-9</p>	<p>137</p>	<p>437</p>	<p>110</p>	<p>31</p>	<p>27</p>	<p>1</p>	<p>0</p>

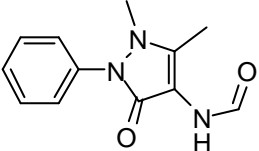
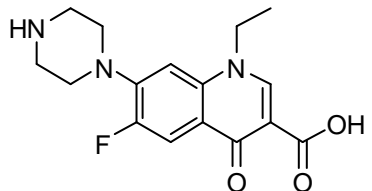
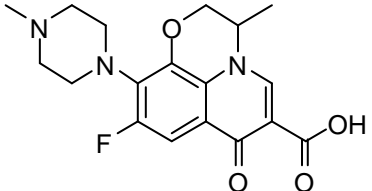
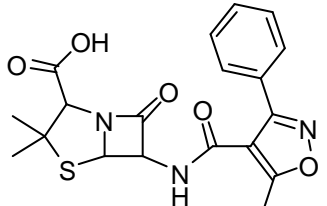
<p>Iopamidol</p> 	<p>42994 (D) 77.0896</p>	<p>X-ray contrast media 62883-00-5</p>	<p>137</p>	<p>463</p>	<p>136</p>	<p>31</p>	<p>152</p>	<p>11</p>	<p>0</p>
<p>Iopanoic acid</p> 	<p>- 570.9348</p>	<p>X-ray contrast media 96-83-3</p>	<p>0</p>	<p>3</p>	<p>6</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>
<p>Iopromide</p> 	<p>65533 (D) 791.1164</p>	<p>X-ray contrast media 73334-07-3</p>	<p>147</p>	<p>477</p>	<p>148</p>	<p>32</p>	<p>54</p>	<p>12</p>	<p>0</p>

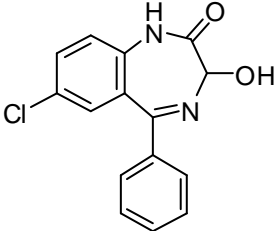
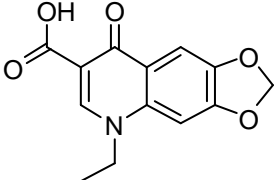
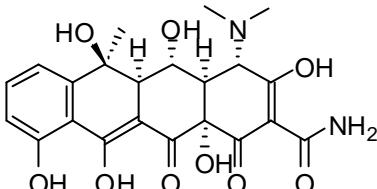
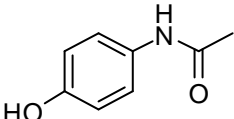
<p style="text-align: center;">Iotalamic acid</p> 	<p style="text-align: center;">- 613.9136</p>	<p style="text-align: center;">X-ray contrast media 2276-90-6</p>	0	17	31	0	0	10	0
<p style="text-align: center;">Ioversol</p> 	<p style="text-align: center;">43581 (D) 807.1158</p>	<p style="text-align: center;">X-ray contrast media 87771-40-2</p>	0	0	0	0	0	0	0
<p style="text-align: center;">Ioxaglic acid</p> 	<p style="text-align: center;">- 1268.8856</p>	<p style="text-align: center;">X-ray contrast media 59017-64-0</p>	0	3	6	0	0	0	0

<p style="text-align: center;">Lactitol</p>  <p>The structure shows a lactose molecule (a disaccharide of galactose and glucose) with an additional hydroxyl group on the glucose ring, making it a polyol.</p>	<p>22967 (D) 344.315</p>	<p>Antihypertensive 585-86-4</p>	0	0	0	0	0	0	0
<p style="text-align: center;">Lorazepam</p>  <p>The structure shows a benzodiazepine core with a chlorine atom at the 5-position, a 2-chlorophenyl group at the 1-position, and a hydroxyl group at the 3-position.</p>	<p>584 (F) 321.1622</p>	<p>Sedative/Hypnotic, Muscle relaxant, Anxiolytic, Amnesic and Anticonvulsant 846-49-1</p>	5	0	27	0	2	0	8
<p style="text-align: center;">Mesalazine</p>  <p>The structure shows a benzene ring with an amino group (-NH₂) at the 4-position, a hydroxyl group (-OH) at the 3-position, and a carboxylic acid group (-COOH) at the 1-position.</p>	<p>56947 (D) 153.1372</p>	<p>Antiinflammatory 89-57-6</p>	0	0	0	0	0	0	0
<p style="text-align: center;">Metamizole sodium</p>  <p>The structure shows a pyrazolone ring system with a phenyl group at the 5-position, a methyl group at the 4-position, and a sodium sulfonate group (-SO₂Na) at the 3-position.</p>	<p>163457 (D) 333.33687</p>	<p>Analgesic 68-89-3</p>	0	14	11	0	0	0	0

<p>Metformin</p> 	<p>716858 (F)</p> <p>129.1644</p>	<p>Antidiabetic</p> <p>657-24-9</p>	5	6	84	0	0	0	3
<p>Methicillin</p> 	<p>-</p> <p>380.4148</p>	<p>Antibiotic</p> <p>61-32-5</p>	0	11	34	0	37	0	0
<p>Metoprolol</p> 	<p>92974 (D)</p> <p>267.3674</p>	<p>Beta-Blocker</p> <p>37350-58-6</p>	24	352	473	36	104	0	8
<p>Metronidazole</p> 	<p>36545 (F)</p> <p>171.1554</p>	<p>Antibiotic</p> <p>443-48-1</p>	19	19	17	1	6	1	0

<p>Mezlocillin</p> 	<p>7429 (D) 539.5772</p>	<p>Antibiotic 51481-65-3</p>	0	54	27	0	0	0	0
<p>Nadolol</p> 	<p>938 (F) 309.4046</p>	<p>Beta-Blocker 42200-33-9</p>	0	12	121	0	21	0	0
<p>Nafcillin</p> 	<p>- 414.4752</p>	<p>Antibiotic 147-52-4</p>	0	11	34	0	37	0	0
<p>Naproxen</p> 	<p>37332 (F) 230.2628</p>	<p>Antiinflamm atory 22204-53-1</p>	60	318	379	30	72	5	8

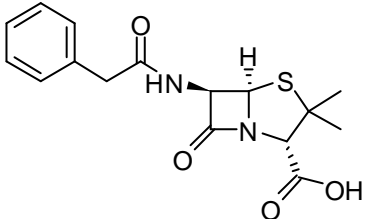
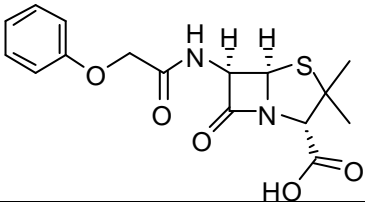
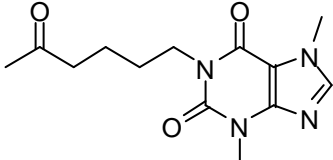
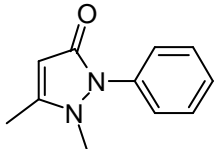
<p>N-Formyl-4-aminoantipyrine (FAA)</p> 	- 231.2505	Metabolite 1672-5-8-8	12	12	21	0	0	0	0
<p>Norfloxacin</p> 	- 319.3349	Antibiotic 70458-96-7	35	50	120	0	0	0	0
<p>Ofloxacin</p> 	4641 (D) 361.3721	Anitbiotic 83380-47-6	46	122	49	0	0	0	0
<p>Oxacillin</p> 	313 (D) 401.4362	Antibiotic 66-79-5	0	78	77	0	53	0	0

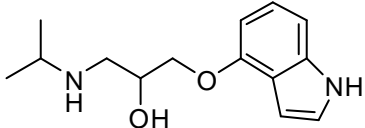
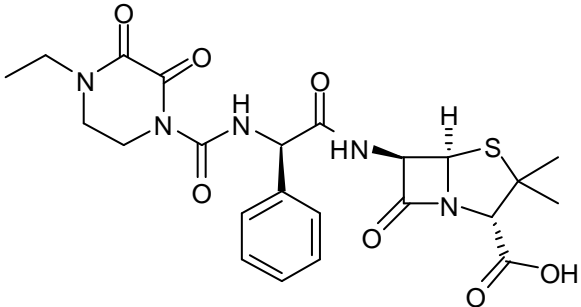
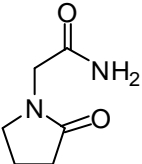
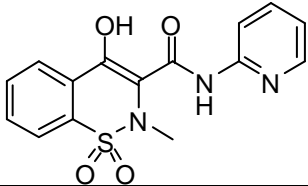
<p>Oxazepam</p> 	<p>6194 (F) 286.7171</p>	<p>Anxiolytic, Anticonvulsant, Sedative</p> <p>604-75-1</p>	<p>16</p>	<p>12</p>	<p>38</p>	<p>0</p>	<p>2</p>	<p>0</p>	<p>8</p>
<p>Oxolinic acid</p> 	<p>- 261.2336</p>	<p>Antibiotic</p> <p>14698-29-4</p>	<p>19</p>	<p>19</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>
<p>Oxytetracycline</p> 	<p>27190 (UK) 460.4396</p>	<p>Antibiotic</p> <p>6153-64-6</p>	<p>22</p>	<p>94</p>	<p>254</p>	<p>0</p>	<p>48</p>	<p>0</p>	<p>0</p>
<p>Paracetamol</p> 	<p>3303076 (F) 151.1646</p>	<p>Antiinflammatory</p> <p>103-90-2</p>	<p>13</p>	<p>120</p>	<p>146</p>	<p>4</p>	<p>2</p>	<p>0</p>	<p>35</p>

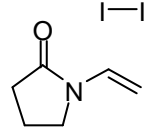
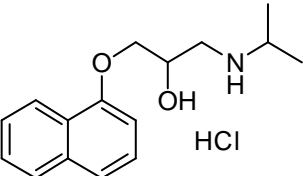
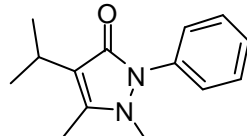
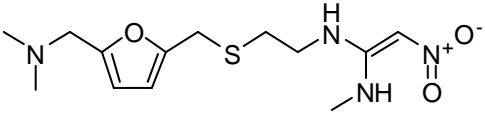
KNAPPE

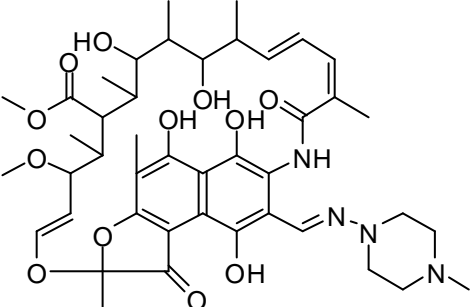
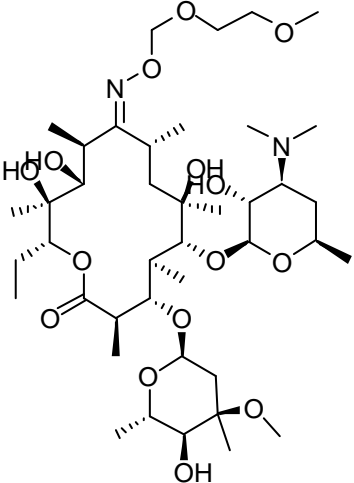
 Knowledge and Need Assessment on Pharmaceutical
 Products in Environmental Waters

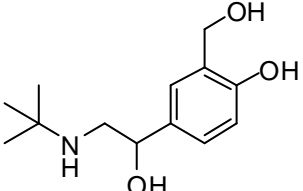
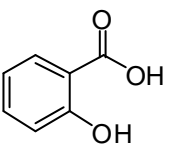
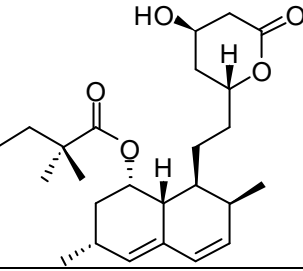
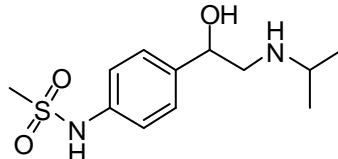
D1.1: List of relevant PPs

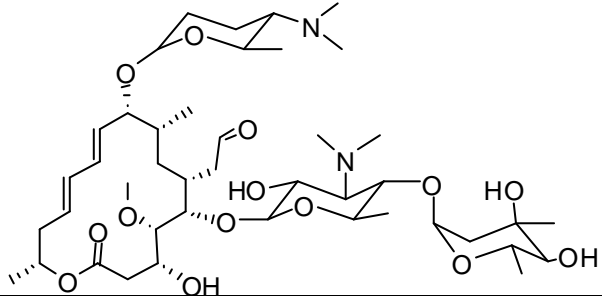
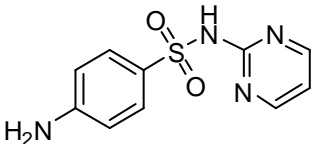
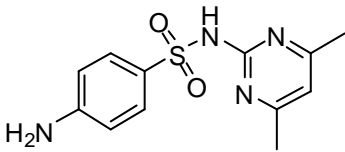
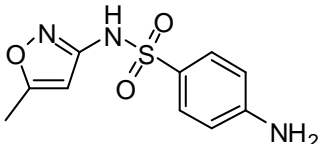
Penicillin G 	7094 (D) 334.3892	Antibiotic 61-33-6	0	78	77	0	48	0	0
Penicillin V 	89983 (D) 350.3886	Antibiotic 87-08-1	0	62	69	0	43	0	0
Pentoxifylline 	103567 (D) 278.3102	treat intermittent claudication 6493-05-6	0	11	105	0	6	0	0
Phenazon 	32534 188.2286	Analgesic 60-80-0	53	334	511	49	222	18	27

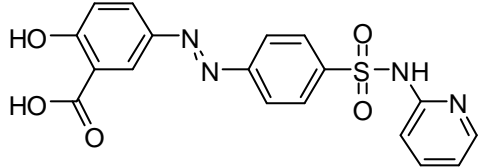
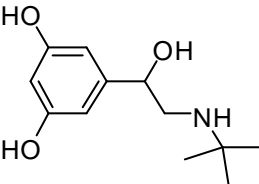
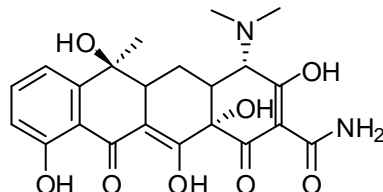
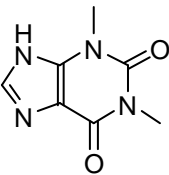
<p>Pindolol</p> 	<p>74 (D)</p> <p>248.3242</p>	<p>Beta-Blocker</p> <p>13523-86-9</p>	0	3	20	0	6	0	0
<p>Piperacillin</p> 	<p>13512 (D)</p> <p>517.5556</p>	<p>Antibiotic</p> <p>61477-96-1</p>	0	54	27	0	0	0	0
<p>Piracetam</p> 	<p>134048</p> <p>142.1572</p>	<p>Nootropic</p> <p>7491-74-9</p>	0	0	0	0	0	0	0
<p>Piroxicam</p> 	<p>2008 (F)</p> <p>331.3454</p>	<p>Antiinflamm atory</p> <p>36322-90-4</p>	1	32	41	0	49	0	0

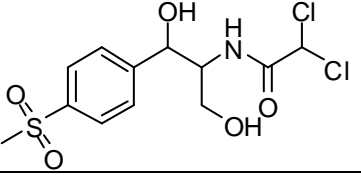
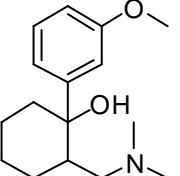
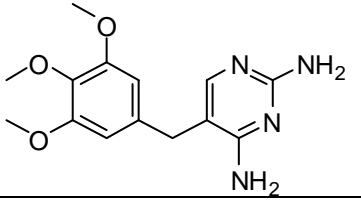
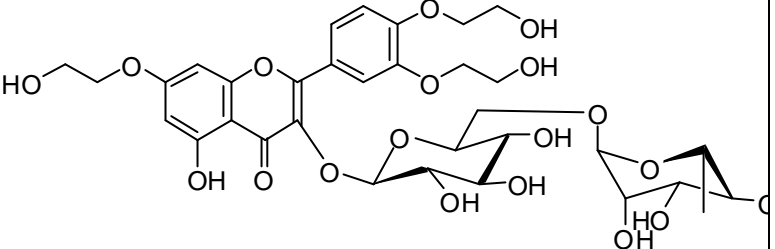
<p>Povidone-iodine</p> 	<p>508694 (D)</p> <p>364.9522</p>	<p>Antiseptics</p> <p>25655-41-8</p>	0	0	0	0	0	0	0
<p>Propranolol</p> 	<p>12486 (F)</p> <p>295.8044</p>	<p>Beta-Blocker</p> <p>318-98-9</p>	30	321	432	32	119	0	8
<p>Propyphenazon</p> 	<p>46016 (D)</p> <p>230.309</p>	<p>Analgesic</p> <p>479-92-5</p>	24	85	213	64	27	0	0
<p>Ranitidine</p> 	<p>85409 (D)</p> <p>314.4018</p>	<p>H2-receptor antagonist, Antihistaminic</p> <p>66357-35-5</p>	19	19	109	0	0	0	3

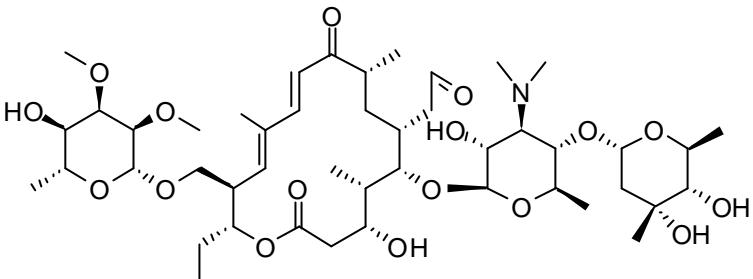
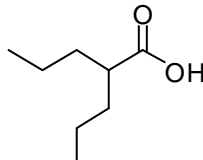
<p style="text-align: center;">Rifampin</p>  <p>The chemical structure of Rifampin is a complex polycyclic molecule. It features a central naphthalene ring system with multiple hydroxyl groups and a dimethylpiperazine ring attached via a methylene bridge. The structure is highly substituted with various functional groups, including a methyl group, a hydroxyl group, and a methoxy group.</p>	<p>2383 (F) 822.9508</p>	<p>Antibiotic 13292-46-1</p>	<p>19</p>	<p>19</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>
<p style="text-align: center;">Roxithromycin</p>  <p>The chemical structure of Roxithromycin is a macrolide antibiotic. It consists of a 14-membered macrolide ring with a hydroxyl group and a methyl group. It is substituted with a diethylamino group, a methyl group, and a propyl chain. The propyl chain is further substituted with a methyl group and a hydroxyl group. The structure is highly complex and contains several stereocenters.</p>	<p>9555 (D) 837.0465</p>	<p>Antibiotic 80214-83-1</p>	<p>146</p>	<p>361</p>	<p>519</p>	<p>14</p>	<p>135</p>	<p>2</p>	<p>0</p>

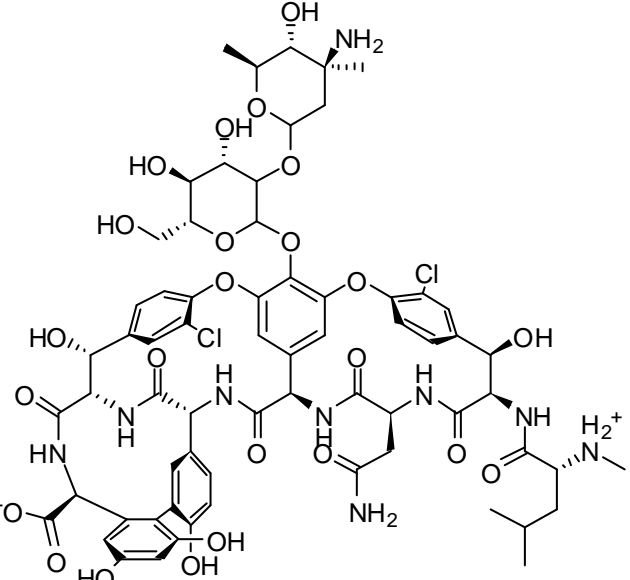
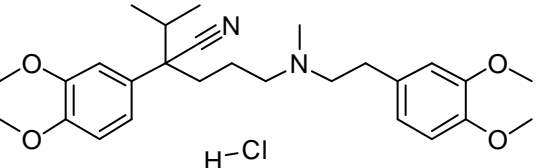
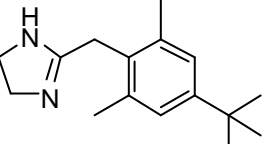
<p>Salbutamol</p> 	<p>460 (D) 239.3138</p>	<p>Antireumatic 18559-94-9</p>	28	280	427	32	93	0	27
<p>Salicylic acid</p> 	<p>89701 (D) 138.1226</p>	<p>Metabolite and antiseptic 69-72-7</p>	26	110	136	0	2	0	0
<p>Simvastatin</p> 	<p>6943 (F) 418.5722</p>	<p>Antihyperlipidemic 79902-63-9</p>	0	10	51	0	6	0	0
<p>Sotalol</p> 	<p>27139 (D) 272.3616</p>	<p>Beta-Blocker 3930-20-9</p>	26	139	246	40	183	0	0

<p style="text-align: center;">Spiramycin</p> 	<p>495 (D) 843.0527</p>	<p>Antibiotic 8025-81-8</p>	<p>28</p>	<p>97</p>	<p>64</p>	<p>0</p>	<p>11</p>	<p>0</p>	<p>0</p>
<p style="text-align: center;">Sulfadiazine</p> 	<p>2082 (D) 250.2746</p>	<p>Antibiotic 68-35-9</p>	<p>0</p>	<p>8</p>	<p>14</p>	<p>0</p>	<p>17</p>	<p>0</p>	<p>0</p>
<p style="text-align: center;">Sulfamethazine</p> 	<p>800 (D) 277.3404</p>	<p>Antibiotic 57-68-1</p>	<p>34</p>	<p>236</p>	<p>553</p>	<p>13</p>	<p>140</p>	<p>1</p>	<p>0</p>
<p style="text-align: center;">Sulfamethoxazole</p> 	<p>58407 (D) 253.2752</p>	<p>Antibiotic 723-46-6</p>	<p>82</p>	<p>219</p>	<p>678</p>	<p>22</p>	<p>245</p>	<p>1</p>	<p>34</p>

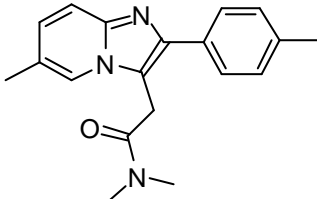
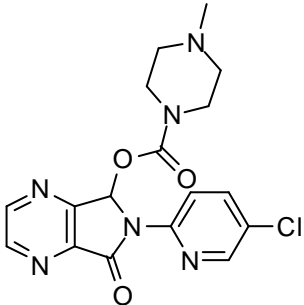
<p>Sulfasalazine</p> 	<p>46420 (UK) 398.3924</p>	<p>Antibiotic 599-79-1</p>	0	0	0	0	0	0	0
<p>Terbutaline</p> 	<p>183 (D) 225.287</p>	<p>Antiasmatic 23031-25-6</p>	12	200	273	16	76	0	0
<p>Tetracycline</p> 	<p>1954 (D) 444.4402</p>	<p>Antibiotic 60-54-8</p>	22	94	254	0	48	0	0
<p>Theophylline</p> 	<p>146431 (D) 180.1658</p>	<p>Antiasmatic 58-55-9</p>	0	0	0	0	0	0	0

<p>Thiamphenicol</p> 	- 356.2202	Antibiotic 15318-45-3	19	19	0	0	0	0	0
<p>Tramadol</p> 	25896 (F) 263.379	Analgesic 27203-92-5	1	1	4	0	0	0	0
<p>Trimethoprim</p> 	12496 (D) 290.3212	Bacteriostatic Antibiotic 738-70-5	70	325	682	20	140	0	34
<p>Troxeutin</p> 	444339 (F) 742.6834	Antihypertensive 7085-55-4	0	0	0	0	0	0	0

<p style="text-align: center;">Tylosin</p> 	<p style="text-align: center;">-</p> <p style="text-align: center;">916.1108</p>	<p style="text-align: center;">Antibiotic</p> <p style="text-align: center;">1401-69-0</p>	22	176	278	1	59	1	0
<p style="text-align: center;">Valproic acid</p> 	<p style="text-align: center;">112162 (F) (Sodium Valproate)</p> <p style="text-align: center;">144.2132</p>	<p style="text-align: center;">Anticonvulsant</p> <p style="text-align: center;">99-66-1</p>	0	0	0	0	0	0	0

<p style="text-align: center;">Vancomycin</p> 	<p>1048 (D) 1449.2704</p>	<p>Antibiotic 1404-90-6</p>	<p>0</p>	<p>54</p>	<p>27</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>
<p style="text-align: center;">Verapamil</p>  <p style="text-align: center;">H-Cl</p>	<p>72393 (D) 491.0691</p>	<p>Antihypertensive 152-11-4</p>	<p>1</p>	<p>1</p>	<p>1</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>
<p style="text-align: center;">Xylometazoline</p> 	<p>486 (D) 244.379</p>	<p>Decongestant 526-36-3</p>	<p>0</p>	<p>0</p>	<p>1</p>	<p>0</p>	<p>0</p>	<p>0</p>	<p>0</p>

KNAPPEKnowledge and Need Assessment on Pharmaceutical
Products in Environmental Waters**D1.1: List of relevant PPs**

<p>Zolpidem</p>  <chem>Cc1ccc(cc1)-c2nc3cc(C)nc3n2CCN(C)C</chem>	3343 (F) 307.3944	Anticonvulsant 82626-48-0	5	0	27	0	2	0	8
<p>Zopiclone</p>  <chem>C1CCN(C1)C(=O)Oc2nc3cc(Cl)nc3n2C(=O)c4ccncc4</chem>	1948 (F) 388.8127	Sedative 43200-80-2	0	0	0	0	0	0	0

8. Annex

List of scientific papers used for the data list on occurrence data

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