National Institute for Public Health
and the Environment
*Ministry of Health, Welfare and Sport*

# Assessment of potential risks of 11 pharmaceuticals for the environment

*Using environmental information from public databases*

RIVM Letter Report 601711003/2011
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# Abstract

**Assessment of potential risks of 11 pharmaceuticals for the environment**
Using environmental information from public databases

The presence of pharmaceuticals and their degradation products in the water environment can be harmful for the ecosystem. For 22 pharmaceuticals some public government databases were searched for information on these harmful effects (environmental endpoint data) for 22 selected pharmaceuticals. These pharmaceuticals were selected because they are frequently consumed in the Netherlands or identified as a problem for the production of drinking water. Their degradation products are excreted in urine and subsequently can reach the water system. Based on environmental endpoint data Predicted No Effect Concentrations (PNECs) can be derived: below this concentration harmful effects are not expected. Combined with Predicted Environmental Concentrations (PECs) can PEC/PNEC ratio's help identify possible risks for the water ecosystem at an early stage.

**One out of three databases contains information on environmental endpoint data**
Neither the Dutch "Geneesmiddeleninformatiebank" nor the European Public Assessment Reports (EPARs) publised on the European Medicines Agency (EMA) website currently contain the requested information. The Swedish Environmental Classification and Information System (SECIS) for pharmaceuticals does contain this information for 15 pharmaceuticals. For 13 pharmaceuticals this information was sufficient to derive preliminary PNECs (Predicted No Effect Concentrations).

**Possible risks for two out of thirteen evaluated pharmaceuticals**
Together with Predicted Environmental Concentrations (PECs) based on yearly consumption of the pharmaceutical in the Netherlands, preliminary PEC/PNEC ratios could be calculated. For two out of the 13 evaluated pharmaceuticals (the antibiotic amoxicillin and the hormone ethinylestradiol) these ratios were above 1. This means that risks for the freshwater ecosystem might be expected from the use of these individual substances as human medicines. To evaluate if these risks actually occur, an extended environmental fate and effect analysis is required.

Keywords:
PEC, PNEC, prioritisation, drinking water, ecotoxicology

# Rapport in het kort

**Schatting van potentiële risico's voor het watermilieu van 11 geneesmiddelen**
Gebruikmakend van openbaar beschikbare milieu-informatie

Restanten van geneesmiddelen in het watermilieu kunnen schadelijk zijn voor het ecosysteem. Het RIVM heeft voor 22 geneesmiddelen onderzocht of enkele openbare databases van overheden informatie bevatten over het optreden van schadelijke effecten (milieu-eindpunten). Deze geneesmiddelen zijn geselecteerd omdat ze veel worden gebruikt in Nederland of zijn aangemerkt als een probleemstof voor de drinkwaterbereiding. Restanten kunnen via urine in het water terechtkomen. Met informatie over milieu-eindpunten kunnen zogeheten Predicted No Effect Concentrations (PNEC' s) worden afgeleid: beneden deze concentraties worden geen negatieve effecten verwacht. In combinatie met een te verwachten concentratie (Predicted Environmental Concentrations, PECs) kunnen PEC/PNEC-ratio's helpen om mogelijke risico's voor het watermilieu vroegtijdig te signaleren.

**Een van de drie databases levert informatie op**
De gezochte informatie blijkt niet beschikbaar te zijn via de Nederlandse Geneesmiddeleninformatiebank, noch de Europese Public Assessment Reports (EPARs) die worden gepubliceerd op de website van het European Medicines Agency (EMA). Van 15 geneesmiddelen is wel informatie over milieu-eindpunten beschikbaar via het Zweedse Environmental Classification and Information System (SECIS). Van 13 van deze geneesmiddelen was voldoende informatie beschikbaar om voorlopige PNEC' s af te leiden.

**Mogelijk risico bij twee van de dertien onderzochte geneesmiddelen**
In combinatie met de berekende PECs op basis van de jaarlijkse consumptie van het geneesmiddel in Nederland, resulteerde dit in voorlopige PEC/PNEC-ratio's. Voor 2 van de 13 geëvalueerde geneesmiddelen (het antibioticum amoxicilline en ethinylestradiol, de werkzame stof in de anticonceptiepil) waren deze ratio's hoger dan 1. Dit betekent dat risico's voor het zoetwaterecosysteem verwacht kunnen worden als gevolg van de consumptie van deze geneesmiddelen. Om te beoordelen of dergelijke effecten daadwerkelijk optreden is een uitgebreidere analyse nodig van de mate waarin de stoffen zich in het milieu verspreiden, alsmede van de effecten.

Trefwoorden:
PEC, PNEC, prioritering, drinkwater, ecotoxicologie

# Contents

# 1 Introduction

## 1.1 Background

Public awareness and concern regarding the occurrence and effects of pharmaceuticals and their residues throughout the water cycle has been growing in the Netherlands since the late 1990s. In the Netherlands, effluents of wastewater treatment plants (WWTPs) represent an important emission route for pharmaceuticals to enter the surface water system. A number of Dutch studies (e.g. Kiwa et al., 2004; Mons et al., 2000; Schrap et al., 2003; Ter Laak et al, 2010) have demonstrated the presence of high concentrations of pharmaceuticals in these effluents (range: 1000–10,000 ng/l) and the receiving surface water (range: 10–1000 ng/l). Groundwater is less affected (usual range: 10–100 ng/l), with higher concentrations having been found in exceptional cases only, possibly due to leakage from sewers.

Most Dutch drinking water companies that use surface water as the production source have started monitoring pharmaceutical levels. However, the very large number of pharmaceutical compounds in combination with the lack of information on occurrence, toxicity and degradability impedes the assessment of the impact of all pharmaceuticals on the water cycle and coerces an arbitrary choice of pharmaceuticals for monitoring programmes. Therefore the approach currently used to select 'drinking water-relevant' pharmaceuticals for these monitoring programmes has been rather pragmatic, based on existing scientific literature on occurrence of pharmaceuticals in the water environment, as well as availability of analytical methods.

Occurrence of pharmaceuticals in the water system can be predicted based on publicly available pharmaceutical sales data in combination with metabolism in the human body and degradability during water treatment, as is shown by e.g. Ter Laak et al. (2010) and STOWA (2011). To be able to predict environmental effects of single active pharmaceutical substances, experimental data on ecotoxicology and environmental fate and behaviour for these pharmaceuticals are needed. Public scientific literature (both scientific journals and research reports) provides a useful source of these type of data but a is relatively time consuming way of data collection. Recently some pilot projects have been started to make information on environmental endpoints, collected within the framework of the registration process of pharmaceuticals in the European Union, publicly accessible.

### *1.1.1 Objective*

The aim of the project was to investigate if environmental endpoint data are available through some public (government) databases and if this information can be used to identify possible risks of pharmaceuticals for the aquatic environment or drinking water production. The following questions will be addressed:

- is it possible to retrieve this information with a limited time investment for 20 selected pharmaceuticals?
- can preliminary Predicted No-Effect Concentrations (PNECs) be derived with this information and compared to preliminary Predicted Environmental Concentrations (PECs) in order to prioritize pharmaceuticals with risks for the aquatic environment?

## 1.2 Selection of compounds

The top 10 most consumed pharmaceuticals in the Netherlands in 2007 were selected based on sales data on kilograms active ingredients (table 1), see also Van der Aa et al. (2008). These data were provided by the SFK, the Foundation for Pharmaceutical Statistics in the Netherlands. The SFK directly gathers its data from a consortium of pharmacies that currently comprises 1.760 (90%) of the 1.940 community pharmacies in the Netherlands (SFK, 2008). The consumption data do not include pharmaceuticals for hospital use or veterinary use nor do they include pharmaceuticals that can be purchased over-the-counter. Total consumption was calculated per pharmaceutical active compound, which for most pharmaceuticals is represented by several ATC5-codes. Gasses, solvents, inorganic salts, auxiliary matter, proteins, vitamins, amino acids and vegetable extracts were removed from the dataset.

**Table 1.** Top 10 most consumed pharmaceuticals in the Netherlands in 2007, selected based on SFK sales data in kilograms active ingredient.

| Group | Substance | Sales in 2007 (kg) |
|---|---|---|
| Gastrointestinal drugs | Lactulose | 327.340 |
| Antidiabetics | Metformin | 207.190 |
| Analgesics | Paracetamol | 104.714 |
| Antirheumatics | Ibuprofen | 28.884 |
| Antidiabetics | Tolbutamide | 28.682 |
| Gastrointestinal drugs | Mesalazine | 23.337 |
| Antihypertensives | Metoprolol | 22.681 |
| Antiinfectives / Antibiotics | Amoxicillin | 20.263 |
| Antithrombotic agents | Carbasalate calcium | 14.856 |
| Antiepileptics | Valproate | 14.593 |

In addition, 12 pharmaceuticals were selected that were identified as "drinking water relevant" pharmaceuticals by Van der Aa et al. (2008), also shown in Table 2. They are considered relevant for drinking water production because they are detected in sources for drinking water or are difficult to remove during drinking water production.

**Table 2.** Twelve additional selected "drinking water relevant" pharmaceuticals with SFK sales data.

| Group | Substance | Sales in 2007 (kg) |
|---|---|---|
| Antihypertensives | Irbesartan | 12.388 |
| Antiepileptics | Carbamazepine | 8.400 |
| Antirheumatics | Diclofenac | 6.227 |
| Antihypertensives | Valsartan | 6.123 |
| Antihypertensives | Furosemide | 3.555 |
| Antiinfectives / Antibiotics | Sulfamethoxazole | 3.165 |
| Analgesics | Codeine | 1.571 |
| Antiinfectives / Antibiotics | Trimethoprim | 1.108 |
| Antiinfectives / Antibiotics | Erytromycine | 888 |
| Antidepressants / Antipsychotics | Fluoxetine | 357 |
| Antiinfectives / Antibiotics | Ofloxacin | 167 |
| Sex hormones | Ethinylestradiol | 15 |

# 2 Predicted No Effect Concentrations

## 2.1 Data sources and data availability

Public scientific literature (both scientific journals and research reports) is a useful source for experimental data on ecotoxicology and environmental fate and behaviour of pharmaceutical substances in the aquatic environment. For PNEC derivation the most reliable method of collecting data is to retrieve the original data sources (reports or publications of the experimental studies) and to carefully evaluate these with respect to validity and usefulness, as described by e.g. Anonymous (2011), Klimisch (1997), Mensink et al. (2008) and Küster et al. (2009). However, for this project, data from scientific literature were not searched, since this is a relatively time consuming way of data collection. When less time is available, one has the option to rely on data collections (databases) where the results of the relevant studies are presented and to use these without further evaluation.

A potentially useful body of information on environmental endpoints is being built in the registration process of pharmaceuticals in the European Union. In the EU, all registration procedures of pharmaceutical products are performed according to Directive 2001/83/EC (EC, 2001b) as amended by Directive 2004/27/EC (EC, 2004a) for human pharmaceuticals and Directive 2001/82/EC (EC, 2001a) as amended by Directive 2004/28/EC (EC, 2004b) for veterinary pharmaceuticals. In this project, focus is on human pharmaceuticals only. The necessity to evaluate the potential environmental risks associated with the use of a pharmaceutical product follows from the legislation cited above. Data requirements and methodology on the performance of the environmental risk assessment (ERA) have been laid down by the European Medicines Agency (EMA) in guideline EMEA/CHMP/SWP/4447/00 (EMEA, 2006). The document is recently updated (EMEA/CHMP/SWP/4447/00 corr 1) with small amendments. Whether or not an ERA is performed in a given registration procedure depends on the type of active ingredient and the type of registration procedure. The ERA entails a PBT assessment, and depending on the expected exposure of the active ingredient, a risk assessment (PEC/PNEC).

There has not been a systematic disclosure of the results (environmental endpoints) of the studies submitted (and evaluated) during the registration procedure since 2006. However, EMA has recently agreed on the format and implementation of a data table in which all results (endpoints) from the environmental part of the registration dossier can be listed. Once the registration procedure is finalised and the product authorised, the data table is to be included in the EPAR, the European Public Assessment Report. These EPARs are published for all products that have received a European authorisation (i.e. registration in all 27 EU member states) and are published on EMA's website (www.ema.europa.eu).

For pharmaceutical products that are registered via either a national, decentralised or mutual recognition registration procedure, the same ERA requirements apply since the EMA guideline on ERA should be followed also for these procedures. However, the responsibility to implement the data table with environmental endpoints as well as to publish PARs (Public Assessment Report) that could include this table is with the respective member state’s competent authority.

For the 10 active ingredients selected in this project (Table 1), we have searched for environmental endpoint data in the following sources:

- the EPARs publised on the EMA website;
- the Geneesmiddeleninformatiebank at www.cbg-meb.nl. This is the database of the Dutch Medicines Evaluation Board (MEB) containing data on all registered pharmaceuticals in the Netherlands.

However, no data for our selection of compounds were found at either location.

We have therefore used the Swedish Environmental Classification and Information System (SECIS) for pharmaceuticals. It can be reached via www.fass.se and was initiated by the Swedish Association for the Pharmaceutical Industry (LIF) and supported by several stakeholders from healthcare (Ågerstrand and Rudén, 2010). No searches for data in other sources were undertaken. Possible data sources (not used for this study) could be:

- Public scientific literature. Both publications in peer reviewed scientific journals as well as grey literature (reports from research agencies, universities, et cetera).
- WikiPharma. A recent initiative funded by Swedish Foundation for Strategic Environmental Research (Mistra) to collect and present public literature data on environmental risks caused by human pharmaceuticals in a database (Molander et al., 2009).
- Environmental quality standards for human pharmaceuticals. To date there is one EQSs adopted for an active ingredient of human pharmaceuticals in the Netherlands (viz. ethinylestradiol). There are no EU –wide EQSs set for pharmaceuticals[1]. The existence of EQS values in other EU member states at the national level has not been investigated. In 2010 diclofenac and ethinylestradiol were nominated as priority substances under the WFD 2000/60/EC.

## 2.2 Derivation of preliminary PNECs

For the 22 active ingredients selected (Table 1 and Table 2) we have searched for environmental endpoint data in the Swedish database SECIS. For 7 of the 22 selected substances, no data could be found in this database, so we have not derived a preliminary PNEC for these compounds.

For the other actives, the available toxicity data were collected in a spreadsheet (Table 3). Toxicity data were separated into acute and chronic toxicity data for the three groups algae, Daphnia and fish. For some substances, data on species from additional taxonomic groups were found. We therefore added the taxa/categories: cyanobacteria, macrophytes and 'extra species' for those –exceptional- cases where a datum on an additional taxon was found.
If more than one test result for one of the above mentioned groups was available, the lowest value was selected for preliminary PNEC derivation. In order to derive the preliminary PNEC, the assessment factor scheme (including footnotes) from the REACH framework was followed (ECHA, 2008). It can be found in the cited guidance document in section 10.3.1.2, Table R.10-4. This scheme is used for the PNEC derivation in several frameworks: REACH (industrial chemicals), biocides and EQS derivation in Europe (current and draft guidance on EQS under the Water Framework Directive), which is also implemented in the Netherlands.

[1] In a strict sense, (national) EQS have been set for some substances that are also in use as pesticide or biocide, like malathion (medicinal use against headlice) and diazinon (veterinary use against pest insects).

The following remarks can be made to the preliminary PNEC derivation.

- A reproduction study with the crustacean species *Ceriodaphnia dubia* (exposure duration of 7 days) was used as valid representative for a chronic study with crustacea. Two of these studies were available. *C. dubia* thus replaced the presence of a chronic toxicity study with *Daphnia magna*, which is more regularly encountered as test species in chronic studies with crustacea.
- Toxicity data for saltwater species were only found for two substances and in both cases it concerned algal toxicity data. Data for saltwater species were combined with those for freshwater species for PNEC derivation.
- All toxicity data for algae were combined. For two substances, toxicity data for algal species not belonging to the green algae (i.c. diatoms, red algae) were found.
- As mentioned, cyanobacteria were treated as a separate taxon, as is also done in EQS derivation, since cyanobacteria are prokaryotes and taxonomically distinct from the (eukaryotic) algae.
- As mentioned, underlying studies were not retrieved, hence data were not further evaluated with respect to reliability and validity.
- Although a test result expressed as NOEC (no observed effect concentration) derived from an acute toxicity test is not directly useful for derivation of a PNEC, it can be used to help complete the base set of toxicity data. If the NOEC and available other toxicity data demonstrate that the species for which the NOEC was obtained is not the most sensitive taxon, the PNEC derivation can continue even though the base set is incomplete (i.c. trimethoprim).
- In case a true chronic NOEC is available, but an L(E)C50 value for the same taxonomic group is lacking (making the base set incomplete), the PNEC derivation can continue if the chronic NOEC demonstrates that the specific taxonomic group is not the most sensitive taxon (i.c. ofloxacine).
- In general, data on bacteria were not included because data are usually pertaining to toxicity of micro-organisms in STP sludge, not to representatives of an aquatic ecosystem. And in general, in the rare case that a test result with a single bacterial species is listed, it can not be inferred from the limited data presented if this concerns a test with a freshwater representative species under representative test conditions. One test with *Vibrio fisheri* was found, which was used (i.c. ofloxacine)

**Table 3**. Preliminary PNECs calculated based on retrieved toxicity data from the Swedish Environmental Classification and Information System (SECIS) for pharmaceuticals (www.fass.se)

| | ACUTE (E/LC50) TOXICITY DATA | | | | | | CHRONIC (NOEC) TOXICITY DATA | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Algae | Crustacea | Fish | Cyano bacteria | Macrophytes | Extra sp. | Algae | Crustacea | Fish | Cyano bacteria | Extra sp1 | Extra sp2 | Assessment factor | preliminary PNEC |
| Active | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [mg/L] | [–] | [**µg/L**] |
| Metformin | 320 | 64 | ≥982 | | 110 | | | | ≥32 | ≥12 | | | 50 | ≥ 240 |
| Paracetamol | 134 | 9.2 | 378 | | | | | | | | | | 1000 | 9.2 |
| Amoxicilline | 630 | > 2300 | >930 | 2.22E-03 | | | 530 | 7.80E-04 | | | | | 10 | 0.078 |
| Valproate [(1)] | > 100 | > 100 | | | | 500-1000 | | | | 5 | | | * | |
| Irbesartan | 79 | 191 | > 290 | | | | 23 | | 10.4 | ≥ 7.04 | | | 10 | ≥ 700 |
| Carbamezepine | | 92 | 43 | | | | 20 | | 17 | | | | 100 | 170 |
| Codeine | | | | | | | | | | | | | * | |
| Diclofenac,acid | | 30.7 | 82 | | | | 10 | | | 4 | | | 1000 | 31 |
| Erytromycine | 0.0366 | | 349 | | | | 10.3 | | | | | | * | |
| Ethinylestradiol | 0.13 | 6.4 | 1.6 | | | | < 0.1 | | ≥0.387 | 0.000001 | | | 10 | 0.0001 |
| Fluoxetine | 0.0273 | 0.234 | 0.705 | 224 | | | | | 0.056 | ≥5 | | | 50 | 1.12 |
| Furosemide | 322 | > 100 | > 500 | | | | 3.13 | | | | | | 1000 | 320000 |
| Ofloxacine | 0.09 | 76.58 | | 0.016 | | >90 | 0.005 | 0.005 | | >16 | 12.5 | 0.0013 | 50 | 0.026 |
| Sulfamethoxazole | 0.81 | NOEC >36 | | 0.0268 | | | 0.22 | 0.0059 | 0.01 | 8 | | | 10 | 0.59 |
| Trimethoprim | 16 | 123 | NOEC 100 | 112 | | | 32 | | | | | | 1000 | 16 |
| Valsartan | 90 | > 100 | > 100 | | | | 58 | | | | | | 1000 | 90 |

Notes

All preliminary PNECs expressed in µg/L and rounded off to two significant digits.

* Base set incomplete, a preliminary PNEC could not be derived.

1. For valproate, the evaluation of the potential teratogenic effects on vertebrates needs careful evaluation. In the limited time frame and data available, a reliable PNEC derivation could not be made.

# 3 Predicted Environmental Concentrations

Predicted Environmental Concentrations (PECs) were calculated using the formulas presented in EMA guidelines. First, $F_{pen}$ was calculated using the equation shown below, which is taken from section 9 of EMEA ( 2006). $F_{pen}$ calculations are also worked out in End note 1 of the Questions and answers document EMA/CHMP/SWP/44609/2010 (EMA, 2011).

$$F_{pen} = \frac{Consumption}{DDD * Inhabitants * 365}$$

| | |
|---|---|
| $F_{pen}$ | penetration factor |
| Consumption | yearly consumption of the pharmaceutical in mg/year in 2007 based on data from the foundation for pharmaceutical statistics (SKF) |
| DDD | defined daily dose consumed by inhabitant in mg/patient/day |
| Inhabitants | number of inhabitants in the Netherlands |
| 365 | number of days in one year |

Table 4 shows the calculated $F_{pen}$ values and the DDD values used. Consumption data are given in Tables 1 and 2.

**Table 4.** Calculated Fpen values.

| # | Substance | *DDD* (mg/patient/d) | $F_{pen}$ (–)[2] |
|---|---|---|---|
| 1 | Metformin | 2000 | 0.0173 |
| 2 | Paracetamol | 3000 | 0.00584 |
| 5 | Ibuprofen | 1200[a] | 0.00403 |
| 6 | Amoxicillin | 1000 | 0.00339 |
| 7 | Valproate | 1500 | 0.00163 |
| 8 | Irbesartan | 150 | 0.0138 |
| 9 | Carbamazepine | 1000 | 0.00140 |
| 10 | Codeine | 100 | 0.00263 |
| 11 | Diclofenac | 100 | 0.0104 |
| 12 | Ethinylestradiol | 0.025 | 0.0988 |
| 13 | Fluoxetine | 20 | 0.00299 |
| 14 | Furosemide | 40 | 0.0149 |
| 15 | Ofloxacin | 400 | 0.0000697 |
| 16 | Sulfamethoxazole | 2000 | 0.000265 |
| 17 | Trimethoprim | 400 | 0.000463 |
| 18 | Valsartan | 80 | 0.0128 |

[a] Two DDD values are available (viz. 30 and 1200 mg/patient/d). The DDD for the most widely used prescription (anti-inflammatory and antirheumatic products, non-steroids) was selected.

*Penetration factor*

The calculated penetration factor represents the fraction 'patients per inhabitants', assuming that the total amount of drug administered in the Netherlands was equally distributed over the country and over one year. In

[2] Although $F_{pen}$ is a fraction, it results from this equation in the pseudo-unit of patients/inhabitants.

other words, this neglects differentiation of drug usage in time and space. Data on this differentiation were not available.

*DDD*
Values for DDD were retrieved from http://www.whocc.no/atc_ddd_index/.

*Inhabitants*
The number of inhabitants in the Netherlands of 2007 was calculated to be 16381500, as the average of the figures for 1/1/2007 (1,6358,000) and 1/1/2008 (1,6405,000). Data were retrieved from Statistics Netherlands (CBS, http://www.cbs.nl).

Next, the $F_{pen}$ is used in the calculations for the $PEC_{surfacewater}$ using the following equations (EMEA, 2006):

$$Elocal_{water} = DOSEai * F_{excreta} * F_{pen} * CAPACITY_{STP}$$

$$PEC_{surfacewater} = \frac{Elocal_{water} * F_{stp,\,water}}{WASTEW_{inhab} * CAPACITY_{stp} * FACTOR * DILUTION}$$

| | |
|---|---|
| $PEC_{surface\ water}$ | predicted environmental concentration in surface water (mg/L) |
| $Elocal_{water}$ | local emission to wastewater of the relevant residue (mg/d) |
| $F_{stp\ water}$ | fraction of emission directed to surface water based on SimpleTreat calculations (-) |
| $WASTEW_{inhab}$ | amount of wastewater per inhabitant per day (200 L/inh/d) |
| $CAPACITY_{stp}$ | capacity of local STP (10000 inh) |
| FACTOR | factor taking the adsorption to suspended matter into account |
| DILUTION | dilution factor (10) |
| *DOSE*ai | daily dose consumed per patient, which is taken here as DDD: defined daily dose consumed by inhabitant (mg/inh/d), |
| $F_{excreta}$ | fraction of parent drug excreted by humans (-) |
| $F_{pen}$ | penetration factor (-) |

These equations are presented in Phase II Tier B of the EMA environmental risk assessment and allow for a more refined PEC estimate. First, the daily emission to the sewage treatment plant (STP) is estimated: $Elocal_{water}$. If available, the emission rate can be refined using $F_{pen}$ (Table 4) and data on metabolism in humans: $F_{excreta}$. Data for $F_{excreta}$ were available from STOWA (2010) and are listed in Table 5. For *DOSE*ai, DDD is used (listed in Table 4), but note that since it also occurs in $F_{pen}$ it equals out.

$F_{stp,\ water}$
In the calculation of $PEC_{surface\ water}$, removal of the pharmaceutical in the STP is expressed by $F_{stp,\ water}$. This parameter can be calculated for each compound, and the following physico-chemical and fate properties are needed: molecular weight ($M_w$), vapour pressure ($P_v$), aqueous solubility ($S_w$), octanol-water partitioning coefficient ($K_{ow}$), Henry's law constant (H) and adsorption constants ($K_p$) to raw sewage and to activated sludge. Since retrieval of these parameters for the 18 pharmaceuticals in this report was ambiguous ($K_{ow}$), unavailable for most ($S_w$, $K_p$) or unavailable for all ($P_v$, H), these values were estimated using QSARs. US EPAs EPISuite (US EPA, 2008) and Bioloom (BioByte, 2006) were used to that end. The various parameters and details on the calculation of

$F_{stp,\ water}$ are given in Appendix 1. Table 5 shows the calculated values for $F_{stp,\ water}$.

For five substances, our $F_{stp,\ water}$ could be compared with experimental data from literature on fractions that are removed in wastewater treatment plants (Ter Laak et al., 2010). For carbamazepine our $F_{stp,\ water}$ is comparable with these experimental data, but for ibuprofen, carbamazepine, diclofenac, sulfamethoxazole en trimethprim our $F_{stp,\ water}$ is a factor 1,5 – 4 times higher, resulting in higher estimated emissions to surface water.

*FACTOR*
EMA refers to the TGD (EC, 2003), section 2.3.8.3 for this parameter, from which it follows that FACTOR equals ($1 + K_{p,\ susp} \times SUSPwater \cdot \times 10^{-6}$), see TGD equation 45. FACTOR expresses the ratio of the total versus dissolved concentration in surface water. Total in this respect means: including the fraction adsorbed onto suspended particulate matter. Table 5 shows the values for FACTOR, Appendix 1 details how FACTOR is calculated.

**Table 5.** Values used for $F_{excreta}$ and calculated values for $F_{stp,\ water}$ and FACTOR.

| # | Substance | $F_{excreta}$ (–) | $F_{stp,\ water}$ (–) | *FACTOR* (–) | *PEC* (mg/L) |
|---|---|---|---|---|---|
| 1 | Metformin | 1 | 0.997 | 1.000040 | 1.73E-02 |
| 2 | Paracetamol | 0.040 | 0.994 | 1.000068 | 3.48E-04 |
| 5 | Ibuprofen | 0.30 | 0.947 | 1.00063 | 6.86E-04 |
| 6 | Amoxicillin | 0.75 | 0.987 | 1.00016 | 1.25E-03 |
| 7 | Valproate | 0.040 | 0.985 | 1.000041 | 4.81E-05 |
| 8 | Irbesartan | 0.020 | 0.903 | 1.0013 | 1.87E-05 |
| 9 | Carbamazepine | 0.12 | 0.859 | 1.0020 | 7.23E-05 |
| 10 | Codeine | 0.12 | 0.920 | 1.0010 | 1.45E-05 |
| 11 | Diclofenac | 0.16 | 0.946 | 1.00069 | 7.88E-05 |
| 12 | Ethinylestradiol | 0.59 | 0.642 | 1.0070 | 4.65E-07 |
| 13 | Fluoxetine | 0.24 | 0.146 | 1.14 | 9.19E-07 |
| 14 | Furosemide | 1 | 0.986 | 1.00017 | 2.93E-04 |
| 15 | Ofloxacin | 0.88 | 0.998 | 1.000018 | 1.23E-05 |
| 16 | Sulfamethoxazole | 0.20 | 0.969 | 1.00039 | 5.13E-05 |
| 17 | Trimethoprim | 0.80 | 0.991 | 1.00011 | 7.34E-05 |
| 18 | Valsartan | 1 | 0.305 | 1.034 | 1.51E-04 |

# 4 PEC/PNEC comparison

Table 5 shows the comparison of PECs and PNECs for the selected pharmaceuticals. For two substances, amoxicillin and ethinylestradiol, ratio's are above 1 which means that risks for the freshwater ecosystem is expected from the use of these individual substances as human medicines. To evaluate if effects actually occur, an extended environmental fate and effect analysis is required in which also biodegradability in wastewater treatment plants and the water environment is included. Also validations against measurements (monitoring) are needed. Although our PEC estimate was based on Phase II Tier B of the EMA environmental risk assessment, which allows for a more refined PEC estimate, removal in wastewater treatment plants was not included in the calculations, which results in rather conservative PEC estimate.

**Table 6. Preliminary PEC/PNEC comparison**

| **Substance** | **Pharmaceutical group** | **$PEC_{surfacewater}$ (µg/L)** | **PNEC (µg/L)** | **PEC/PNEC ratio** |
|---|---|---|---|---|
| Amoxicilline | Antiinfective / Antibiotics | 1.25E+00 | 0.078 | 16.03 |
| Carbamazepine | Antiepileptics | 7.23E-02 | 170 | 0.0004 |
| Codeine | Analgesics | 1.45E-02 | - | - |
| Diclofenac (total) | Antirheumatics | 7.88E-02 | 31 | 0.0025 |
| Ethinylestradiol (total) | Sex hormones | 4.65E-04 | 0.0001 | 4.65 * |
| Fluoxetine (as hydrochloride) | Antidepressants/ Antipsychotics | 9.19E-04 | 1.12 | 0.0008 |
| Furosemide | Antihypertensive | 2.93E-01 | 320000 | 0.000001 |
| Ibuprofen | Antirheumatics | 6.86E-01 | - | - |
| Irbesartan | Antihypertensive | 1.87E-02 | ≥ 700 | ≥ 0.000028 |
| Metformin hydrochloride | Antidiabetic | 1.73E+01 | ≥ 240 | ≥ 0.072 |
| Ofloxacin (total) | Antiinfective / Antibiotics | 1.23E-02 | 0.026 | 0.47 |
| Paracetamol | Analgesics | 3.48E-01 | 9.2 | 0.038 |
| Sulfamethoxazole | Antiinfective / Antibiotics | 5.13E-02 | 0.59 | 0.087 |
| Trimethoprim | Antiinfective / Antibiotics | 7.34E-02 | 16 | 0.0046 |
| Valproate | Antiepileptics | 4.81E-02 | - | - |
| Valsartan | Antihypertensive | 1.51E-01 | 90 | 0.0017 |

* for ethinylestradiol a maximum permissible concentration (MPC) of 0.000016 µg/L was determined in the Netherlands. Using this concentration instead of the PNEC, results in a ratio of 29.

The sulfamethoxazole concentration in the rivers Meuse and Rhine, measured in 2005-2005, was 51-56 ng/L, which coincides with the PEC calculated in table 6 (Montforts et al 2007). On the other hand it should be noted that hospital use is not included in this study, nor are over-the-counter use or veterinarian use. Including these in the calculations would lead to higher PEC/PNEC ratios. Especially the antiinfectives amoxicillin, sulfamethoxazole, and trimethoprim are used in substantial amounts by veterinarians. In 2007 veterinarian use of penicillins was 64 tonnes (FIDIN, 2010), of which an estimated 20-30 tonnes is contributed to amoxicillin (personal communication Utrecht University). This is comparable to the SFK sales data on human prescription use for amoxicillin (Table 1). In 2007 veterinarian use of all trim-sulfacombinations was 101 tonnes (FIDIN, 2010). Although this group includes more substances than only sulfamethoxazole and trimethoprim, this is roughly a factor 25 more than the

human use in 2007, hospitals excluded. However, the entry route to surface water is via the manure, soil application, and drainage, and even the hydrophilic sulfa's are found in only low concentrations (<30 ng/L) in water in rural areas (Montforts et al., 2007). Ofloxacin, with a PEC/PNEC ratio close to 1, is not used by veterinarians.

A comparable but more extensive study with SECIS-data was performed by Ågerstrand and Rudén (2010). They concluded that for a substantial number of the evaluated substances, the risk classification was altered when effect data from the open scientific literature were used. For 11 substances our PEC/PNEC ratio's could be compared with PEC/PNEC ratios by Ågerstrand and Rudén (2010). In their study amoxicillin and ethinylestradiol have also ratio's above 1, although the numbers differ. In their study also carbamazepine has a ratio above 1. That the PECs in their study differ from ours can be attributed to differences in pharmaceutical consumption between Sweden and the Netherlands. The PNECs in their study differ a factor 1 to 22 with our PNECs, with the exception of furosemide which shows a difference of 4 orders of magnitude. The reasons for these differences can not be explored, but as Ågerstrand and Rudén (2010) point out, the risk assessments performed by different companies within SECIS can differ substantially.

# 5 Conclusions and discussion

## 5.1 Conclusions

This research showed that experimental environmental endpoint data for a selection of 22 pharmaceuticals are currently not or difficult to retrieve through public government databases. Neither the Dutch "Geneesmiddelen-informatiebank" nor the European Public Assessment Reports (EPARs) published on the European Medicines Agency (EMA) website, currently contains this information. The Swedish Environmental Classification and Information System (SECIS) for pharmaceuticals does contain this information for 15 out of the 22 selected pharmaceuticals. For 13 pharmaceuticals this information was sufficient to derive preliminary PNECs (Predicted No Effect Concentrations).

Together with Predicted Environmental Concentrations (PECs) preliminary PEC/PNEC ratios could be calculated. For two out of the 13 evaluated pharmaceuticals (amoxicillin and ethinylestradiol) these ratios were above 1. This means that risks for the freshwater ecosystem might be expected from the use of these individual substances as human medicines. To evaluate if these risks actually occur, an extended environmental fate and effect analysis is required in which effect data from the open scientific literature should be used and validations with measurements are needed. It should also be noted that hospital use is not included in this study, nor over-the-counter and veterinarian use. Including these in the calculations would lead to higher PEC/PNEC ratios.

## 5.2 Discussion

This study showed that currently environmental endpoint data are to a limited extent available through only 1 out of 3 public (government) databases. It is expected that in the coming years more results (environmental endpoints) from the environmental part of the registration dossier will become publicly available through EPARs, the European Public Assessment Report on the EMA website. This will make it easier to calculate PNECs for more pharmaceuticals. In this respect the results of Ågerstrand and Rudén (2010) who performed a more extensive study with SECIS-data, are relevant. They concluded, among others, that for a substantial number of the evaluated substances, the risk classification was altered when effect data from the open scientific literature were used.

Derivation of PNECs based on a scientific literature search has the advantage that original publications of the experimental studies can be retrieved and evaluated. This is not possible with the SECIS-data. Using SECIS-data normally should be a less time consuming way of PNEC derivation compared to a complete scientific literature search. Time needed for the latter however, is very much dependent on the amount of relevant studies retrieved. Working with the SECIS database in our study was not optimal, probably due to our unfamiliarity and language problems using this Swedish database.

According to WHO (2011) future research should focus on developing methods or protocols for prioritizing pharmaceuticals in the context of an overall risk assessment for all drinking water hazards. Although the presence of even harmless concentrations of pharmaceuticals and their residues in drinking water is undesirable with respect to public acceptance, PEC/PNEC ratios are one way to identify possible risks for the environment or drinking water production at an earlier stage. However, the reliability of this method depends on availability and

quality of the data on pharmaceutical consumption and environmental endpoints that are used.

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# Appendix 1. Physico-chemical and fate properties of 18 pharmaceuticals and SimpleTreat calculations

**SimpleTreat**
Simple Treat 3.0 was used to calculate the distribution and elimination of the pharmaceuticals in a modelled sewage treatment plant (STP). Model details are given in Struijs (1996). SimpleTreat 3.0 is implemented in EUSES, the model used to model environmental exposure assessment within the framework of REACH and biocides. Tier IIB equations to calculate $PEC_{surface\ water}$ used in the ERA of human pharmaceuticals are derived from EUSES, including SimpleTreat. In order to calculate the relative distribution of the API over the various compartments (air, water, sludge and fraction degraded), Simple Treat requires the following chemical parameters: molecular weight, water solubility, vapour pressure, hydrophobicity ($K_{ow}$), and ready biodegradability testing. If available, sludge adsorption constants can be used.

**Parameter estimates**
For the 18 selected pharmaceuticals, physico-chemical parameters were collected as follows. Molecular weight ($M_w$) and vapour pressure ($P_v$, selected value at 25°C) were taken from EPI Suite (US EPA, 2008). Vapour pressure was recalculated to 15°C using the Arrhenius equation (Enthalpy of vaporisation 50 kJ $mol^{-1}$; EUSES default). This temperature was chosen because the default temperature in the STP in SimpleTreat is 15°C. Water solubility ($S_w$) was also taken from EPI Suite. If an experimentally determined value from EPI's database was available, this value was selected together with the experimental temperature. If an experimental value was not available, the WSKOW module from EPI Suite was used to calculate the water solubility, with the selected $K_{ow}$ value (see below) as input. In these cases, an $S_w$ at 25°C is calculated. Each $S_w$ was recalculated to 15°C using the Arrhenius equation (Enthalpy of dissolution 10 kJ $mol^{-1}$; EUSES default). $K_{ow}$ was estimated using BioLoom (BioByte, 2006). An experimental database value (MlogP) was preferred, if an experimental value was not available, an experimental database value from EPI Suite was used. In absence of experimental values, a calculated Bioloom value (ClogP) was selected. Henry's law constant $H$ (Pa $m^{-3}$ $mol^{-1}$) was calculated for 15°C from $P_v$ and $S_w$ with $H = P_v * M_w / S_w$. Unless experimental data were retrieved from www.fass.se, $K_{oc}$ was estimated using EPI Suite's KOCWIN module, selecting the MCI based value.
From the $K_{oc}$ values obtained, two $K_p$ values were calculated as input in SimpleTreat, using: $K_p = K_{oc} \times f_{oc}$. $K_{p,\ raw\ sewage}$ was calculated with $f_{oc} = 0.3$ and $K_{p,\ activated\ sludge}$ with $f_{oc} = 0.37$. Both $f_{oc}$ values are EUSES (and SimpleTreat) defaults.

**Degradation in STP**
Incorporating data on biodegradation in the STP model calculations would enhance reliability of the outcome. Since correct interpretation of biodegradation data requires careful attention and information retrieved on biodegradability was scarce, it was decided to exclude biodegradation from SimpleTreat calculations for all 18 pharmaceuticals.

All retrieved, calculated and selected values are shown in Table 1.1.
The last column presents the calculated fraction of active emitted to surface water ($F_{STP}$), as calculated by SimpleTreat.

**Total and dissolved surface water concentration**
The fraction of active emitted to surface water resulting from SimpleTreat calculations is a total concentration, i.e. it is the sum of the dissolved concentration and the concentration adsorbed to suspended particulate matter. Recalculation of $PEC_{surface\ water}$ to a dissolved rather than a so called 'total' concentration is established by the parameter FACTOR in the Tier IIB $PEC_{surface\ water}$ equation (see main report).

From the TGD (EC, 2003), section 2.3.8.3, equation 45, it follows that FACTOR equals $(1 + K_{p,\ susp} \times SUSPwater \cdot \times 10^{-6})$.
FACTOR expresses the ratio: total concentration over dissolved concentration.

In FACTOR, the following parameters and default values apply:
$K_{p,\ susp} = K_{oc} \times f_{oc,\ susp}$ , with $f_{oc,\ susp} = 0.1$ (EUSES default).
SUSPwater is the concentration of suspended matter in surface water. The default value is 15 mg $L^{-1}$.
$10^{-6}$ is the reciprocal of the conversion factor that converts kg to mg.

Table 1.1. Physico-chemical characteristics of the 18 active pharmaceutical ingredients (APIs). Columns shaded grey contain values used as input for SimpleTreat calculations.

| API (INN) | CAS # | SMILES | $M_w$ [g mol$^{-1}$] | $S_w$ [mg L$^{-1}$] | source[b] | T for $S_w$ [°C] | $S_w$@15°C [mg L$^{-1}$] | $P_v$@25° [Pa] | $P_v$@15°C [Pa] | $H$@15°C [Pa m$^{-3}$ mol$^{-1}$] |
|---|---|---|---|---|---|---|---|---|---|---|
| Metformin | 657-24-9 | N=C(N)NC(=N)N(C)C | 129.17 | 1000000 | EPI, -1.25 exp log Kow | 25 | 869363 | 1.01E-02 | 5.02E-03 | 7.45E-07 |
| Paracetamol | 103-90-2 | O=C(Nc(ccc(O)c1)c1)C | 151.17 | 14000 | EPI, exp | 25 | 12171 | 2.59E-04 | 1.29E-04 | 1.60E-06 |
| Ibuprofen | 15687-27-1 | O=C(O)C(c(ccc(c1)CC(C)C)c1)C | 206.3 | 21 | EPI, exp | 25 | 18 | 2.48E-02 | 1.23E-02 | 1.39E-01 |
| Amoxicillin | 26787-78-0 | c1cc(O)ccc1C(N)C(=O)NC2C(=O)N3C(C(=O)O)C(C)(C)SC23 | 365.41 | 3433 | EPI, exp | 25 | 2985 | 6.26E-15 | 3.11E-15 | 3.81E-16 |
| Valproate | 99-66-1 | CCCC(CCC)C(O)=O | 144.22 | 2000 | EPI, exp | 20 | 1863 | 1.13E+01 | 7.92E+00 | 6.13E-01 |
| Irbesartan | 138402-11-6 | CCCCC1=NC2(CCCC2)C(=O)N1CC3=CC=C(C=C3)C4=CC=CC=C4C5=NNN=N5 | 428.54 | 0.01413 | EPI, 6.04 MlogP | 25 | 0.012 | 1.64E-13 | 8.14E-14 | 2.84E-09 |
| Carbamazepine | 298-46-4 | NC(=O)N2c1ccccc1C=Cc3ccccc23 | 236.28 | 112 | EPI, exp | 25 | 97 | 1.17E-05 | 5.81E-06 | 1.41E-05 |
| Codeine | 76-57-3 | COc1ccc2CC5C3C=CC(O)C4Oc1c2C34CCN5C | 299.37 | 9000 | EPI, exp | 20 | 8382 | 2.55E-08 | 1.79E-08 | 6.38E-10 |
| Diclofenac | 15307-86-5 | OC(=O)Cc1ccccc1Nc2c(Cl)cccc2Cl | 296.16 | 2.8 | EPI, 4.75 MlogP | 25 | 2.4 | 8.19E-06 | 4.07E-06 | 4.92E-04 |
| Ethinylestradiol | 57-63-6 | OC(C#C)(C(C(C(C(C(c(c(cc(O)c1)C2)c1)C3)C2)C4)(C3)C)C4 | 296.41 | 11.3 | EPI, exp | 25 | 10 | 2.60E-07 | 1.29E-07 | 3.90E-06 |
| Fluoxetine | 56296-78-7[a] | CNCCC(c2ccccc2)Oc1ccc(cc1)C(F)(F)F | 309.33 | 38 | EPI, 4.05 MlogP | 25 | 33 | 3.36E-03 | 1.67E-03 | 1.55E-02 |
| Furosemide | 54-31-9 | NS(=O)(=O)c2cc(C(O)=O)c(NCc1ccco1)cc2Cl | 330.75 | 73.1 | EPI, exp | 30 | 59 | 4.08E-09 | 1.45E-09 | 8.08E-09 |
| Ofloxacin | 82419-36-1 | C1CN(C)CCN1c2c(F)cc3C(=O)C(C(=O)O)=CN4c3c2OCC4C | 361.38 | 28260 | EPI, est Kow | 25 | 24568 | 1.31E-10 | 6.51E-11 | 9.57E-13 |
| Sulfamethoxazole | 723-46-6 | Cc1cc(NS(=O)(=O)c2ccc(N)cc2)no1 | 253.3 | 610 | EPI, exp | 37 | 454 | 1.74E-05 | 3.96E-06 | 2.21E-06 |
| Trimethoprim | 738-70-5 | COc2cc(Cc1cnc(N)nc1N)cc(OC)c2OC | 290.32 | 400 | EPI, exp | 25 | 348 | 1.00E-06 | 4.97E-07 | 4.15E-07 |
| Valsartan | 137862-53-4 | CCCCC(=O)N(CC1=CC=C(C=C1)C1=CC=CC=C1C1=NNN=N1)C(C(C)C)C(O)=O | 435.52 | 0.123 | EPI, Kow 4.86 MlogP | 25 | 0.11 | 1.09E-13 | 5.41E-14 | 2.20E-10 |

Abbreviations used: EPI = EPI Suite, exp = experimentally determined value, MlogP = measured log $K_{ow}$ value from BioLoom database.

[a]Alternative CAS nrs found for fluoxetin are: 59333-67-4 and 54910-89-3.

[b]In case a value is reported in the source column, this represents the log $K_{ow}$ value used to calculate $S_w$ with EPI Suite's WSKOW module.

Table 1.1-continued. Physico-chemical characteristics of the 18 active pharmaceutical ingredients (APIs). Columns shaded grey contain values used as input for SimpleTreat calculations. The calculated fraction of API released to surface water ($F_{STP}$) is also presented.

| API (INN) | log $K_{ow}$ | remark on $K_{ow}$ | $K_{oc}$ | remark on $K_{oc}$ | $K_p$ raw sewage | $K_p$ act sludge | $F_{STP}$ |
|---|---|---|---|---|---|---|---|
| | [-] | | [L kg$^{-1}$] | | [L kg$^{-1}$] | [L kg$^{-1}$] | [-] |
| Metformin | -1.25 | EPI, measured | 26.77 | EPI MCI | 8.031 | 9.9049 | 0.997 |
| Paracetamol | 0.51 | EPI and BioLoom, measured | 45.09 | EPI MCI | 13.527 | 16.6833 | 0.994 |
| Ibuprofen | 3.50 | BioLoom, measured | 422.2 | EPI MCI | 126.66 | 156.214 | 0.947 |
| Amoxicillin | -1.99 | BioLoom, measured | 108.4 | EPI MCI | 32.52 | 4.01E+01 | 0.987 |
| Valproate | 2.75 | EPI and BioLoom, measured | 27.21 | EPI MCI | 8.163 | 10.0677 | 0.985 |
| Irbesartan | 6.04 | BioLoom, calculated | 869[c] | exp[c] | 260.7 | 321.53 | 0.903 |
| Carbamazepine | 2.45 | EPI and BioLoom, measured | 1328 | EPI MCI | 398.4 | 491.36 | 0.859 |
| Codeine | 1.14 | BioLoom, measured | 699.2 | EPI MCI | 209.76 | 258.704 | 0.920 |
| Diclofenac | 4.75 | BioLoom, measured | 458 | EPI MCI | 137.4 | 169.46 | 0.946 |
| Ethinylestradiol | 3.67 | EPI and BioLoom, measured | 4678 | exp | 1403.4 | 1730.86 | 0.642 |
| Fluoxetine | 4.05 | BioLoom, measured | 9.35E+04 | EPI MCI | 28050 | 34595 | 0.146 |
| Furosemide | 2.03 | EPI and BioLoom, measured | 111 | EPI MCI | 33.15 | 40.885 | 0.986 |
| ofloxacin | -0.39 | EPI and BioLoom, measured | 12.2 | EPI MCI | 3.66 | 4.514 | 0.998 |
| sulfamethoxazole | 0.89 | EPI and BioLoom, measured | 258 | EPI MCI | 77.49 | 95.571 | 0.969 |
| trimethoprim | 0.91 | EPI and BioLoom, measured | 760 | exp | 22.8 | 28.12 | 0.991 |
| valsartan | 4.86 | BioLoom, measured | 2.26E+04 | EPI MCI | 6780 | 8362 | 0.305 |

Abbreviations used. EPI = EPI Suite, exp = experimentally determined value, MCI = $K_{oc}$ calculated using molecular connectivity index method.

[c]Two experimental values were retrieved: 110 and 869 L/kg. Based on log $K_{ow}$ estimate, preference was given to the highest value.

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