TEXTE
67/2019

The database "Pharmaceuticals in the Environment" - Update and new analysis

Final report

German Enviroment Agency

Umwelt Bundesamt

TEXTE 67/2019
Project No. 97778
FB000079

The database "Pharmaceuticals in the Environment" - Update and new analysis

Final report

by

Dusi Eike, Rybicki Marcus, Jungmann Dirk
GWT-TUD GmbH, Dresden, Germany

On behalf of the German Environment Agency

Imprint

Publisher
Umweltbundesamt
Wörlitzer Platz 1
06844 Dessau-Roßlau
Tel: +49 340-2103-0
Fax: +49 340-2103-2285
info@umweltbundesamt.de
databasepharmaceuticals@uba.de
Internet: www.umweltbundesamt.de

/umweltbundesamt.de
/umweltbundesamt

Report performed by:
GWT-TUD GmbH
Freiberger Straße 33
01062 Dresden
Germany

Report completed in:
October 2018

Edited by:
Section IV 2.2 Environmental Risk Assessment of Pharmaceuticals
Hein Arne

Publication as pdf:
http://www.umweltbundesamt.de/publikationen

ISSN 1862-4804

Dessau-Roßlau, Juni 2019

Abstract: The database "Pharmaceuticals in the Environment" - Update and new analysis

Pharmaceutical residues occur frequently in our environment. As they are used either in human but also in veterinary medicine, they are especially released via wastewater treatment plants, from livestock or production. The residues of pharmaceuticals are a potential risk to the environment and their occurrence raised an increasing concern. In the last years, studies on this potential risk increased. Hence, the exposure of the natural environment is characterized much better. These studies present only data on a respective number of pharmaceuticals in a given sampling area. To organize the huge amount of information caused by the global environmental exposure situation, the German Environment Agency initiated this project to collect all these data within one publicly available database.

A former project [1]already started to determine the occurrence of pharmaceutical in different environments, collecting and compiling datasets from publications and reports until 2013 in a first database[2]. Within the present project, we updated and optimized this database. Data were collected from a literature survey of pharmaceuticals in several environmental compartments worldwide. From 504 peer-reviewed articles published between 2010 and 2016, additional 54,947 measured environmental concentrations were integrated into the original database. The updated database contained finally 178,708 data entries of 1,519 publications. Available reports of pharmaceuticals are from 75 countries worldwide. In total, 771 substances were detected above their respective detection limit, and 269 substances were found above their limit of detection within Germany. Within the report, we provide an exemplary evaluation on the global distribution of the active pharmaceuticals substances from the European Watch List (WL) for emerging water pollutants, and the main antibiotic groups.

Kurzbeschreibung: Die Datenbank „Arzneimittel in der Umwelt“ – Aktualisierung und neue Auswertungen

Rückstände von Arzneimitteln gelangen regelmäßig in die Umwelt. Da sie sowohl in der Human- als auch Tiermedizin Anwendung finden, erreichen sie vor allem über Abwasser, durch Tierzucht oder durch Produktion. die Umwelt. Arzneimittelrückstände stellen ein potenzielles Risiko für Mensch und Umwelt dar und werden zunehmend kritisch betrachtet. In den letzten Jahren stieg die Zahl der Untersuchungen und das Gefahrenpotenzial für die Umwelt wird daher immer besser charakterisiert. Die einzelnen Studien sind aber jeweils auf eine gewisse Anzahl an Arzneimitteln in einem bestimmten Untersuchungsgebiet beschränkt. Um die enorme Menge an Informationen bezüglich der Umweltbelastung durch Arzneimittel zu überschauen, initiierte das Umweltbundesamt ein Projekt, in dem die Daten in eine gemeinsame öffentlich zugängliche Datenbank überführt werden.

Im Vorgängerprojekt[1] wurde das Vorkommen von Arzneimittelrückständen in verschiedenen Umweltkompartimenten untersucht. Dafür wurden Datensätze aus Publikationen, die bis 2013 veröffentlicht wurden, zusammengetragen und in einer Datenbank[2] gesammelt. In diesem Projekt wurde diese Datenbank aktualisiert und optimiert. Aus 504 Artikeln, veröffentlicht zwischen 2010 und 2016, wurden 54.947 gemessene Umweltkonzentrationen neu in die Datenbank überführt. Die aktualisierte Datenbank enthält damit 178.708 Einträge aus 1.519 Publikationen mit Daten aus 75 Ländern. Weltweit wurden 771 Arzneimittelwirkstoffe und alleine in Deutschland wurden 269 Wirkstoffe oberhalb ihrer Nachweisgrenze gemessen. Dieser Bericht gibt einen kurzen Überblick über das weltweite Vorkommen von Wirkstoffen, die als Pharmazeutika auf der Europäischen Beobachtungsliste für gewässergefährdende Stoffe stehen sowie zu den Hauptgruppen der Antibiotika gehören.

[1] www.umweltbundesamt.de/en/publikationen/pharmaceuticals-in-the-environment-global
[2] www.uba.de/db-pharm

Table of content

List of figures 10
List of tables 12
List of abbreviations 14
Summary 15
Zusammenfassung 17
1 Introduction 19
2 Project aim 21
3 Literature survey and Data collection 22
3.1 Protocol of literature search and defining search parameters 22
3.2 Evaluation of literature survey 22
3.3 Article review and bibliographic database 23
3.4 Issues during literature survey 23
4 Creating the database 24
4.1 Analysing the existing database 24
4.2 Deduction of optimized data base scheme 25
4.2.1 General modifications 25
4.2.2 Specific modifications of “mec_global” 25
4.2.3 Specific modifications of “pharma_agents” 28
4.2.4 The table “literature” 28
4.2.5 The table “sampling_country_information” 28
4.2.6 Further tables 29
4.3 Transfer of data into and between DBs as well as final DB corrections 29
4.3.1 Import data from Access to MySQL 29
4.3.2 Export data from MySQL back to Access 29
4.3.3 Import of huge data sets 30
4.3.4 Final DB modifications and remarks 31
4.4 Data analysis and map creation 33
5 General overview of the database 35
5.1 Classification of environmental matrices 35
5.2 Worldwide occurrence of pharmaceuticals 38
5.3 Global occurrence of pharmaceuticals 39
6 Occurrence of pharmaceuticals (EU watch list) 41
6.1 17-beta-Estradiol (E2) 41

6.1.1 General occurrence of E2 41
6.1.2 Specific occurrence of E2 42
6.1.3 Specific distribution of E2 43
6.2 17-alpha-Ethinylestradiol 44
6.2.1 General occurrence of EE2 44
6.2.2 Specific occurrence of EE2 47
6.2.3 Specific distribution of EE2 47
6.3 Diclofenac 49
6.3.1 General occurrence of diclofenac 49
6.3.2 Specific occurrence of diclofenac 50
6.3.3 Specific distribution of diclofenac 51
6.4 Azithromycin 52
6.4.1 General occurrence of azithromycin 52
6.4.2 Specific occurrence of azithromycin 53
6.4.3 Specific distribution of azithromycin 56
6.5 Clarithromycin 57
6.5.1 General occurrence of clarithromycin 57
6.5.2 Specific occurrence of clarithromycin 60
6.5.3 Specific distribution of clarithromycin 60
6.6 Erythromycin 61
6.6.1 General occurrence of erythromycin 61
6.6.2 Specific occurrence of erythromycin 62
6.6.3 Specific distribution and loads of erythromycin 63
6.7 Ciprofloxacin 64
6.7.1 General occurrence of ciprofloxacin 64
6.7.2 Specific occurrence of ciprofloxacin 65
6.7.3 Specific distribution of ciprofloxacin 67
6.8 Amoxicillin 68
6.8.1 General occurrence of amoxicillin 68
6.8.2 Specific occurrence of amoxicillin 69
6.8.3 Specific distribution of amoxicillin 69
7 Occurrence of antibiotic groups 71
7.1 Aminoglycosides 71
7.1.1 General occurrence of aminoglycoside 71

7.2 Beta-lactams ... 73
7.2.1 General occurrence of beta-lactams ... 73
7.2.2 Specific distribution of beta-lactams ... 74
7.3 Macrolides ... 75
7.3.1 General occurrence of macrolides ... 75
7.3.2 Specific distribution of macrolides ... 77
7.4 Quinolones/Fluoroquinolones ... 78
7.4.1 General occurrence of quinolones and fluoroquinolones ... 78
7.4.2 Specific distribution of quinolones and fluoroquinolones ... 79
7.5 Sulfonamides ... 80
7.5.1 General occurrence of sulfonamides ... 81
7.5.2 Specific distribution of sulfonamides ... 82
7.6 Tetracyclines ... 83
7.6.1 General occurrence of tetracyclines ... 83
7.6.2 Specific distribution of tetracyclines ... 85
7.7 Chloramphenicol and related substances ... 86
7.7.1 General occurrence of chloramphenicol and related substances ... 86
7.7.2 Specific distribution of chloramphenicol and related substances ... 87
7.8 Trimethoprim ... 88
7.8.1 General occurrence of trimethoprim ... 89
7.8.2 Specific occurrence of trimethoprim ... 90
7.8.3 Specific distribution of trimethoprim ... 91
7.9 Reserve antibiotics ... 92
8 Cytostatic drugs ... 93
9 Conclusion and outlook ... 94
List of references ... 95
A Appendix ... 103

List of figures

Figure 1: Overview over the original DB design 24
Figure 2: Optimized DB scheme. Enhanced entity–relationship-diagram created with MySQL-Workbench 26
Figure 3: Distribution of publications reporting MECs 38
Figure 4: Distribution of MECs 39
Figure 5: Maximum MECs for 17-beta-estradiol found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 43
Figure 6: Maximum MECs for 17-beta-estradiol found in solid immission media (sediment/soil/SPM) 44
Figure 7: Maximum MECs for 17-alpha-ethinylestradiol found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 48
Figure 8: Maximum MECs for 17-alpha-ethinylestradiol found in solid immission media (sediment/soil/SPM) 48
Figure 9: Maximum MECs for diclofenac found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 51
Figure 10: Maximum MECs for diclofenac found in solid immission media (sediment/soil/SPM) 52
Figure 11: Maximum MECs for azithromycin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 57
Figure 12: Maximum MECs for clarithromycin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 61
Figure 13: Maximum MECs for erythromycin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 63
Figure 14: Maximum MECs for erythromycin found in solid immission media (sediment/soil/SPM) 64
Figure 15: Maximum MECs for ciprofloxacin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 67
Figure 16: Maximum MECs for ciprofloxacin found in solid immission media (sediment/soil/SPM) 67
Figure 17: Maximum MECs for amoxicillin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 70
Figure 18: Number of positively detected MECs for the antibiotic group beta-lactams found in liquid immission matrices (surface water/groundwater/bank filtrate/drinking and tap water) 75

Figure 19: Number of positively detected MECs for the antibiotic group macrolides found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 77
Figure 20: Number of positively detected MECs for the antibiotic group macrolides found in solid immission media (sediment/soil/SPM).....78
Figure 21: Number of positively detected MECs for the antibiotic group quinolones and fluoroquinolones found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 80
Figure 22: Number of positively detected MECs for the antibiotic group quinolones and fluoroquinolones found in solid immission media (sediment/soil/SPM).....80
Figure 23: Number of positively detected MECs for the antibiotic group sulfonamides found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 82
Figure 24: Number of positively detected MECs for the antibiotic group sulfonamides found in solid immission media (sediment/soil/SPM).....83
Figure 25: Number of positively detected MECs for the antibiotic group tetracyclines found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 85
Figure 26: Number of positively detected MECs for the antibiotic group tetracyclines found in solid immission media (sediment/soil/SPM).....86
Figure 27: Number of positively detected MECs for chloramphenicol and related substances found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water) 88
Figure 28: Number of positively detected MECs for chloramphenicol and related substances found in solid immission media (sediment/soil/SPM).....88
Figure 29: Number of positively detected MECs for trimethoprim in all liquid media/ immission (surface water/groundwater/bank filtrate/drinking and tap water) 91
Figure 30: Number of positively detected MECs for trimethoprim in all solid media/ immission (sediment/soil/SPM) 91
Figure 31: Maximum MECs for azithromycin found in solid immission media 103
Figure 32: Maximum MECs for clarithromycin found in solid immission media 103
Figure 33: Number of positively detected MECs for the antibiotic group beta-lactams found in solid immission media.....103

List of tables

Table 1: CAS numbers with two substance names in the DB.....32
Table 2: Different matrices of the database and their classification in aggregate status and emission and immission classification as well as the number of MECs with positive detection (>LOD). MECs with no or wrong units were not considered during counting of MECs.....36
Table 3: Overview of the relevant numbers on a global scale, in the EU and Germany.....39
Table 4: Number of positively detected MECs in surface water, groundwater or drinking water for substances occurring in all five UN-regions: WEOG – Western Europe and Others Group, GRULAC – Latin American and Caribbean Group, EEG – Eastern Europe Group, ASG – Asien Group, AFG – African Group.....40
Table 5: Occurrence of 17-beta-estradiol on a global scale, in the EU and Germany.....42
Table 6: Maximum MECs of 17-beta-estradiol on a global scale, in the EU and Germany.....43
Table 7: Occurrence of 17-alpha-ethinylestradiol on a global scale, in the EU and Germany.....45
Table 8: Maximum MECs of 17-alpha-ethinylestradiol on a global scale, in the EU and Germany.....47
Table 9: Occurrence of diclofenac on a global scale, in the EU and Germany.....49
Table 10: Maximum MECs of diclofenac on a global scale, in the EU and Germany.....50
Table 11: Occurrence of azithromycin on a global scale, in the EU and Germany.....52
Table 12: Maximum MECs of azithromycin on a global scale, in the EU and Germany.....54
Table 13: Occurrence of clarithromycin on a global scale, in the EU and Germany.....58
Table 14: Maximum MECs of clarithromycin on a global scale, in the EU and Germany.....60
Table 15: Occurrence of erythromycin on a global scale, in the EU and Germany.....61
Table 16: Maximum MECs of erythromycin on a global scale, in the EU and Germany.....62
Table 17: Occurrence of ciprofloxacin on a global scale, in the EU and Germany.....64
Table 18: Maximum MECs of ciprofloxacin on a global scale, in the EU and Germany.....65

Table 19: Occurrence of amoxicillin on a global scale, in the EU and Germany 68
Table 20: Maximum MECs of amoxicillin on a global scale, in the EU and Germany 69
Table 21: Occurrence of aminoglycosides on a global scale, in the EU and Germany 72
Table 22: Occurrence of beta-lactams on a global scale, in the EU and Germany 73
Table 23: Occurrence of macrolides on a global scale, in the EU and Germany 76
Table 24: Occurrence of quinolones and fluoroquinolones on a global scale, in the EU and Germany....78
Table 25: Occurrence of sulfonamides on a global scale, in the EU and Germany 81
Table 26: Occurrence of tetracyclines on a global scale, in the EU and Germany 84
Table 27: Occurrence of chloramphenicol, thiamphenicol and florfenicol on a global scale, in the EU and Germany 86
Table 28: Occurrence of trimethoprim on a global scale, in the EU and Germany 89
Table 29: Maximum MECs of trimethoprim on a global scale, in the EU and Germany 90

List of abbreviations

AB	Antibiotic
AFG	African Group
ASG	Asian Group
CAS	Chemical Abstracts Service
DB	Database
DOI	Digital Object Identifier
E2	17-beta-Estradiol
EE2	17-alpha-Ethinylestradiol
EEG	Eastern Europe Group
EU	European Union
GIS	Geographic Information System
GRULAC	Latin American and Caribbean Group
GUI	Graphical user interface
IT	Information technology
LOD	Limit of Detection
LOQ	Limit of Quantification
MDA	3,4-Methylendioxyamphetamin
MDMA	3,4-Methylendioxy-N-methylamphetamin
MEC	Measured environmental concentration
NA	Not Available
SAICM	Strategic Approach to International Chemicals Management
UBA	German Environment Agency
USA	United States of America
WEOG	Western Europe and Others Group
WHO	World Health Organisation
WL	Watch List of emerging water pollutants
WWTP	Wastewater treatment plant

Summary

Pharmaceuticals are used either in human but also in veterinary medicine. The extensive usage leads to their release especially via wastewater, wastewater treatment plants (WWTP), from livestock or production. The residues of pharmaceuticals are a potential risk to the environment and their occurrence raised an increasing concern. Hence, the exposure of the natural environment is characterized much better. However, measured environmental concentrations (MEC) have been mostly reported for a respective number of pharmaceuticals in a given sampling area within one publication. To organize the huge amount of information on the global environmental exposure situation, the German Environment Agency initiated this project to collect all these data within one publicly available database (DB). Datasets from publications and reports until 2013 were already collected in a former project and compiled in the database "Pharmaceuticals in the environment".

Aim of the project

Aim of the project was the update and optimization of the current database "Pharmaceuticals in the environment" of the UBA. Therefore, MECs of human and veterinary pharmaceuticals residues worldwide from recent studies (2010 – 2016) were implemented into the existing database of UBA. Afterwards, the occurrence of several pharmaceutical were illustrated by comparing data from Germany with data from the EU and worldwide.

Literature survey

Within a literature survey, publications reporting MECs of pharmaceuticals were collected from articles and reports published between 2010 and 2016. In total, 1200 publication were identified for this topic and timeframe. Data of 504 publications were transferred to the database, as they were not already included.

Optimization of the database

In order to enable a consistent and user-friendly extension of the existing database , the old DB schema was optimized. The DB schema was implemented into a MySQL-DB coupled to a web-server, which enabled usage of standard web browsers and specific DB-graphical user interfaces (GUIs) for introduction of new MEC values. Basic data sets from the original DB were imported in the new DB to keep consistency of old and new entries. A semi-automated data import was established for large data sets utilizing the script language R to increase the speed of MEC introduction by keeping high accuracy. After termination of data acquisition, the new data entries were exported to the original DB and a basic analysis of the entire data set was performed.

Global Occurrence of pharmaceuticals

Within this project, pharmaceuticals in the environment have been reported for 75 countries worldwide. In total, 504 publications reported MEC data resulting in 54,947 new database entries. Therefore, the updated database contains 178,708 data entries from 1,519 publications. Most measurements have been reported for the EU with 108,628 MECs, whereas 20% of this European MECs were measured in Germany.

On a global scale, 771 substances have positively been detected above the detection limits of the analytical method employed in the publication, which means 140 substances more than in the previous report. Within the EU, 596 substances were positively detected and 269 substances in Germany.

As pharmaceuticals occur in a variety of environmental matrices, we clustered the matrices into emission or immission and their aggregate status. This result in four matrix groups: liquid emission, liquid immission, solid emission and solid immission.

Occurrence of substances on the Watch List

Within the report, the occurrence and distribution of the following eight substances included in the Watch List (WL) are presented: 17-beta-estradiol, 17-alpha-ethinylestradiol, diclofenac, azithromycin, clarithromycin, erythromycin, ciprofloxacin and amoxicillin. Diclofenac is the most detected substance with 3,996 positively detected MECs. Further, this prevalent anti-inflammatory drug was measured above the detection limit in 55 countries. In contrast, environmental analysis for amoxicillin are much lower. Only 51 publications reported MECs data for amoxicillin resulting in 134 positively detected MECs. Extreme concentration in surface water have been reported for ciprofloxacin. In India, 6,500 µg/L were detected in a lake.

Occurrence of AB-groups

The AB-groups aminoglycosides, beta-lactams, macrolides, quinolones and fluoroquinolones, sulfonamides, tetracyclines as well as chloramphenicol and its relative substances and trimethoprim, single member of the diaminopyrimidines, were further investigated with focus on their global distribution. The sulfonamides were the worldwide most detected group: 21,742 data entries have been generated from 571 publications, whereas 7,552 of these MECs were found above the detection limit. However, also the number of positively detected MECs for trimethoprim is respectable, as for a single antibiotic, 2,000 positively detected MECs have been reported for 31 countries. Finally, we also analyzed the occurrence of reserve antibiotics. None of these reserve antibiotics is listed in the database.

Conclusion and outlook

The main aim of the project, an update of the MEC DB in order to include scientific publications and reports released in the period 2010 to 2016, has ben fulfilled. During the update we noted some optimisation potential for the next DB project: DB transfer to a relational and normalized DB scheme, connected literature management, data visualization, but also data handling. We also suggest the development of a guideline for a standardized data input into the DB.

Zusammenfassung

Arzneimittel werden sowohl in der Human- als auch in der Tiermedizin verwendet. Deren hoher Verbrauch führt zur Freisetzung von Rückständen in die Umwelt hauptsächlich durch Abwasser und Kläranlagen, durch Tierzucht oder durch Produktion. Arzneimittel können unerwünschte Wirkungen auf Tiere sowie Pflanzen haben und insbesondere Antibiotika können die Entwicklung von Resistenzen fördern. In den letzten Jahren stieg die Zahl der Untersuchungen zum Vorkommen und Effekten Arzneimitteln, so dass die Gefahrenpotenziale für die Umwelt immer besser charakterisiert werden können. In Veröffentlichungen sind gemessene Konzentrationen von Arzneimittelrückständen in der Umwelt hauptsächlich für eine bestimmte Anzahl an Wirkstoffen in einem definierten Untersuchungsgebiet dargestellt. Um jedoch die enorme Menge an Publikationen zur Thematik Umweltbelastung durch Arzneimittel zu überschauen, initiierte das Umweltbundesamt (UBA) ein Projekt, in dem weltweit gemessen Umweltkonzentrationen in eine gemeinsame Datenbank überführt werden und diese öffentlich verfügbar ist. In dem Vorgängerprojekt (FKZ 371265408)[3] wurden bereits die Datensätze aus Veröffentlichungen und Berichten bis 2013 in einer Datenbank zusammengetragen.

Projektziel

Ziel des Projektes war die Aktualisierung und Optimierung der bestehenden Datenbank „Pharmaceuticals in the environment“ des UBA[4]. Gemessene Umweltkonzentrationen aus aktuellen Studien (2010–2016) wurden in die bestehende Datenbank des UBA überführt. Anschließend wurden diese Daten im Hinblick auf das Vorkommen von bestimmten Arzneimittelwirkstoffen in Deutschland, in den Ländern der EU und Vorkommen weltweit analysiert.

Literaturrecherche

Innerhalb der Literaturrecherche wurde nach Publikationen gesucht, die gemessene Umweltkonzentrationen von Arzneimitteln enthielten. Dabei wurde nach Publikationen aus dem Zeitraum 2010 bis 2016 gesucht. Für den Zeitraum wurden 1.200 Publikationen gefunden, wobei nur 504 Publikationen neue Daten für die Datenbank enthielten.

Datenbankoptimierung

Um eine konsistente und nutzerfreundliche Erweiterung der Datenbank (DB) zu ermöglichen, wurde das originale Datenbanksch ema zuerst optimiert. Das neue Schema wurde zur Verwendung im Projekt schließlich in eine MySQL-Datenbank implementiert. Durch Anbindung an einen Web-Server wurde die Dateneingabe mittels Web-Browser bzw. spezifischer Datenbank-GUIs ermöglicht. Grundlegende Datensätze der originalen Datenbank wurden überführt, um die Konsistenz von alten und neuen Datenbankeinträgen zu gewährleisten. Außerdem wurde ein halbautomatischer Datenimport unter Nutzung der Skriptsprache R etabliert, um große Datensätze schnell und exakt einzulesen. Nach Beendigung der Dateneingabe erfolgte schließlich eine erste Auswertung des Gesamtdatensatzes.

Weltweites Vorkommen von Arzneimitteln

Aus weltweit 75 Ländern gibt es Nachweise von Arzneimittelrückständen in der Umwelt. Innerhalb des Projektes wurden 54.947 neue Datenbankeinträge aus 504 Publikationen generiert. Die aktualisierte Datenbank enthält nun 178.708 Einträge, die aus 1.603

[3] https://www.umweltbundesamt.de/en/publikationen/pharmaceuticals-in-the-environment-global
[4] www.uba.de/db-pharm

Publikationen stammen. Mit 108.628 Einträgen wurden am häufigsten Umweltkonzentrationen in der EU gefunden, wobei 20% davon allein in Deutschland gemessen wurden.

Weltweit wurden 771 Arzneimittelwirkstoffe und Transformationsprodukte sicher nachgewiesen, das heißt oberhalb der Nachweisgrenzen der in den Publikationen angegebenen analytischen Methode. Das sind 140 Zusätzliche zur alten Datenbank. Innerhalb der EU gab es Nachweise von 596 und in Deutschland von 269 Wirkstoffen und Transformationsprodukten.

Die Arzneimittelrückstände wurden in vielen verschieden Umweltkompartimenten gemessen. Daher wurden die verschiedenen Kompartimente zur Analyse in Gruppen anhand des Aggregatzustandes und der Einteilung Emission/Immission eingeteilt. Es ergaben sich vier Gruppen: flüssig Emission, flüssig Immission, fest Emission und fest Immission.

Vorkommen von Arzneimitteln der Beobachtungsliste

Das weltweite Vorkommen und die Verbreitung der acht Arzneimittel, die auf der EU-Beobachtungsliste (Watch List - WL) gelistet sind bzw. waren, wurden analysiert: 17-beta-Estradiol, 17-alpha-Ethinylestradiol, Diclofenac, Azithromycin, Clarithromycin, Erythromycin, Ciprofloxacin und Amoxicillin. Diclofenac ist die am häufigsten nachgewiesene Substanz mit 3.996 gemessenen Umweltkonzentrationen. Weiterhin ist es die am weitesten verbreitete Substanz, da sie in 55 Ländern weltweit gefunden wurde. Im Gegensatz dazu wurden nur 51 Publikationen mit Amoxicillin-Funden ermittelt. Daraus konnten 134 bestimmte Umweltkonzentrationen in die Datenbank übernommen werden. Für Ciprofloxacin wurden extrem hohe Umweltkonzentrationen in Oberflächengewässern gemessen.

Vorkommen von Antibiotikagruppen

Die Antibiotikagruppen Aminoglykoside, Beta-Laktame, Makrolide, Quinolone und Fluor-quinolone, Sulfonamide, Tetrazykline sowie Chloramphenicol und verwandte Substanzen und Trimethoprim, als einziger Vertreter der Diaminopyrimidine wurden bezüglich ihrer globalen Verbreitung untersucht. In 571 Publikationen gab es weltweit für die Sulfonamide mit 21.742 die meisten Dateneinträge, wobei 7.552 positiv detektiert wurden. Für Trimethoprim (als Einzelsubstanz) sind 2.000 MECs oberhalb der Nachweisgrenze in 31 Ländern weltweit in der DB gelistet. Diese Substanz wurde detektiert. Schließlich haben wir das Vorkommen der Reserveantibiotika untersucht. Keines der gelisteten konnte in der Datenbank aufgefunden werden.

Schlußfolgerung

Die UBA-Datenbank „Arzneimittel in der Umwelt wurde im Hinblick auf wissenschaftliche Veröffentlichungen und Berichte für dem Zeitraum 2010 bis 2016 aktualisert. Dabei traten Herausforderungen auf, die vor einer erneuten Aktualisierung optimiert werden sollten: Überführung der DB in ein relationales und normalisiertes DB-Schema, Verknüpfung mit der Literaturverwaltung, Datenvisualisierung, aber auch Datenhandling. Wir schlagen daher vor, für die nächste Aktualiserung der DB auch eine Anleitung zur standardisierten Dateneingabe zu entwickeln.

1 Introduction

The occurrence and fate of pharmaceutical residues in the environment has been recognized as a global emerging issue (aus der Beek et al. 2016). Due to their extensive usage in human and veterinary medicine, pharmaceuticals occur frequently in different environmental compartments. After medical application, most active substances are not completely eliminated in human and animal body, but renally or biliary excreted (Heberer 2002). These pharmaceutical residues enter mainly into urban wastewater treatment plants (WWTP). In 1998, Ternes already reported that wastewater treatment processes were not able to completely remove the active substances (Ternes 1998). Therefore, the majority of pharmaceutical residues are released via wastewater, wastewater treatment plants but also emissions from livestock and production are relevan. Consequently the residues reach surface waters, groundwater, sediments and soils. Furthermore, substances can accumulate in the sewage sludge or manure and are thereafter transferred to soils (Heberer 2002).

Pharmaceutical residues have been frequently detected worldwide in various environmental compartments such as surface water, groundwater or soil (aus der Beek et al. 2016, Heberer et al. 2002, Carvalho et al. 2016). Their occurrence in the environment raised an increasing concern, due to their potential risk of negative impacts on organisms. Prominent examples are the detrimental effect of diclofenac on vulture populations in Pakistan (Oaks et al. 2004) or the impact of EE2 on fish populations (Kidd et al. 2007). In the last years, studies on the potential risk mainly on non-target organism increased (reviewed by Fent et al. 2006, Brausch et al. 2016) as well as the number of monitoring campaigns (aus der Beek et al. 2016). Hence, the exposure of the natural environment is nowadays characterized much better. However, single studies present only data on a respective number of pharmaceuticals in a given sampling area. A global overview about the occurrence and distribution of pharmaceuticals in the environment is missing.

In order to limit or even prevent pharmaceuticals in the environment, organizations and regulatory agencies worldwide took action e.g. by establishing specific guidelines, water policy actions (EU Wacth List), public relations work on this topic, by funding and initiating research projects and sampling campaigns.

Prominent measures stimulating public awareness are e.g. the European Water Framework Directive, sampling projects like NORMAN or respective WHO publications like “Pharmaceuticals in Drinking water” (WHO 2014). A specific European measure is the release of the European watch list for emerging water pollutants[5]. Main goal of this measure is to increase monitoring for substances with a significant risk for human health and environment to enable an EU-wide risk assessment. Several pharmaceuticals are listed on the WL and will be considered later on.

A global approach is the adoption of “environmentally persistent pharmaceutical pollutants” as an emerging policy issue under the Strategic Approach to International Chemicals Management (SAICM). The overall objective of SAICM is good chemicals management to minimize significant adverse effects on human health and the environment. To support the discussion process on pharmaceuticals with regard to SAICM, measured environmental concentrations (MEC) of pharmaceuticals from publications and reports until 2013 have been compiled in a database[6] (aus der Beek et al. 2016). Finally, the database included 123,761 database entries that were generated from 1,519 publications. In total, 731 substances or their respective transformation

[5] http://publications.jrc.ec.europa.eu/repository/bitstream/JRC111198/wl_report_jrc_2018_04_26_final_online.pdf
[6] www.uba.de/db-pharm

products were found in the environment and 631 of these substances were measured above their respective detection limit.

Aim of the present project was the update and optimization of this existing database. Therefore, MEC values were collected from a literature survey of pharmaceuticals in surface water, groundwater, tap/drinking water, manure, soil and sediment but also in the influent, effluent and sludge of wastewater treatment plants worldwide. Data published in identified peer-reviewed articles from 2010 to 2016 were compiled into the original database. In this project, non-peer reviewed publications, e. g. of local authorities or research institutes were not included. It is acknowledged that this restricts the amount of data and potentially also the number of substances or the geographical distribution. The research was restricted to articles published in English.

2 Project aim

Aim of the project was the update of the current database of the UBA. We further analysed the data in focussing on the occurrence in Germany, the EU and worldwide.

- Implementing MECs of human and veterinary pharmaceuticals worldwide from recent studies into the existing database of the UBA
- Comparing regional data from Germany with the data of the EU and worldwide
- Providing databases and maps to illustrate the global occurrence of pharmaceuticals in the environment

3 Literature survey and Data collection

Within this study, the same definition of “pharmaceutical” was used as described in aus der Beek et al. (2016). Pharmaceuticals were defined as substances that are mainly used for therapeutic purpose. Therefore, homeopathic drugs, natural substances, personal care products, recreational drugs, such as cocaine, MDA and MDMA or caffeine have not been considered for the survey.

3.1 Protocol of literature search and defining search parameters

In the literature survey, publications reporting MECs of pharmaceuticals were collected. Literature survey was restricted to literature published between 2010 and 2016, since all earlier published data have been analysed by aus der Beek et al. (2016). The survey was performed with Web of Knowledge (including the databases “Web of Science®”, “BIOSIS Citation IndexSM”, “BIOSIS Previews®”, “MEDLINE®” and “Journal Citation Reports®”). First query using the items pharmaceutical and water resulted in 6194 publications. Therefore, a more specific query using the following items was performed:

pharmaceutical AND surface NEAR water OR groundwater OR "drinking water" OR "tap water" OR soil OR manure OR "waste water" OR wastewater OR sediment

Further, the following research areas were excluded as they were seen as irrelevant:

Anesthesiology, Anthropology, Biomedical, Social Sciences, Biophysics, Business Economics, Communication, Computer Science, Criminology Penology, Critical Care Medicine, Cultural Studies , Demography, Dentist, Oral Surgery Medicine, Dermatology, Education, Educational Research, Electrochemistry, Emergency Medicine, Energy Fuels, Engineering, Ethnic Studies, Food Science, Technology, General Internal Medicine, Genetics Heredity, Geography, Geology, Geriatrics, Gerontology, Government, Law, Health Care Sciences, Services, History, Imaging Science, Photographic Technology, Infectious Diseases, Information Science, Library Science, Instruments Instrumentation, Integrative Complementary Medicine, International Relations, Legal Medicine, Materials Science, Mathematical Computational Biology, Mathematics, Medical Informatics, Medical Laboratory Technology, Nursing, Nutrition Dietetics, Obstetrics, Optics, Gynecology, Oncology, Ophthalmology, Orthopedics, Otorhinolaryngology, Parasitology, Pediatrics, Pharmacology, Pharmacy, Physics, Polymer Science, Psychiatry, Psychology, Radiology, Nuclear Medicine, Medical Imaging, Rehabilitation, Research Experimental Medicine, Respiratory System, Social Issues, Sociology, Sport Sciences, Substance Abuse, Surgery, Transplantation, Tropical Medicine, Urology, Nephrology, Virology, Chemistry organic, Mycology, Acoustics, Developmental Biology, Evolutionary Biology, Thermodynamics, Behavioral sciences, Hematology, Paleontology, Physiology, Horticulture, Neurosciences, cell biology, zoology, Immunology, Entomology, Endocrinology Metabolism

This query resulted in 3966 publications including 279 review articles.

3.2 Evaluation of literature survey

Evaluation of the query was performed for example using the items: *Pharmaceutical* AND surface water limited by the years 2010-2016. This query without any further restriction accounts for 1953 publications including 98 review articles. An evaluation was performed by chance, 1, 5 and 10% of 1953 publications were tested for the relevance of the data and MEC values data. Half of these publications have been identified as not relevant for the database, which means that there were no MEC data published. Hence further work has to be performed to identify useful search items and combinations to increase the ratio of relevant publications.

In the next step, the review articles were of interest. The query results in 98 review articles but only 44 of these dealt with the topic “pharmaceutical concentrations in the environment”. References of three latest review articles (Zhao et al. 2016, Kim et al. 2016) were compared with the publications found in Web of knowledge. We found that 60% of these references were part of the performed query, 22% were not of interest, but 18% of the references were not part of the literature survey. Nearly half of the latter references were national reports, which were not available in Web of knowledge. However, we also had references, which are available in Web of knowledge but not in the literature survey. Most of these articles contain neither the item “pharmaceutical” nor “surface water” like the review article “Occurrence and their removal of micropollutants in water environment” (Kim et al. 2016). In this case, literature survey should be performed more specific with items like the name of the pharmaceutical or a stronger definition of “surface water” e.g. “river” or “lake”. Anyhow, we also found articles of the reference list which contains one or both items but were not part of the literature survey. Therefore, we estimated the losing rate as 4-10%.

3.3 Article review and bibliographic database

All 3966 identified publications were transferred in a bibliographic database (Zotero ©, Corporation for Digital Scholarship and Roy Rosenzweig Center for History and New Media, Virginia, USA). This programme was used as it is an open source programme and is able to save libraries in several other formats.

First, references were compared with the bibliographic database of the previous report (aus der Beek et al. 2016). Afterwards, title and abstracts of the publications were reviewed for MEC data. In case of uncertainty, full text article was checked for MEC data. Finally 1200 publications were identified, whereas MEC data of 500 new publications could be transferred to the database. These publications were then categorized according to their country of detection.

3.4 Issues during literature survey

During the review process, access for some publications was limited. We therefore contacted authors via mail and researchgate.com, but the return was low. Publications with potential MECs data were stored in an extra depot within ZOTERO. Further, data return might occur after finalization of this project. These data will be transferred to the UBA for a later update of the DB.

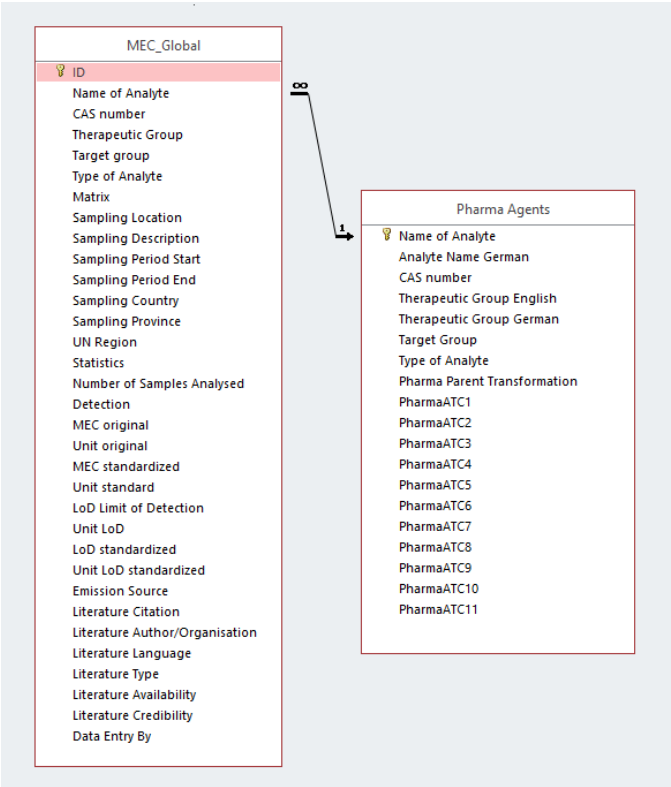
4 Creating the database

4.1 Analysing the existing database

The original database (DB) was provided as a Microsoft-Access-DB (v. 2010) consisting of two tables; one for the pharmaceuticals (substance table, 19 columns) and the other for the respective MECs and further meta information (MEC table, 33 columns). The tables were connected by a 1:n-relationship using the English substance names as key (Figure 1). This rather simple DB design, caused a high amount of general data redundancy, like the occurrence of specific columns independently in both tables (e.g. CAS number, Target Group), and inconsistencies like multiple occurrence of the same substance using different names (e.g. N4-Acetylsulfamethoxazole) or different spellings of repetitive entries (e.g. country names). Furthermore, DB extension capabilities, e.g. to include ISO-country codes to link the MEC data to GIS applications, were complicated by the simple design and required additional scripting effort during data analysis. In total, the capabilities and advantages of a DB solution were not exhausted.

Further challenges arose by the complex project structure with different project employees working at different locations in different networks. Although Access generally provides multi-user usage, this was not usable within the project, due to regulations and limitations of the used IT infrastructure. Therefore, we decided to reimplement a normalized version of the original DB utilizing state of the art open source web technology by a LAMP-server (Linux – Ubuntu 16.04 LTS, Apache 2.4.18, MySQL 5.7.23, PHP 7.0.32) hosted within the campus net of the TU Dresden. User - DB interactions were provided utilizing a specific PHP based web frontend and the MySQL Workbench (v. 6.3).

Figure 1: Overview over the original DB design



Source: own illustration, GWT-TUD GmbH

4.2 Deduction of optimized data base scheme

To overcome the described issues of the original DB, a normalization of the DB design was performed. However, due to time limitations at the beginning of the project, caused by the vast amount of new entries to be recorded within the short project time, the new design is still a compromise of applying the first three DB normal forms and a good usability. Hence, the new DB should be seen as a first step with potential for further optimization.

4.2.1 General modifications

The two tables of the original design were generally kept. However, the MEC table was cleaned from redundant attributes, which belonged to the substance table. Moreover, six additional tables were created to split the information based on the thematic background and prevent redundant inconsistent text entries:

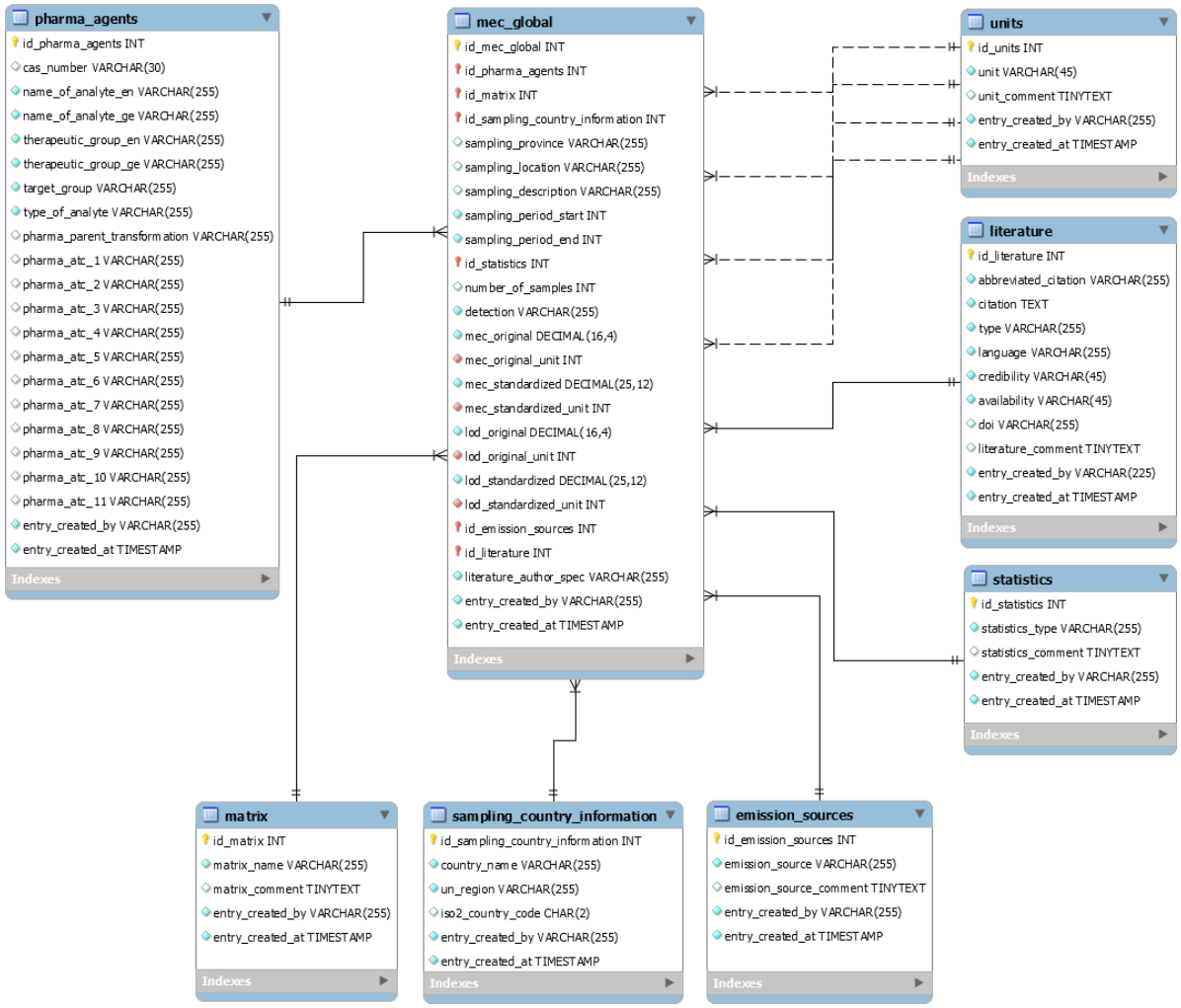
- matrix – classification of the sample matrix of a MEC
- sampling_country_information – classification of the sampling country and related information of the specific MEC
- emission_sources – classification of the emission source of a MEC if available
- statistics – classification of the statistical background of the MEC
- literature – classification of the used publication and related information of the MEC
- units – one table including all occurring units

All tables were equipped with a unique numerical primary key to decrease DB size, increase the speed of DB fetches and enable the possibility to directly refer to numeric indices instead of using complex text strings, which strongly increase the probability of mistakes e.g. when using the chemical names of the pharmaceuticals. Moreover, a basic modification tracking within each table was introduced. The original MEC table already included the attribute “Data Entry By” referring the user, who entered the data to the DB. This attribute was renamed to “entry_created_by” and introduced to all tables together with a new timestamp attribute “entry_created_at”. Furthermore, most of the tables were equipped with a comment field to add specific comments or descriptions to entries. Further smaller alterations include the consequent usage of lower case and underscore-separated naming style for table names and attributes as well as the usage of the prefix “id_” for primary and foreign keys, which eases the usage of the DB in scripting languages like R. An overview of the optimized DB scheme is shown in Figure 2. Specific changes, challenges and further optimization potential of the single tables will be briefly addressed in the following sections.

4.2.2 Specific modifications of “mec_global”

This is the central DB table containing the specific measured concentrations and further additional information. Although different attributes were already transferred to specific tables, the table still covers four topics.

Figure 2: Optimized DB scheme. Enhanced entity–relationship-diagram created with MySQL-Workbench



Source: own illustration, GWT-TUD GmbH

The first remaining topic covers different attributes concerning the sampling description. The sampling country, which is highly repetitive, was separated. Remaining attributes are:

- *sampling_province* [VARCHAR(255)] a specification of the sampling country
- *sampling_location* [VARCHAR(255)] a specification of the exact sampling location e.g. coordinates
- *sampling_description* [VARCHAR(255)] further descriptions of the sampling process or location
- *sampling_period_start* [INT, NOT NULL] start year of the sampling, -9999 if not available
- *sampling_period_end* [INT, NOT NULL] the final year of the sampling, -9999 if not available

A separation of the topic in an entirely own table is possible, but was rejected within the project, due to limited redundancy of the remaining attributes and the resulting additional creation step during data acquisition. The describing attributes were implemented using VARCHAR with a maximum of 255 characters to limit text amount within these attributes.

The next topic was the statistical background of the respective entity. The statistical parameter itself was separated to a specific table as it has a high probability to be used as index for DB querys. The remaining attribute was:

- number_of_samples [INT, '-9999'] number of samples used for the specified statistical parameter

The main topic of this table was the measured concentration itself as well as information about the detection. The occurring units of MECs, standardized MECs as well as LOD and standardized LOD were separated into an own table and addressed during fetching using four different joins on the unit table.

The remaining attributes were:

- *mec_original* [DECIMAL (16,4)] the originally publishes MEC value
- *mec_standardized* [DECIMAL (25,12)] the standardized MEC value
- *lod_original* [DECIMAL (16,4)] if available the originally published LOD else -9999
- *lod_standardized* [DECIMAL (25,12)] the standardized LOD value or -9999 if not available
- *detection* [VARCHAR (255)] a statement about the validity of the MEC referring to the LOD

We used the data type DECIMAL to save the MEC values, to prevent accuracy difficulties caused by floating point numbers. As the original published value is usually reported in suitable/readable unit, we used for the original MEC and LOD values a size of 16 digits with 4 digits behind the decimal separator. In contrast standardized values can vary strongly, hence, we chose a size of 25 digits with 12 digits behind the decimal separator i.e. 4 orders of magnitude before and behind.

As the standardized values can be calculated based on the original unit, a direct calculation of standardized values from the DB using a specific function seems possible in terms of DB optimization. This is also true for the attribute detection, as it simply compares the standardized MEC with the standardized LOD. The approach of automatically calculating the respective values was e.g. used during the script based data import.

The last remaining topic are the literature information. The literature was nearly entirely separated to an own table, except for the attribute literature_author_spec [VARCHAR (255)], which is a specification of the authorship used for big reports with several authors. In the majority of cases, this attribute contains the same text string as the attribute abbreviated_citation from the literature table and is therefore of limited value for data fetches. A better solution to reduce redundancy would be to split big reports on the level of the literature table in several entries.

4.2.3 Specific modifications of “pharma_agents”

This table contains all information about the captured pharmaceuticals. Due to time issues, we kept this table nearly in the original state, but introduced a numerical primary key as mentioned before. However, according to our experience we think that the design of the current table is not suitable for such a complex topic. Hence, an optimization is strongly recommended.

One problem arise e.g. from the fact that pharmaceuticals often have several trivial names for the same substance. This occurred e.g. for N4-Acetylsulfamethoxazole, which occurred 3 times in the old DB (using the same CAS number) and was additionally introduced using a fourth different name by one of our project employees7. This problem is intensified by the usage of the English and German names. A solution could be the separation of all additional names into an extra table. A numerical surrogate key, as introduced by us, is recommendable, as the CAS number, which seems to be the first choice, is not assigned for all captured substances especially some metabolites.

Similar problems occur with the attributes therapteutic_group, target_group and type_of_analyte, which currently occur double in English and German language, which is somehow redundant. Considering that substances may be used for several therapeutic purposes or for human and veterinary treatment (e.g. different antibiotics) reveals further difficulties with the current DB design. For optimization purposes, we suggest to split this table into different sub tables and resolve the problem of multiple usage of single attributes for one substance by utilization of joint tables. Although this would complicate the introduction of new substances, it will provide a much higher flexibility while being less redundant.

4.2.4 The table “literature”

Apart from the main literature DB managed using ZOTERO as described in section 3.3, some basic literature data were required for the MEC DB as well. We moved all literature related attributes from the original MEC table to the literature table, except for literature_author_spec (see section 4.2.2 for explanation). All attributes, except for id_literature, citation and literature_comment, used VARCHAR as data type. The column citation is the full citation entry, including all authors and publishing information. Therefore, we used a TEXT data type. We used a simple numerical ID as primary key. However, in order to increase the link between the two literature DBs and decrease redundant work, the usage of a global key e.g. from the public ZOTERO library, would be recommendable, as it complies the requirements of a key and may be directly used to import or access literature data from an external source. The utilization of the Digital Object Identifier (DOI) for this purpose was unfortunately not possible, as the DB contain unpublished reports. The attributes *type, language, credibility and availability* contain redundant text strings and may be separated in order to further optimize the DB.

4.2.5 The table “sampling_country_information”

This table contains information about the sampling country of a specific MEC value. We introduced an additional column called *iso2_country_code* (CHAR(2)), which contained the ISO 3166-1 ALPHA-2 code (ISO-2) of the respective country. ISO-2 country codes are usually available as attributes in official GIS world maps, hence; they can be utilized to map information from the MEC DB to the DB of the GIS shape file. We used again a simple numerical primary key, although the usage of the ISO-2 code seems more recommendable. However, this attribute contains a political dimension, which makes it variable and may cause problems when using it as

[7] Finally, we used only N4-Acetylsulfamethoxazole for all new entries.

primary key. The attribute *un_region* is currently implemented as simple VARCHAR, but may be shifted to a separate column during further DB optimization.

4.2.6 Further tables

The remaining tables are emission_sources, matrix, statistics and units. These tables have in principle the same structure containing a numerical ID, the main attribute, e.g. unit, a comment attribute and the two attribute for alteration tracking. For the main attribute, usually VARCHAR (255) was used except for the unit table, where the length of VARCHAR was limited to 45 characters.

4.3 Transfer of data into and between DBs as well as final DB corrections

Data transfer between the original Access and the MySQL project DB was required twice, at the beginning to import existing entries for the different sub tables and at the end to export all new entries back into the original DB. Furthermore, a semi-automated import was established for huge data sets. All data transfer was performed using the script language R (ver. 3.4 or higher, R Development Core Team, 2018) and the RODBC (Ripley and Lapsley, 2017) and RMySQL (Ooms et al., 2018) package.

4.3.1 Import data from Access to MySQL

A data import from Access to the MySQL DB was only performed for the entries of the sub tables at the beginning of the project to enable the usage of existing entries (e.g. countries, matrices, emission sources). An import of the entire DB was not done, as additional work is required to create all necessary entries in the literature DB.

Data import to the sub tables was realized utilizing the "SELECT DISTINCT" command. As SQL-query's in Access are case insensitivity, the results were already corrected against duplicates 8 and could be directly written to the respective new DB tables.

4.3.2 Export data from MySQL back to Access

Whereas the import of data into the project DB was a rather simple task, the export back to Access was more difficult. The main challenges were caused by special characters and reserved signs as well as varying encodings. The standard procedure of handling special chars and signs in web environments, used also in the present project, is to escape these characters e.g. by using HTML-entities. During the export process, these entities are back transformed to respective characters in the respective encoding of the target DB. Moreover, the MySQL DB as well as the web frontend forced the usage of UTF-8 encoding, to prevent problems caused by differing encodings on the server and client side. This procedure worked well for ca. 99% of the entries, but failed for a low number of entries, resulting in unreadable characters in certain attributes. Identified reasons for the failure were located at different levels of this procedure and are listed below:

- Failure of the PHP conversion function "*htmlentities( )*". This occurred only for the character – ğ.

[8] Duplicates caused by different usage of upper and lower case e.g. Germany vs. germany

- No R functions was found that reliably converted all HTML-entities back to the respective character, hence, an own function was written based on available entity lists. However, additional attention was required for the following entities:
- ’ ‘ ' - (') e.g. used for coordinates – interfere with the SQL code
- è - (è)
- ° - (°)

Apart from these challenges, the export was performed via a twostep approach. During the first step, all newly entered substances were identified and written into the Access table "Pharma Agents". The export of the MECs was performed in the second step, by loading the entire new dataset into R and iteratively write the single MECs into the Access DB. Finally, the data export was validated by comparison of the number of exported entries as well as by comparison of the sum of the columns MEC original and MEC standardized. As the Access DB uses the standard encoding of the operating system (usually Latin 1), all text entries were converted from UTF-8 to Latin 1 during the export process. The export was complicated by the low communicative competence of Access, when working with external programs like R. In detail, Access does not create error or warning messages, when faced to unexpected data formats or missing keys, resulting in missing entries or even wrong values due to misinterpretation. Hence, great care must be spend to data validation.

4.3.3 Import of huge data sets

Several publications with hundreds of entries were found during the literature survey. A manual transfer of such amounts of data is highly frustrating for the operator and has an increased probability of mistakes.

The variability of published data tables in terms of table formats and content is great. Specific information required for a DB entry are often only available in the text and not listed in the tables itself. A fully automated data import from publications into the DB was therefore not possible, but neither in the scope of the project. However, a semi-automated data import was developed during the project, which required a data pre-processing by the project employees before import, while being still time saving and finally more accurate.

The import consisted of the following work steps:

1. **Harmonization:** Transfer of raw data into Excel and transformation into a generalised data format
2. **Data Completion**: Assignment of required and available data as well provision of further required information e.g. from the text
3. **DB Preparation**: Creation of new entries in sub tables if required.
4. **Data Import:** Test, final corrections and data transfer

To overcome the problem of variable data table structure, a general but flexible framework was developed. The framework consisted of two worksheets in an Excel-file. The first worksheet called "meta table" contained all information required to create an entry within the MySQL DB, given that all required entries in the related sub tables already exist. An information is thereby defined as a specific value, an ID or entry name of a sub table or a pointer to a column or row of the second work sheet. Due to the fact that all secondary information of the sub tables are defined by the respective sub table entries, e.g. the CAS-Number or therapeutic group by a

specific substance, not all attributes of the original Access-DB were required in the Meta table. In fact, the meta table contained only 17 attributes compared to 32 in the original Access DB. The second worksheet of the Excel-file called “value table” contained a harmonized copy of the original DB table. The first columns contained MEC dependent variable attributes e.g. MEC specific matrices. Attributes that are constant over the entire publication, e.g. sampling times, were noted in the meta table and treated as constants. In the following columns of the value table, the single substances were listed with respective MEC values as rows. In the final columns, the LODs of the substances are listed if available. The LODs are marked with the prefix “LOD-“ followed by the substance name, which allows a pattern match to identify the correct LOD for each substance.

During the first work step of the semi-automated import, the harmonization, original tables were transformed to fit into the structure of the value table. Constant attributes were removed from the table and noted in the meta table. In the second step, the data completion, the text of the publication was screened for further constant attributes, which were required to complete the meta table. In the third step, the DB preparation, the DB was checked for missing sub table entries, e.g. missing substances, and completed if necessary. While the first three work steps were performed by the project employees, the final step, the real data import, was performed by an DB administrator utilizing a specific import script. The work step include the check of the provided Excel-files as well as an import of the data into a test DB to resolve problems e.g. caused by misspelling of substance names. After application of necessary corrections and successful test of the import file the data was finally imported to the project DB. This import procedure required in total roughly one hour per publication, which could include several thousand MECs. Hence, saving the employee’s hours or even days, which would be required for manual data input.

4.3.4 Final DB modifications and remarks

After export of the new MECs into the original Access DB, final modifications on the Access DB were performed to resolve obvious inconsistencies of the old DB and enhance script based analysis. The following section briefly lists all modifications made on the Access DB.

- The substance N4-Acetylsulfamethoxazole (CAS: 21312-10-7) occurred three times with the additional name Acetyl-sulfamethoxazole and N-Acetyl sulfamethoxazole. All MEC entries of this substance were set to the name N4-Acetylsulfamethoxazole and both additional entries in the “Pharma Agents” table were deleted.
- The attribute *Detection* contained two versions of “positive detection”. We corrected all entries with the wrong spelled version. However, we did not recalculate this attribute by comparison of standardized MEC and standardized LOD.
- Empty CAS numbers occurred in both tables in two versions (NULL and #N/A). We set all empty CAS entries to NULL.
- Matrices occurred in different capitalization, due to the missing case sensitivity of Access. We standardized all entries to the versions Access returns when using the “SELECT DISTINCT” command.
- Substance names occurred in different capitalization, too. We standardized the substance name of all entries to the one defined in the table “Pharma Agents”.

Further inconsistencies of the DB remained unresolved and should be addressed in the next project.

- The attribute “Detection” is not clearly defined. Two different interpretations occurred in the DB. The strict interpretation used for the semi-automated MEC import used “positive detection” only in cases were a LOD was reported and entered to the DB. The attribute was calculated by logical comparison of standardized MEC and standardized LOD. Cases were no value or respectively -9999 was entered to the DB, due to missing indication in the publication or provision of the LOQ only, used the term “below detection”. The second interpretation was less strict and used the term “positive detection” also for cases were no clear LOD value was reported, but values marked with “<LOD” existed for the respective substance or the text indicated a proper analysis. The second interpretation led to a higher frequency of “positive detections”. However, this interpretation cannot be implemented in the semi-automated import. Therefore, filtered results based on this attribute must be interpreted with care. In order to optimize the DB, we suggest to introduce an additional attribute to the MEC table, to distinguish LOD and LOQ values. Furthermore, a clear definition is required in which cases a MEC is rated as “positive detection” e.g. MEC > LOD or MEC > LOQ. Finally,” we suggest to introduce the value “unclear detection” for the attribute “Detection” in cases were the analytical methodology is incomplete.
- Some entries from the old DB are marked as “positive detection” but contain a MEC of 0
- 1450 MECs contain no unit and are therefore excluded from analysis, e.g. ID 3625
- In the course of the analysis, further substances were identified, which occur at least two times in the DB with different names or where the CAS number is wrong (Table 1). This leads to incomplete search results, when using the substance name as identifier or even to false search results when using a CAS, which is wrong.

Table 1: CAS numbers with two substance names in the DB

CAS Number	Substance Names from DB	Comment
100-90-3	N4-Acetyl sulfamethazine Sulfamethazine-n4-acetyl	
11015-37-5	Flavomycin Flavophospholipol	
1672-58-8	4-Formylaminoantipyrine N-formyl-4-aminoantipyrine	
214217-86-6	o-Hydroxyatorvastatin p-Hydroxyatorvastatin	Different isomers of the same substance.
36507-30-9	10,11-Dihydro-10,11-Epoxycarbamazepine Carbamazepine-10,11-epoxide	

CAS Number	Substance Names from DB	Comment
4618-18-2	Enulose Lactulose	
481-96-9	17-beta-Estradiol-3-sulfate Estradiol-3-sulfate	
4812-40-2	Hydroxy-Metronidazole Metronidazole-OH	
50-28-2	17-beta-Estradiol Estradiol	
517-09-9	d-Equilenin Equilenin	
53949-53-4	1-Hydroxy Ibuprofen Hydroxyibuprofen	
56392-14-4	Atenolol acid Metoprolol acid	Metabolite of different parent substances.
569-65-3	Meclizine Meclozine	
57-68-1	Sulfadimidine Sulfamethazine	
58-15-1	4-Dimethylaminoantipyrine Dimethylaminophenazone	
651-06-9	Sulfamethoxine Sulfametoxydiazine	
67-20-9	Furadoxyl Nitrofurantoin	
71-58-9	6-alpha-methyl-hydroxyprogesterone Medroxyprogesterone acetate	
72-33-3	17-alpha-Ethinylestradiol 3-methyl ether Mestranol	
7206-76-0	2-Ethyl-2-phenylmalonamide Phenylethylmalonamide	
83-15-8	4-Acetaminoantipyrine Acetoaminoantipyrine	
93413-62-8	Desvenlafaxine o-Desmethylvenlafaxine	

4.4 Data analysis and map creation

Data analysis and visualization was performed using the script language R (ver. 3.4 or higher, R Development Core Team, 2018) and the RODBC (Ripley and Lapsley, 2017) and RMySQL (Ooms et al., 2018) packages for data base communication.

A major problem of the data analysis was the data aggregation. The amount of different attributes and respective attribute entries caused a strong fragmentation of the data and

subsequently a strong reduction of publications and MECs with increasing complexity of a search query. Hence, entries with an originally high abundance of MECs often contain only a very low number of specific MECs. Therefore, the data filtering was limited to important attributes like the matrices or geographical scales and specific higher-level aggregates were created, which include multiple attribute entries. All matrices have been associated to their origin as emission and immission in combination with the aggregate state of the sample (liquid or solid based on the MEC unit) and the location based on the country information (global, EU member states, Germany). An overview of the matrices and their assignment is given in Table 3 (Section 5.3).

For geographical data visualization, the GIS-world map TM_WORLD_BORDERS-0.39 was used. As interface between GIS and the MEC database the ISO2-Codes of countries (Section 4.2.5) were utilized. Maps were created using the R packages maptools (Bivand and Lewin-Koh, 2017), rgeos (Bivand and Rundel, 2017) and rgdal (Bivand, et al., 2018) as well as RColorBrewer (Neuwirth, 2014) for the creation of colour gradients.

The map creation was performed in three steps. First, the data was fetched from the DB and aggregated, e.g. the highest reported MEC of each country was identified. Moreover, based on the aggregation results the colour gradient was scaled. The minimum of the gradient was calculated by rounding the lowest aggregated value to the next minor order of magnitude i.e. a minimum value of 5 would be rounded to 1. The maximum value of the gradient was defined in the opposite way by rounding up to the next higher order of magnitude, i.e. a maximum of five would result in 10. The resulting minimum and maximum values were used to normalize all aggregation results within a number space between 0 and 1, which was necessary to assign the aggregated values to the colours of the gradient. The used colour gradient itself was created by linear interpolation between the dark UBA red and the dark UBA green with the UBA yellow in the middle of the gradient.

In the second step, the aggregated data and the resulting colours (hex notation) were written to the attribute table of the shape-file using the ISO2-codes to identify the single countries.

In the final step, the shape file was plotted and the polygons of the countries were coloured according to the specified colour based on the aggregation results. It should be noted that for most of the maps the data was log transformed before aggregation, as the concentrations to be plotted covered several orders of magnitude.

[9] Bjorn Sandvik - www.thematicmapping.org – from July 2008

5 General overview of the database

The complete database contains currently 178,708 published MEC entries of 1,519 publications. Plus 240 review articles which are included in the literature database.

In this study, single and aggregated MECs were entered to the DB. If available and clearly identifiable, the specific MECs of every single sampling were entered to the DB. In case the MECs were already aggregated or different statistical parameter were available for one sampling, the maximum MEC or respectively the mean MEC of the aggregated data was entered to the DB. Most of the database entries belong to aggregated data type of different measurements in time and/or space. As written in aus der Beek et al. (2016), the exact number of measurements can be expected to be much higher. As the sampling number, sampling period or detection limit are often missing in publications, the total number of measurements behind the MECs cannot be specified. In the following, the indicator for monitoring intensity was therefore the number of DB entries (aus der Beek et al. 2016).

However, the following consideration was performed on the DB entries. As publications until 2016 were considered, the database contains data from 1987 to 2016, whereas “only” 5816 data entries were available for 2016 (in comparison 2011 with 11920 or 2010 with 27311). Due to longtime measurement campaign followed by peer-review processes, higher number of data for 2016 will be available in the next year. Moreover, publications of 2017 and 2018 were not part of the recent database update and will further increase the number of data of the last years.

5.1 Classification of environmental matrices

Pharmaceuticals have been reported for different environmental matrices (Table 2). For the following consideration within this report, these different environmental matrices were classified into aggregate status (liquid and solid) as well as “immission” or “emission” matrix (Table 2). Immission covers all matrices receiving possible contaminated water respectively soil and sediments. The emission aggregate includes all possible sources of pharmaceutical release and were further separated into human and veterinary origin for the analysis of the antibiotic groups.

Some matrices e.g. “leachate”, “unknown” or “surface water/sediment – unspecific” were excluded from the following analysis as they contain data of liquid and solid measurements or their description was unspecific. We further excluded data from the sea/ocean for the analysis as these matrices are considered as final sinks for contaminations. Furthermore, MECs of wastewater treatment plants (WWTP) inflow and internal sewage treatment steps e.g. WWTP primary/secondary/disinfected effluent or WWTP primary/secondary sludge were not considered as pharmaceuticals usually should not enter and affect the environment in this form. Moreover, MECs from these matrices were often very high and therefore strongly bias the analysis. Hence, only effluent data were considered. All matrices that are not covered by the following analysis are still part of the database.

Table 2: Different matrices of the database and their classification in aggregate status and emission and immission classification as well as the number of MECs with positive detection (>LOD). MECs with no or wrong units were not considered during counting of MECs.

Aggregate Status	Immission/Emission	Environmental Matrix	Number of MECs
Liquid	Human emission	Reclaimed Water	12
		Sewage hospital (treated)	347
		Sewage hospital (untreated)	2144
		Sewage industrial (untreated)	314
		Sewage urban (untreated)	1083
		WWTP effluent (treated)	19397
	Veterinary emission	Manure – liquid	374
		Sewage livestock (treated)	27
		Sewage livestock (untreated)	208
		Surface Water – Aquaculture	242
	Immission	Drinking Water	980
		Groundwater	2647
		Reservoir drainage	10
		Riverbank filtration	168
		Soil Water	174
		Surface Water - Estuary	486
		Surface Water - Lake	1104
		Surface Water - River/Stream	22868
		Tap Water	223
		Well Water (untreated)	682
	excluded	Dissolved activated sludge	6
		Leachate	73
		Rain	4
		Sea ice	0
		Surface Water - Sea or Ocean	1037
		Surface Water - unspecific	2019
		WWTP desinfection effluent	94

Aggregate Status	Immission/Emission	Environmental Matrix	Number of MECs
		WWTP inflow (untreated)	11257
		WWTP primary effluent	73
		WWTP secondary effluent	84
		Unknown	87
Solid	Human emission	Sewage sludge	30
		Suspended particulate matter - Sewage	50
		Suspendet particular matter (WWTP-Effluent)	9
		WWTP biosolid	275
		WWTP dehydrated sludge	11
		WWTP digested sludge	8
		WWTP sludge	2469
	Veterinary emission	Manure – dung	938
		Sediment - Aquaculture	108
	Immission	Sediment - Estuary	70
		Sediment - Lake	109
		Sediment - River/Stream	1122
		Soil	1260
		Suspended particulate matter - Estuary	0
		Suspended particulate matter - River/Stream	87
	excluded	Dust	12
		Sediment - Sea or Ocean	80
		Sediment - unspecific	229
		Suspended particulate matter - Sea or Ocean	2
		Suspended particulate matter - unspecific	4
		Suspended particular matter (WWTP-Inflow)	9
		WWTP primary sludge	31
		WWTP secondary sludge	18

In this report, we will therefore refer to the following four classes of matrices:

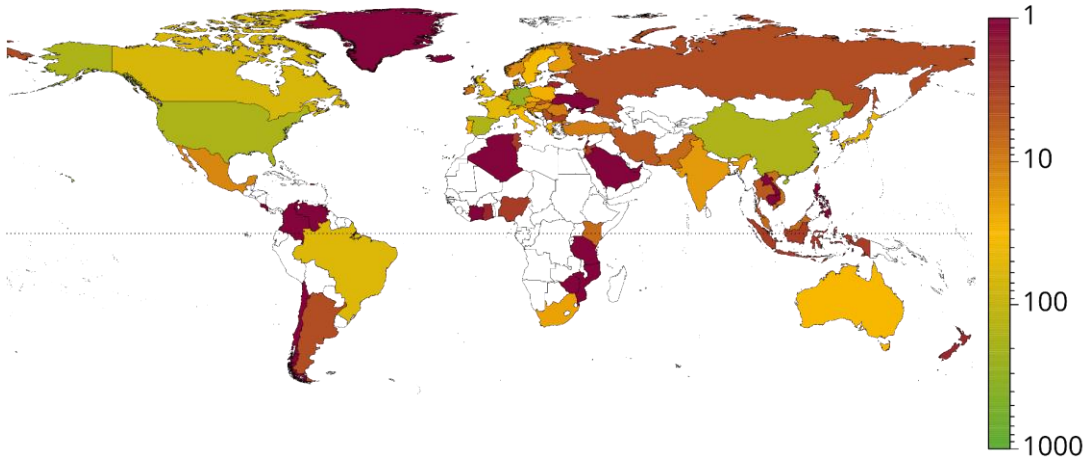
- liquid immission
- liquid emission with the subclasses liquid human emission and liquid veterinary emission for analysis of antibiotic groups
- solid immission
- solid emission with the subclasses solid human emission and solid veterinary emission for analysis of antibiotic groups

Most positively detected MECs have been reported for matrices clustered within liquid immission followed by the matrices clustered in liquid emission (Table 4). On a global scale, only 5.3% of all positively detected MECs belong to MECs of clustering within solid-emission and only 3.6% to MECs clustering within solid-immission, even less in Germany and the EU (Table 4).

5.2 Worldwide occurrence of pharmaceuticals

In total, measurements of pharmaceutical in the environment were reported for 75 countries (Figure 3 and Figure 4). The distribution of this measurement, shown as number of publication, is presented in Figure 3. Countries with a high number of publication are shown in green, whereas countries with a low number of publications are shown in red. Most publications reporting MECs were found for China, USA, Spain and Germany.

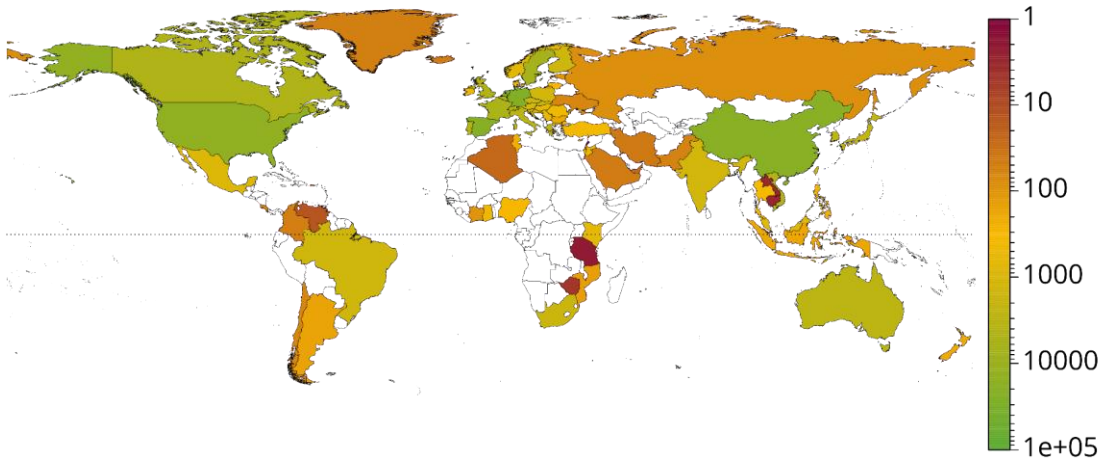
Figure 3: Distribution of publications reporting MECs



Source: own illustration, GWT-TUD GmbH

The distribution of the published MECs is presented in Figure 4. Countries with a high number of MECs are shown in green and countries with a low number of MEC data in red. As the number of publications, most reported MECs were found for China, USA, Spain and Germany.

Figure 4: Distribution of MECs



Source: own illustration, GWT-TUD GmbH

5.3 Global occurrence of pharmaceuticals

Globally, 771 active pharmaceutical substances or their transformation products were detected above their respective detection limit (Table 3). In Germany, 269 active substances or their transformation products were detected above their detection limits. Most of these substances were found in wastewater treatment plants (liquid emission). However, 528 positively detected substances globally and 159 in Germany were found in surface water, groundwater or drinking water or (liquid immission matrices; Table 3).

Table 3: Overview of the relevant numbers on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**1519**	**773**	**271**
MECs	**178.708**	**108.628**	**24.014**
Positively detected MECs	**76.690**	**43.144**	**10.238**
Liquid-emission	24.314	15.006	2.083
Liquid-immission	29.400	17.542	6.421
Solid-emission	4.083	1.808	180
Solid-immission	2.763	755	134
Positively detected substances	**771**	**596**	**269**
Liquid-emission	613	474	216
Liquid-immission	528	384	159
Solid-emission	145	84	17
Solid-immission	184	132	24

To get an overview on the most prominent pharmaceuticals, we analysed the occurrence of all pharmaceuticals focusing on their occurrence in the five UN-regions. Thereby, we found 19 substances occurring in all five UN-regions. In comparison to aus der Beek et al. 2016, the five substances indometacin, ketoprofen, sulfamethazine, triclocarban and triclosan have now been detected in all five UN-regions (Table 4).

Table 4: Number of positively detected MECs in surface water, groundwater or drinking water for substances occurring in all five UN-regions: WEOG – Western Europe and Others Group, GRULAC – Latin American and Caribbean Group, EEG – Eastern Europe Group, ASG – Asien Group, AFG – African Group

Substance	WEOG	GRULAC	EEG	ASG	AFG
17-alpha-Ethinylestradiol	226	10	46	3	40
17-beta-Estradiol	162	14	86	27	61
Acetylsalicylic acid	22	6	14	3	7
Carbamazepine	1258	202	164	20	42
Ciprofloxacin	102	4	125	6	7
Clofibric acid	240	17	74	1	5
Diclofenac	2034	234	127	15	31
Estriol	64	5	32	1	13
Estrone	211	28	124	49	32
Ibuprofen	1970	210	132	19	32
Indometacin	110	2	37	1	2
Ketoprofen	212	66	42	2	9
Naproxen	536	169	95	5	42
Paracetamol	289	19	72	13	20
Sulfamethazine	152	3	261	3	2
Sulfamethoxazole	829	148	414	36	17
Triclocarban	37	1	66	5	3
Triclosan	250	39	133	6	36
Trimethoprim	343	11	267	15	8

6 Occurrence of pharmaceuticals (EU watch list)

The following eight substances were selected based on the European watch list (WL) for emerging water pollutants. This WL reports potential water pollutants that should be carefully monitored by the EU Member States to determine their risk posing to the aquatic environment (Loos et al. 2018). The following substances from the WL were considered:

- 17-beta-estradiol
- 17-alpha-ethinylestradiol
- Diclofenac
- Erythromycin
- Clarithromycin
- Azithromycin
- Amoxicillin
- Ciprofloxacin

Diclofenac was part of the WL released in 2015, but was removed from the second WL released 2017, due to its strong monitoring background. Instead, the antibiotics amoxicillin and ciprofloxacin were included (Loos et al. 2018).

Within this report, the MEC data of these substances were analyzed in order to get an overview of their occurrence in Germany, the EU and worldwide.

6.1 17-beta-Estradiol (E2)

The steroid hormone 17-beta-Estradiol (E2) is a natural occurring estrogen and is mainly excreted by humans (males about 1.6 µg/day and females up to 259 µg/day; Wise et al. 2011). E2 is moreover utilized in several drugs used for hormone replacement therapy, treatment of female infertility and, breast and prostate cancer in advanced stages (Kunz et al. 2015). Classified as endocrine disrupter E2 is causing negative effects on aquatic ecosystems already at very low concentrations (Kutz et al. 2015).

6.1.1 General occurrence of E2

E2 was already detected in countries of all five UN-regions in the previous report (aus der Beek et al. 2016). Moreover, several metabolites of E2 were found in different environmental matrices including: 17-beta-Estradiol-glucuronide, 17-beta-Estradiol-3-glucuronide sodium salt, 17-beta-Estradiol-2-sulfate, 17-beta-Estradiol-3-sulfate, 17-beta-Estradiol-sulfate sodium salt, 17-beta-Estradiol-acetate. However, this report will focus on the parental substance E2 only.

For E2 2,308 database entries have been generated from 256 publications. On a global scale 1,213 MECs were found above the detection limit. Nearly half of this positively detected MEC belong to measurements in EU member states (Table 5).

Table 5: Occurrence of 17-beta-estradiol on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**256**	**99**	**25**
MECs	**2,308**	**1,020**	**190**
Liquid emission (effluent/sewage)	681	310	54
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	873	289	72
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	86	46	8
Solid immission (sediment/soil/SPM)	184	149	0
Else	484	226	56
Positively detected MECs	**1,213**	**478**	**79**
Liquid emission (effluent/sewage)	421	178	34
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	405	131	23
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	46	29	8
Solid immission (sediment/soil/SPM)	35	13	0
Else	306	127	14

Although, on the global scale, most measurements have been undertaken within the matrix group liquid immission including surface water, ground- and drinking water, most positively detected MECs were found for the matrix group liquid emission (Table 5). E2 is easily eliminated during wastewater treatment, but removal is mostly incomplete (Kunz et al. 2015). Therefore, WWTP effluents are one of the most important sources for aquatic contaminations with E2 (Kunz et al. 2015).

6.1.2 Specific occurrence of E2

Globally, the highest concentration has been detected in the USA in a WWTP effluent with 25.2 µg/L (liquid emission; Kvanli et al. 2008) and in Brazil with 13.45 µg/L in the Atuba river (liquid immision; Machado 2010). These concentrations are much higher than values reported within the EU. Here, highest concentrations for the group liquid immission was found in Schussen in the inflow of lake Constance, Germany with 0.32 µg/L (Triebkorn & Hetzenauer, 2012), whereas the highest reported concentration for emission in Germany was only 0.05 µg/L for a WWTP effluent (Table 6; Robakowski, 2000). Table 6 summarizes the highest measured concentration for Germany, the EU and worldwide.

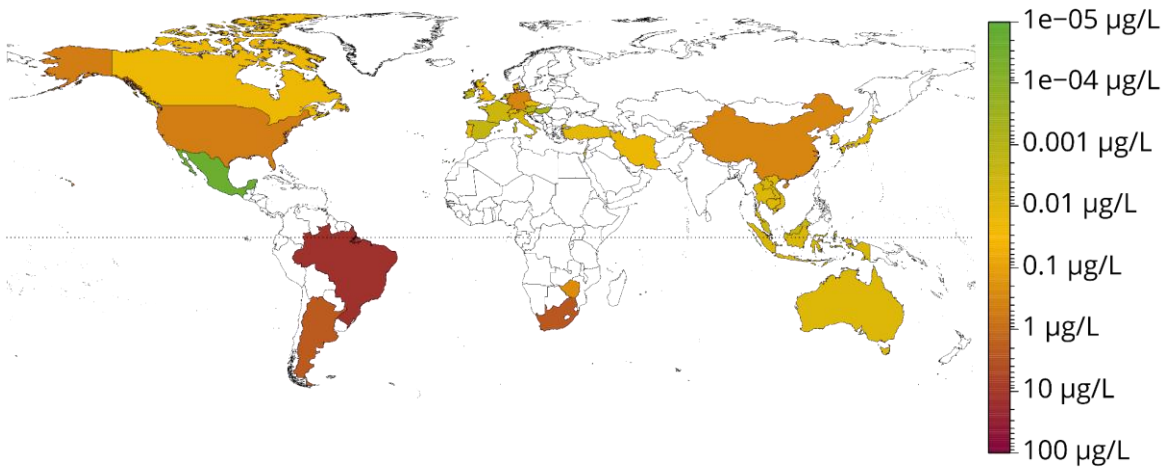
Table 6: Maximum MECs of 17-beta-estradiol on a global scale, in the EU and Germany

Maximum MEC	Global	European Union	Germany
Liquid emission (µg/L)	25.2 (USA; WWTP effluent (treated); Kvanli et al. 2008)	0.81 (Spain; WWTP effluent (treated); Camacho-Munoz et al. 2012)	0.05 (WWTP effluent (treated); Robakowski 2000)
Liquid immission (µg/L)	13.45 (Brazil; Surface Water - River/Stream; Machado 2010)	0.32 (Germany; Surface Water - River/Stream; Triebkorn & Hetzenauer 2012)	0.32 (Germany; Surface Water - River/Stream; Triebkorn & Hetzenauer 2012)
Solid emission (mg/kg)	3.33 (Canada; Suspended particular matter (WWTP-Effluent); Darwano et al. 2014)	0.836 (Spain; WWTP sludge; Martin et al. 2012)	0.115 (WWTP sludge; Kunst 2002)
Solid immission (mg/kg)	0.149 (Italy & Canada, Sediment - River/Stream & Suspended particulate matter - River/Stream; Darwano et al. 2014 & Karnjanapiboonwong, Suski et al. 2011)	0.149 (Italy, Sediment - River/Stream; Vigano et al. 2008)	-

6.1.3 Specific distribution of E2

The global distribution of E2 for liquid and solid immission is presented in Figure 5 and Figure 6. Here, the maximum concentration per country is represented as a colour gradient with green for low concentrations to red for high concentration.

Figure 5: Maximum MECs for 17-beta-estradiol found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)

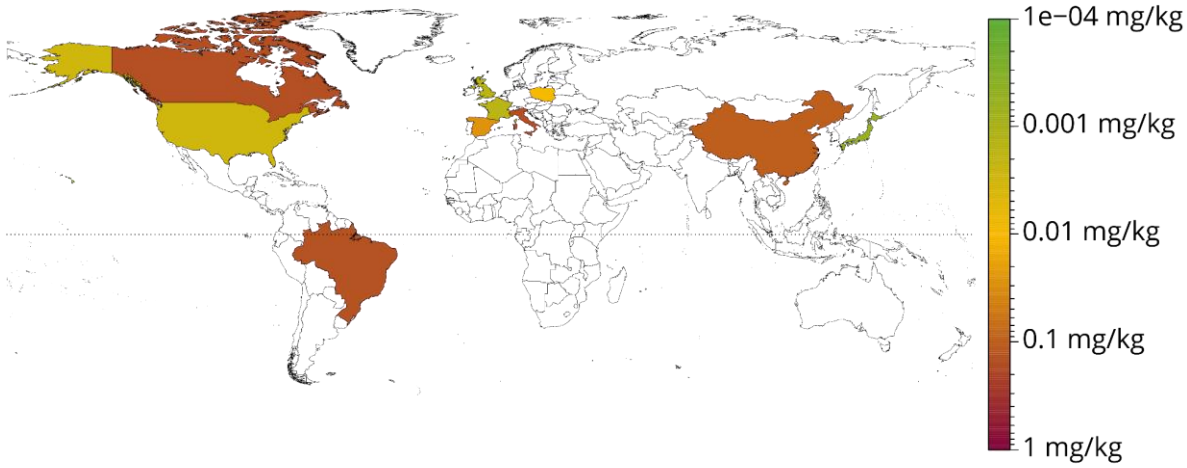


Source: own illustration, GWT-TUD GmbH

Positively detected MECs for liquid immission matrices were found for 41 countries. Concentrations ranged from 0.00084 µg/L in Japan and up to 13.45 µg/L in Brazil.

In contrast, the numbers of E2 data entries for all solid matrices are much lower, which can be attributed to the fact that sewage sludge is not a significant sink/source of E2 contamination, due to its fast biodegradation within this compartment (Tiedeken et al. 2017), and the respectively low number of publications and monitoring campaigns (Table 5). However, sediment concentrations of up to 3.33 mg/kg (suspended particle matter of an effluent in Canada; Darwano et al. 2014) contradict this hypothesis and more attention should be spend to this compartment.

Figure 6: Maximum MECs for 17-beta-estradiol found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

6.2 17-alpha-Ethinylestradiol

The synthetic hormone 17-alpha-ethinylestradiol (EE2) also belongs to the group of endocrine disrupters (Aris et al. 2014). It is a derivate of the natural occurring estradiol, but it is more efficient than E2 (Aris et al. 2014). EE2 is mainly used as estrogenic ingredient in oral contraceptives (Clouzot et al. 2008; Wise et al. 2011), but also used in drugs for hormone replacement therapy or for the treatment of menopausal and post-menopausal symptoms (Kunz et al. 2015). Further, EE2 is used to increase livestock productivity and to threat several animal diseases (Gadd et al. 2010, Aris et al. 2014, Kunz et al. 2015). Therefore, urban wastewater and livestock sewage are considered as main emission source for this substance.

6.2.1 General occurrence of EE2

Literature survey revealed MEC data for EE2 and one metabolites (17-alpha-ethinylestradiol 3-methylether). In the following, only the global distribution of EE2 was of interest.

Table 7: Occurrence of 17-alpha-ethinylestradiol on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**237**	**110**	**28**
MECs	**2,033**	**1,081**	**224**
Liquid emission (effluent/sewage)	538	317	63
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	851	356	93
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	83	62	5
Solid immission (sediment/soil/SPM)	188	150	0
Else	373	196	63
Positively detected MECs	**800**	**382**	**145**
Liquid emission (effluent/sewage)	201	113	46
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	324	118	54
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	46	34	5
Solid immission (sediment/soil/SPM)	32	7	0
Else	197	110	40

For EE2, 237 publications reported MEC data resulting in 2,033 database entries. Globally, 800 MECs were found above the detection limit and were reported from countries of all five UN-regions. In the EU, 382 positively detected MECs have been reported, whereas 145 of these were measurements within Germany (Table 6).

Most MECs and also most positively detected MECs have been reported for the matrix group liquid immission including surface water, ground- and drinking water (

Table 7). EE2 mainly enters the aquatic environment via urine either directly (mainly as veterinary pharmaceuticals) or, due to an incomplete removal, via wastewater treatment plants (WWTP). In comparison to E2, EE2 is more stable under aerobic conditions of the activated sludge process of WWTP (Kunz et al. 2015). This may indicate a higher stability under environmental conditions, but also a higher release via WWTP effluent.

However, database entries do not confirm this statement, as the number of corresponding data entries for EE2 are lower than for E2. Anyhow, the database is only a snapshot on published data until 2016. The focus of the project was data collection and not the analysis of such topics.

The number of MECs for solid matrices is lower than the number of MECs for liquid matrices. Worldwide, 32 positively detected MECs have been reported for matrices clustered within solid immission and 46 for solid emission (

Table 7). Within Germany, positively detected MECs could only be collected for solid emission. Sewage sludge and manure were not thought to be a main contamination source for EE2 as the substance is readily biodegradable (Kunz et al. 2015).

6.2.2 Specific occurrence of EE2

The highest concentration has been detected in a WWTP effluent of Almuñécar city in Spain with 6.62 µg/L (liquid emission; Camacho-Munoz et al. 2012) and in Brazil in the Atuba river with 5.9 µg/L (liquid immision; Machado 2010). As aus der Beek et al. 2016 already discussed this high immission value of Brazil in comparison to the other reported MECs in the previous report, this value is not plausible.

Table 8: Maximum MECs of 17-alpha-ethinylestradiol on a global scale, in the EU and Germany

Maximum MEC	Global	European Union	Germany
Liquid emission (µg/L)	6.62 (Spain; WWTP effluent (treated); Camacho-Munoz et al. 2012)	6.62 (Spain; WWTP effluent (treated); Camacho-Munoz et al. 2012)	0.81 (WWTP effluent (treated); Robakowski 2000)
Liquid immission (µg/L)	5.9 (Brazil; Surface Water - River/Stream; Machado 2010)	0.28 (Spain, Surface Water - River/Stream; Camacho et al. 2010)	0.117 (Surface Water - River/Stream; Vallejo et al. 2013)
Solid emission (mg/kg)	6.8 (Sweden; WWTP sludge; Andersson et al. 2006)	6.8 (Sweden; WWTP sludge; Andersson et al. 2006)	0.015 (WWTP sludge; Andersen et al. 2003)
Solid immission (mg/kg)	3.32 (Canada; Soil; Karnjanapiboonwong et al. 2011)	0.0673 (UK; Soil; Zhang et al. 2011)	-

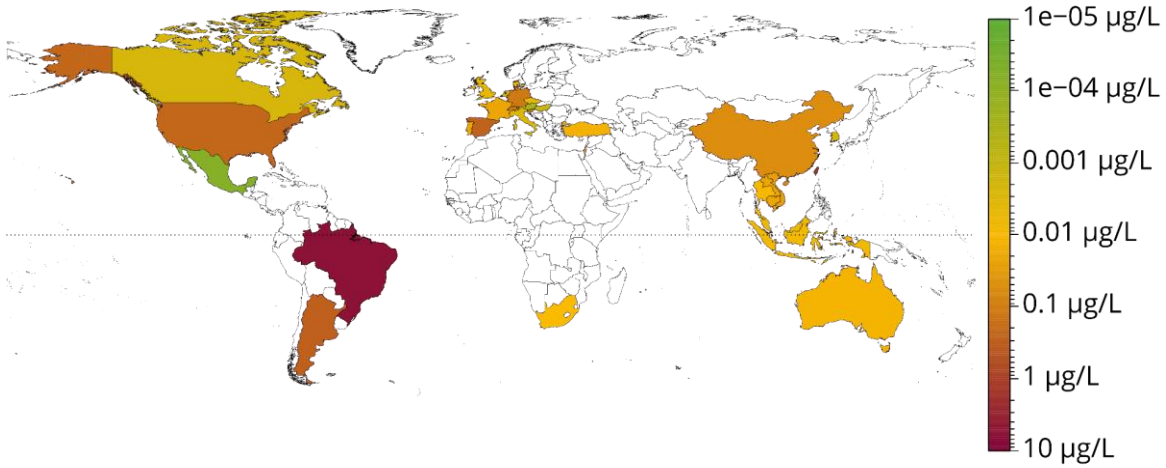
While the highest liquid emission value was found in Spain with 6.62 µg/L, the detected liquid immission MECs in the EU were much lower than in Brazil. The highest concentrations for the group liquid immission was found in La Rocina stream in Sevilla, Spain with 0.28 µg/L (Camacho et al. 2010). However, the highest concentration of the group liquid immission in Germany was found in the Saale river in Brachwitz with 0.117 µg/L (Vallejo et al. 2013). The highest emitted concentration in Germany was 0.81 µg/L for a WWTP effluent (Table 8; Robakowski, 2000) and, therefore, also much lower than the maximum MEC of Spain. Table 8 summarizes the highest measured concentration of EE2 for Germany, the EU and on a global scale.

6.2.3 Specific distribution of EE2

The global distribution of EE2 is shown in Figure 7 for liquid immission and in Figure 8 for solid immission. MECs above the detection limit for liquid immission matrices were found for 32

countries. The maximum MECs for each country are represented in Figure 7, whereas the lowest concentration is in Mexico (0.00006 µg/L,) and the highest in Brazil (5.9 µg/L).

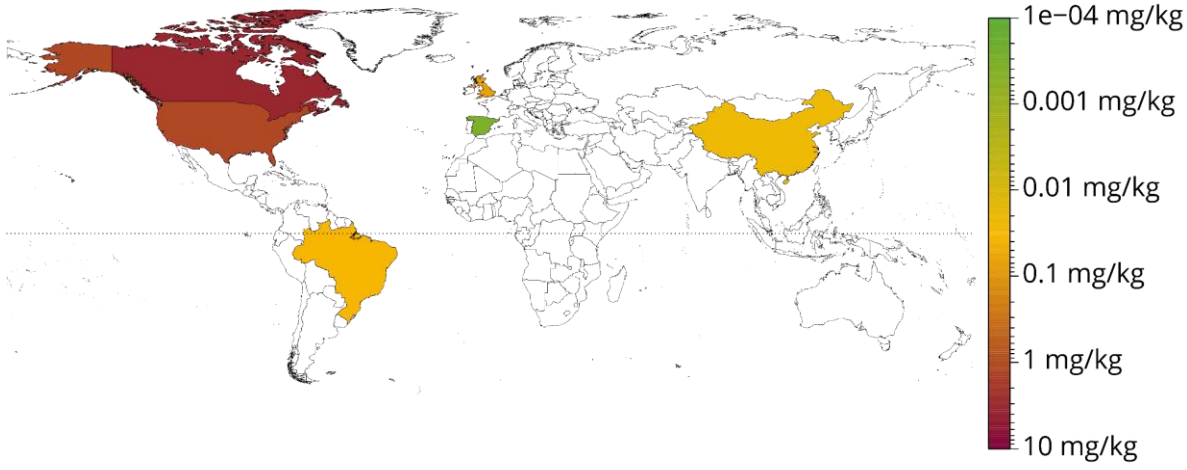
Figure 7: Maximum MECs for 17-alpha-ethinylestradiol found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

As already mentioned, the number of MECs for solid matrices is much lower. Anyhow, highest loads have been detected in sandy soil in Ottawa, Canada with 3.32 mg/kg (Karnjanapiboonwong et al. 2011) and in WWTP sludge in Sweden (Andersson et al. 2006; Table 8). In the EU, the load of solid immission matrices was much lower with 0.0673 mg/kg, detected in an agriculture soil in Scotland, UK (Zhang et al. 2011). In Germany, EE2 was not detected in solid immission matrices. The maximum MECs for each country are represented in Figure 8, whereas the lowest concentration is marked in green (0.00035 mg/kg, Spain); the highest is marked in red (3.32 mg/kg, Canada).

Figure 8: Maximum MECs for 17-alpha-ethinylestradiol found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

6.3 Diclofenac

Diclofenac, a prevalent anti-inflammatory drug, is one of the most used pharmaceutical in the world. In 2007, 877 tons of diclofenac containing drugs were sold in 76 countries accounting for about 96% of the global market (Zhang et al. 2008). As human and veterinary drug, diclofenac has a high consumption rate with approximately 940 tons per year worldwide (Zhang et al. 2008). In Europe, 179.8 tons per year were used (Ferrari et al. 2003), whereas most was applied in Germany with 82 tons in 2009 (Bergmann et al. 2011).

6.3.1 General occurrence of diclofenac

Diclofenac was the most detected substance. Only two metabolites of diclofenac were found during literature survey: 4-Hydroxydiclofenac (dehydrate), 5-Hydroxydiclofenac. However, they are not considered in this report.

In total, 442 publications reported MEC data resulting in 6,491 data entries worldwide, whereof 3,996 MECs were above the detection limit. Moreover, 75% of all positively detected MECs have been reported for EU member states and 1,599 MECs for Germany only (Table 9).

Table 9: Occurrence of diclofenac on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**442**	**266**	**63**
MECs	**6,491**	**5,129**	**2,165**
Liquid emission (effluent/sewage)	1,227	908	80
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	4,302	3,661	2,038
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	137	104	2
Solid immission (sediment/soil/SPM)	147	90	0
Else	678	366	45
Positively detected MECs	**3,996**	**3,170**	**1,599**
Liquid emission (effluent/sewage)	893	638	78
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	2,443	2,171	1,476
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	95	66	2
Solid immission (sediment/soil/SPM)	49	7	0

Number of	Global	European Union	Germany
Else	516	288	43

In general, most measurements have been reported for liquid immission matrices (Table 9). In groundwater, surface and drinking water (grouped in liquid immission), 2,443 MECS within 55 countries were detected above the detection limit (Table 9). 20 of these positively detected MECS were found in drinking water within several European countries and China.

6.3.2 Specific occurrence of diclofenac

WWTPs are one of the major sources (Verlicchi et al. 2012, Vieno et al. 2014), because the conventional treatment process in WWTPs is mostly ineffective for diclofenac removal (Fatta-Kassinos et al., 2011) and therefore diclofenac can end up in surface water (Velicchi et al. 2012, Lonappan et al. 2016). Modern treatment steps in WWTP (UV treatment or ozonation) can eliminate diclofenac (Vieno et al. 2014). However, these processes are still not absolutely efficient (Vieno et al. 2014). In liquid emission matrices, concentrations above the detection limit have been reported from 50 countries. In 49 of these countries, the maximum diclofenac value was above 0.01 µg/L and in 44 already above 0.1 µg/L. The maximum emitted concentration with 2,051 µg/L was detected in an untreated urban sewage outlet in the WWTP Hlohovec of Váh, Slovakia (NORMAN 2012).

Table 10: Maximum MECs of diclofenac on a global scale, in the EU and Germany

Maximum MEC	Global	European Union	Germany
Liquid emission in µg/L	2,051 (Slovakia; Sewage urban (untreated); NORMAN 2012)	2,051 (Slovakia; Sewage urban (untreated); NORMAN 2012)	29 (WWTP effluent (treated); Engelmann et al. 2011)
Liquid immission in µg/L	18.74 (Spain; Surface Water - River/Stream; Ginebreda et al. 2010)	18.74 (Spain; Surface Water - River/Stream; Ginebreda et al. 2010)	15.033 (Surface Water - River/Stream; Jux et al. 2002)
Solid emission in mg/kg	2.376 (Canada; Suspendet particular matter (WWTP-Effluent); Darwano et al. 2014)	0.627 (Spain; WWTP biosolid; Albero et al. 2014)	0.212 (WWTP sludge; Ivashechkin 2005)
Solid immission in mg/kg	0.468 (Spain, Sediment - River/Stream; Ferreira da Silva et al. 2011)	0.468 (Spain, Sediment - River/Stream; Ferreira da Silva et al. 2011)	-

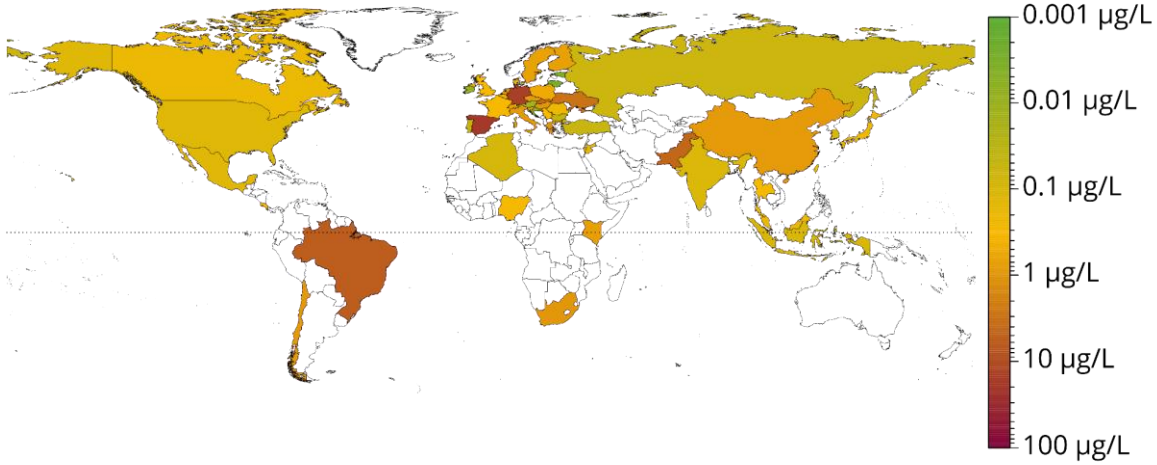
In liquid immission matrices, positively detected MEC have been reported for 55 countries and in the EU in 27 of 28 EU member states. The highest concentration of 18.74 µg/L was found in the Llobregat River and its tributaries (Spain; Ginebreda et al. 2010). The highest value reported for Germany was 15.033 µg/L, which was determined in the Rhine tributary Erft in 1998 (Jux et al. 2002; Table 10 and Figure 9).

High concentration of diclofenac in drinking water were thereby detected in Sweden with 0.14 µg/L (Fick et al. 2011) and Poland with 0.114 µg/L (Kot-Wasik et al. 2016).

6.3.3 Specific distribution of diclofenac

The global distribution of diclofenac is shown for liquid immission in Figure 9 and for solid immission in Figure 10. The maximum MECs for each country are represented in these two figures, whereas the lowest concentration is marked in green the highest is marked in red. For liquid immission matrices, maximum concentrations in the EU ranged from 0.002933 µg/L in Lithuania to 18.74 µg/L measured Spain.

Figure 9: Maximum MECs for diclofenac found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



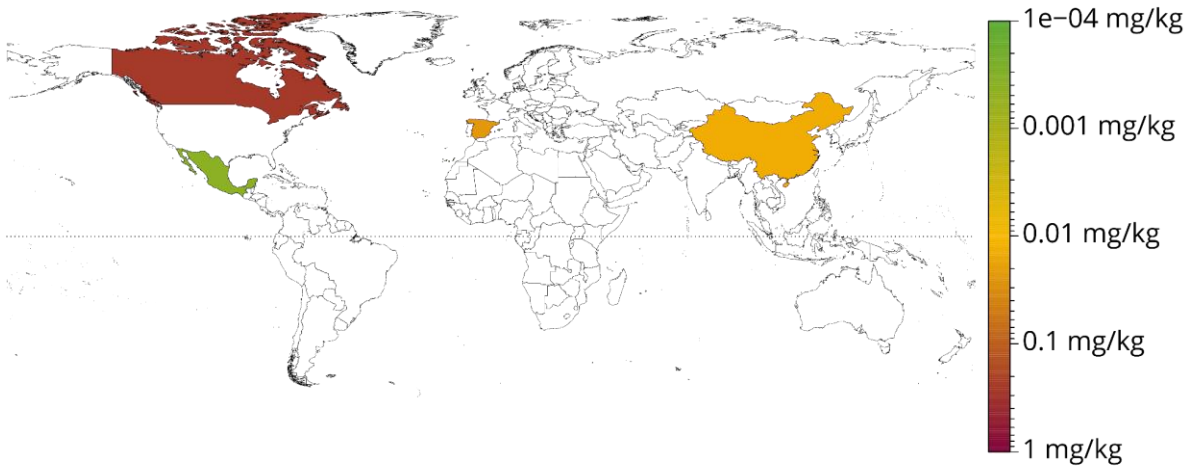
Source: own illustration, GWT-TUD GmbH

As for E2 and EE2, the number of data entries for solid matrices is lower in comparison to liquid matrices (Table 9). Diclofenac may potentially reach soil through the application of sewage sludge (Lonappan et al. 2016). Diclofenac is highly absorbed by organic rich soils and thereafter readily degraded (Al-Rajab et al., 2010, Xu et al., 2009). However, Lonappan and colleagues discussed that diclofenac may be washed out to groundwater (Lonappan et al. 2016).

For diclofenac, higher measured concentration with incomplete analytical description were available in the database. In Spain, highest load was found the sediment of the Ebro basin with 0.468 mg/kg (Ferreira da Silva et al. 2011).

Globally, the maximum load was detected in suspended particles matters of a WWTP effluent in Canada with 2.376 mg/kg. (Darwano et al. 2014). In the EU, highest load was found in biosolid of a WWTP in Madrid (Spain) with 0.627 mg/kg (Albero et al. 2014). In Germany, the maximum load was lower with 0.212 mg/kg, measured in WWTP sludge (Ivashechkin 2005). Highest load of immission matrices (soil or sediments) was found in the sediment of the Segre River near Puigcerdà with 0.024 mg/kg (Ruhí et al. 2016).

Figure 10: Maximum MECs for diclofenac found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

6.4 Azithromycin

The following three substances (azithromycin, clarithromycin and erythromycin) belong to the antibiotic (AB) group macrolides. These antibiotics inhibit the protein biosynthesis, thus bacterial growth is stopped (Carvalho et al. 2016). All three antibiotics are regularly used in human medicine. Here, we first analzed the occurrence and distribution of azithromycin.

6.4.1 General occurrence of azithromycin

For azithromycin, 1,462 database entries have been generated from 118 publications. On a global scale, 540 MECs were above the detected limit. Half of all positively detected MECs have been reported for EU member states, but only 32 MECs for Germany (Table 10).

Table 11: Occurrence of azithromycin on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**118**	**57**	**7**
MECs	**1,462**	**713**	**59**
Liquid emission (effluent/sewage)	274	126	11
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	919	454	36
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	25	11	0
Solid immission (sediment/soil/SPM)	7	1	0
Else	237	121	12
Positively detected MECs	**540**	**274**	**32**

Liquid emission (effluent/sewage)	154	101	8
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	192	67	16
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	18	6	0
Solid immission (sediment/soil/SPM)	4	1	0
Else	172	99	8

For azithromycin, most measurements have been reported for liquid immission matrices, and most positively detected MECs have been reported within liquid immission (Table 11).

6.4.2 Specific occurrence of azithromycin

In the effluent of WWTP, aquacultures or direct sewage outlets (clustered in liquid emission matrices) concentrations above the detection limit have been reported from 16 countries. In all of these countries, the highest azithromycin value was above 0.01 µg/L.

Table 12: Maximum MECs of azithromycin on a global scale, in the EU and Germany

Maximum MEC	Global	European Union	Germany
Liquid emission (µg/L)	16.63 (Spain; Surface Water – Aquaculture; Moreno-González et al. 2014)	16.63 (Spain; Surface Water – Aquaculture; Moreno-González et al. 2014)	0.956 (WWTP effluent (treated); Rossmann et al. 2014)
Liquid immission (µg/L)	2.8 (USA; Surface Water - River/Stream; Jones-Lepp et al. 2012)	0.38 (Germany; Surface Water - River/Stream; Bayerisches Landesamt für Umwelt (LfU) 2009)	0.38 (Surface Water - River/Stream; Bayerisches Landesamt für Umwelt (LfU) 2009)
Solid emission (mg/kg)	6.1489 (China; WWTP sludge; Yuan et al. 2015)	5.77 (Croatia; WWTP sludge; Senta et al. 2013)	-
Solid immission (mg/kg)	0.2651 (France; Sediment - River/Stream; Feitosa-Felizzola et al. 2007)	0.2651 (France; Sediment - River/Stream; Feitosa-Felizzola et al. 2007)	-

The maximum emitted concentration was found in an aquaculture in Spain with 16.63 µg/L (El Albujon, Mar Menor Lagoon; Moreno-Gonzalez et al. 2014;

Table 12). In Germany, the maximum MEC is much lower than the concentration found in Spain. An azithromycin concentration of 0.956 µg/L was determined for the effluent of the WWTP Dresden-Kaditz, which drains into river Elbe (

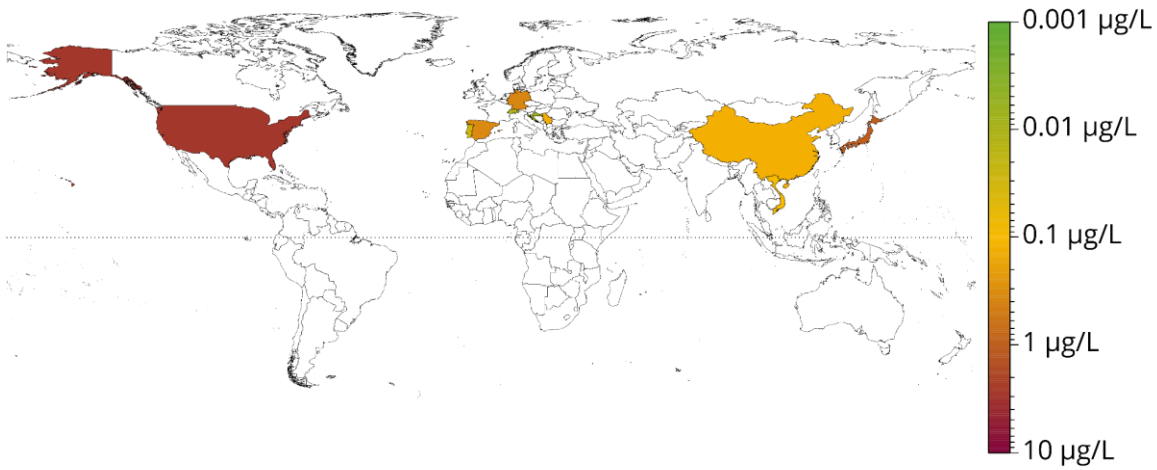
Table 12; Rossmann et al. 2014).

6.4.3 Specific distribution of azithromycin

In 13 countries, positively detected MEC have been reported for liquid immission matrices (Figure 11). Maximum MECs were detected downstream of the WWTP of Las Vegas (USA) with 2.8 µg/L (Jones-Lepp et al., 2012). The highest concentration in the EU of was measured in Germany. Here, a concentration of 0.38 µg/L was detected in the Bavarian village Ebrach, downstream of the WWTP Ebersberg (

Table 12; Bayerisches Landesamt für Umwelt (LfU) 2009). Concentrations in the EU ranged from 0.008 µg/L in Croatia to 0.38 µg/L in Germany. Global distribution of azithromycin is shown in Figure 11 for liquid immission.

Figure 11: Maximum MECs for azithromycin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

Only 23 positively detected MECs were found for solid matrices. Globally, highest emitted load was found in WWTP sludge with 6.1489 mg/kg in Wuxi City (Jiangsu Province, China; Yuan et al. 2015). Sewage sludge of a WWTP in Zagreb contained 5.77 mg/kg (Senta et al. 2013), which was the highest load in EU.

For solid immission matrices including soil and river or lake sediments, only two positively detected MECs have been reported (Table 11). We therefore do not present data as map but rather the two values. In the Arc river sediment near Aix en Province 0.2651 mg/kg of azithromycin were measured (Feitosa-Felizzola et al. 2007) and in mean 0.015 mg/kg of this antibiotic was detected in US river sediments (Bernot et al. 2016).

6.5 Clarithromycin

In the following, the occurrence and distribution of clarithromycin is presented.

6.5.1 General occurrence of clarithromycin

For clarithromycin, 192 publications reported MEC data resulting in 2,177 database entries. On a global scale, 985 MECs were found above the detection limit. Further, 408 of these MECs have been reported for an EU member state, whereas 213 MECs were above the detection limit in Germany (Table 13).

Table 13: Occurrence of clarithromycin on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**192**	**106**	**47**
MECs	**2,177**	**960**	**190**
Liquid emission (effluent/sewage)	476	209	46
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	1,181	603	114
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	111	21	4
Solid immission (sediment/soil/SPM)	105	13	0
Else	304	102	26
Positively detected MECs	**985**	**408**	**158**
Liquid emission (effluent/sewage)	332	154	45
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	374	166	85
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	38	13	4
Solid immission (sediment/soil/SPM)	29	6	0
Else	212	69	24

For clarithromycin, most measurements and most positively detected MECs have been reported for liquid immission matrices (

Table 13).

6.5.2 Specific occurrence of clarithromycin

For liquid immission matrices, concentrations above the detection limit have been reported for 28 countries. Highest global concentration was found was found in untreated sewage of the hospital in Waldbröl (Germany) with 62.241 µg/L (Pinnekamp et al. 2009; Table 14). Generally, clarithromycin was positively detected in only nine EU member states.

The highest concentration of liquid immission matrices was found in Germany with 5.705 µg/L. This MEC is the maximum detected value of a sampling campaign in several rivers in Saxony, Saxony-Anhalt, Thuringia (Hug et al. 2015; Table 14).

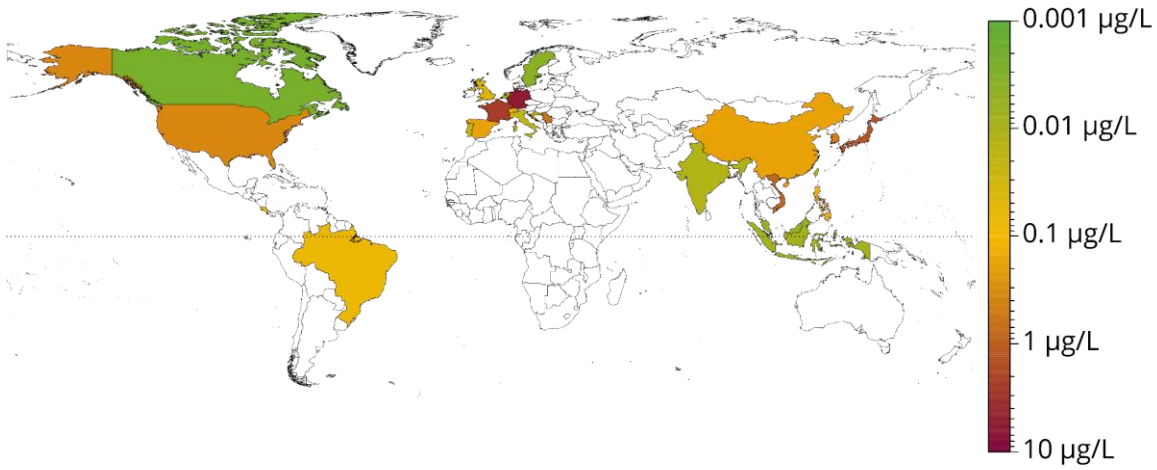
Table 14: Maximum MECs of clarithromycin on a global scale, in the EU and Germany

Maximum MEC	Global	European Union	Germany
Liquid emission in µg/L	62.241 (Sewage hospital (untreated); Pinnekamp 2009)	62.241 (Germany; Sewage hospital (untreated); Pinnekamp 2009)	62.241 (Sewage hospital (untreated); Pinnekamp 2009)
Liquid immission in µg/L	5.705 (Germany; Surface Water - River/Stream; Hug et al. 2015)	5.705 (Germany; Surface Water - River/Stream; Hug et al. 2015)	5.705 (Surface Water - River/Stream; Hug et al. 2015)
Solid emission in mg/kg	0.503 (Japan; WWTP sludge; Okuda et al. 2009)	0.18 (Germany; WWTP sludge; Ivashechkin 2005)	0.18 (WWTP sludge; Ivashechkin 2005)
Solid immission in mg/kg	0.261 (Spain; Sediment - River/Stream; Ferreira da Silva et al. 2011)	0.261 (Spain; Sediment - River/Stream; Ferreira da Silva et al. 2011)	-

6.5.3 Specific distribution of clarithromycin

Global distribution of clarithromycin is shown in Figure 12 for liquid immission. Globally, the highest load for immission matrices was found in the sediment of the river Ebro, Spain with 0.261 mg/kg (Ferreira da Silva et al. 2011). Further, clarithromycin was also detected in the Arc river sediment near Aix en Province (France) with 0.0038 mg/kg and in soil of the Mezquital Valley (Mexico) with 0.0038 mg/kg (Bernot et al. 2016).

Figure 12: Maximum MECs for clarithromycin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

Only 57 MECs above the detection limit were found for solid matrices (Table 14). Highest emitted load was found in WWTP sludge with 0.18 mg/kg in Germany (Ivashechkin 2005). For solid immission matrices, positively detected MECs were found in three countries. We therefore do not present data as map here, but rather the maximum MECs for these countries.

6.6 Erythromycin

Erythromycin belongs to the antibiotic group macrolides like azithromycin and clarithromycin. This antibiotic is frequently used in human therapies. Within the database, the following metabolites are listed: Anhydroerythromycin, Erythromycin-A dehydrate, Erythromycin-H_2O, but occurrence and distribution are only analysed for the parent substance.

6.6.1 General occurrence of erythromycin

For erythromycin, 2,177 database entries have been generated from 231 publications. On a global scale, 985 MECs were above the detection limit. In the EU, 408 positively detected MECs have been reported, whereas 158 of these were measurements within Germany (Table 15).

Table 15: Occurrence of erythromycin on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**231**	**108**	**38**
MECs	**2,177**	**960**	**190**
Liquid emission (effluent/sewage)	476	209	46
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	1,181	603	114
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	111	21	4

Number of	Global	European Union	Germany
Solid immission (sediment/soil/SPM)	105	25	0
Else	304	102	26
Positively detected MECs	**985**	**408**	**158**
Liquid emission (effluent/sewage)	332	154	45
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	374	166	85
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	38	13	4
Solid immission (sediment/soil/SPM)	29	6	0
Else	212	69	24

For erythromycin, most measurements and most positively detected MECs have been reported for liquid immission matrices (Table 15).

6.6.2 Specific occurrence of erythromycin

In liquid emission matrices, concentrations above the detection limit have been reported from 23 countries. In all of these countries, the maximum erythromycin value was above 0.01 µg/L. The maximum emitted concentration of 7.84 µg/L was detected in an untreated industrial sewage in Taipai (China; Tsai et al. 2009; Table 16). This is quite similar to the highest emitted concentration in the EU with 7.54 µg/L, detected in an untreated hospital sewage of the Maternity hospital in Coimbra (Portugal; Santos et al. 2013) and in Germany with 6 µg/L, detected by Sadezky et al. (2013) in an WWTP effluent (Table 16).

Table 16: Maximum MECs of erythromycin on a global scale, in the EU and Germany

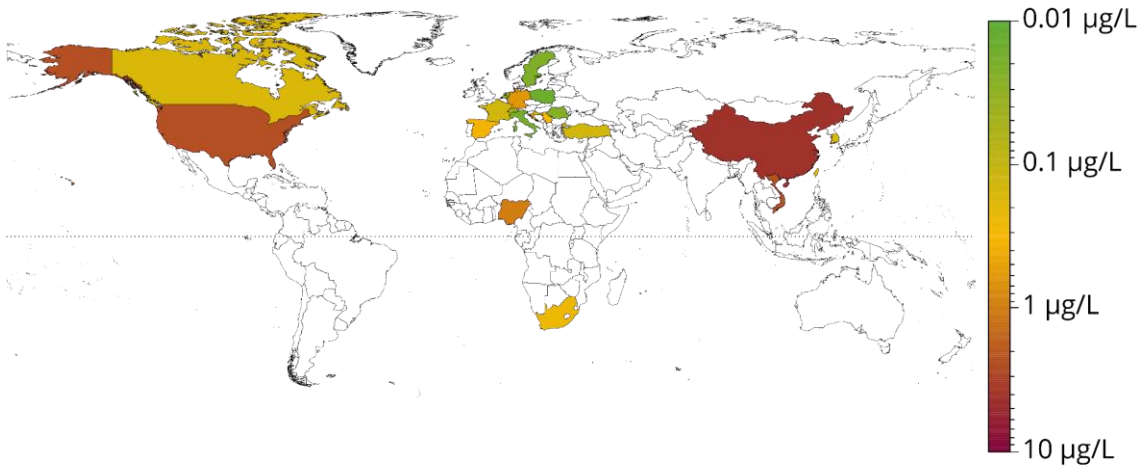
Maximum MEC	Global	European Union	Germany
Liquid emission (µg/L)	7.84 (China; Sewage industrial (untreated); Tsai et al. 2009)	7.54 (Portugal; Sewage hospital (untreated); Santos et al. 2013)	6.0 (WWTP effluent (treated); Sadezky et al. 2008)
Liquid immission (µg/L)	4.2 (China; Surface Water - River/Stream; Luo, Y., L. Xu, et al. 2011)	0.62 (Germany; Surface Water - River/Stream; Hirsch et al. 1998)	0.62 (Surface Water - River/Stream; Hirsch et al. 1998)
Solid emission (mg/kg)	1.0 (Sweden; WWTP sludge; TemaNord 2012)	1.0 (Sweden; WWTP sludge; TemaNord 2012)	0.036 (WWTP sludge; Alexy et al. 2003a)
Solid immission (mg/kg)	3.04	0.005	-

Maximum MEC	Global	European Union	Germany
	(China; Sediment – Lake; Li et al. 2012)	(Croatia; Sediment - River/Stream; Smital et al. 2013)	

6.6.3 Specific distribution and loads of erythromycin

For liquid immission matrices, concentrations above the detection limit have been reported for 20 countries worldwide (Figure 13). These concentrations ranged between 0.014 and 4.2 µg/L). For the EU, the highest concentration was found in the German river Lutter with 0.62 µg/L (Hirsch et al. 1998; Table 16).

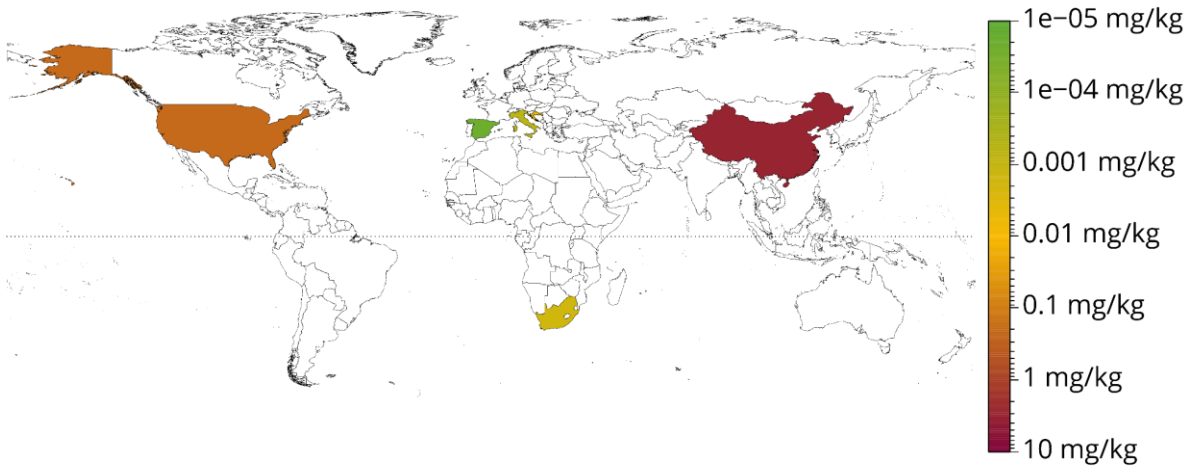
Figure 13: Maximum MECs for erythromycin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

As for the previous substances, the number of data entries for solid matrices is much lower in comparison to liquid matrices (Table 15). In total, only 67 MECs above the detection limit have been reported. The highest emitted load was found in WWTP sludge with 1 mg/kg within the EU in Sweden (Fick et al., 2011).

Figure 14: Maximum MECs for erythromycin found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

Globally, erythromycin was detected positively in solid immission matrices in only six countries (Figure 14). The highest load in immission matrices was thereby found in the sediment of the Baiyangdian Lake in with 3.04 mg/kg (Li et al. 2012), which is higher than the maximum emission load. Further, erythromycin was also detected in the Sava river sediment in Zagreb (Croatia) with 0.005 mg/kg (Smital et al. 2013).

6.7 Ciprofloxacin

Ciprofloxacin belongs to the AB group quinolones and is frequently used to treat human bacterial infections.

6.7.1 General occurrence of ciprofloxacin

For ciprofloxacin, 261 publications reported MEC data resulting in 2,064 database entries. Globally, 1,289 MECs were found above the detection limit and were reported from countries of all five UN-regions. In the EU, 494 positively detected MECs have been reported, whereas 72 of these were measurements within Germany (Table 17).

Table 17: Occurrence of ciprofloxacin on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**261**	**111**	**21**
MECs	**2,064**	**807**	**107**
Liquid emission (effluent/sewage)	591	269	38
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	689	270	37
Solid emission	186	60	14

Number of	Global	European Union	Germany
(manure/dung/sediment from aquaculture/SPM/biosolids/sludge)			
Solid immission (sediment/soil/SPM)	181	38	0
Else	417	170	18
Positively detected MECs	**1,289**	**494**	**72**
Liquid emission (effluent/sewage)	463	229	33
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	271	59	10
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	155	58	14
Solid immission (sediment/soil/SPM)	100	7	0
Else	300	141	15

For ciprofloxacin, most measurements have been reported for liquid immission matrices, whereas most positively detected MECs were found in matrices clustered within liquid emission. In groundwater, surface and drinking water (grouped in liquid immission), 271 MECS within 28 countries were detected above the detection limit (Table 17).

6.7.2 Specific occurrence of ciprofloxacin

On a global scale, positively detected MECs within the liquid immission matrices have been reported for 28 countries (Figure 15). In 26 of these countries, the maximum ciprofloxacin value was above 0.01 µg/L and in 15 countries respectively above 0.1 µg/L.

Table 18: Maximum MECs of ciprofloxacin on a global scale, in the EU and Germany

Maximum MEC	Global	European Union	Germany
Liquid emission (µg/L)	31,000 (India; WWTP effluent (treated); Larsson et al. 2007)	17,480 (Croatia; Sewage industrial (untreated); Dolar et al. 2012)	38.691 (Sewage hospital (untreated); Pinnekamp 2009)
Liquid immission (µg/L)	6,500 (India; Surface Water – Lake; Fick et al. 2009)	9.66 (France; Surface Water - River/Stream; Feitosa-Felizzola & Chiron 2009)	1.0 (Soil Water;Weiss et al. 2007)
Solid emission (mg/kg)	45.59 (China; Manure – dung; Zhao, L., Y. H. Dong, et al. 2010)	41.8 (Netherlands; WWTP sludge; Butkovskyi et al. 2015)	3.5 (WWTP sludge; Giger 2005)

Maximum MEC	Global	European Union	Germany
Solid immission (mg/kg)	54.248 (India; Surface Water - River/Stream; Kristiansson et al. 2011)	0.392 (Finland; Suspended particulate matter - River/Stream; Lahti & Oikari 2011)	-

An extremely high concentration of ciprofloxacin was detected in the effluent of a WWTP close to Patancheru, India (31,000 mg/kg; Table 18; Larsson et al. 2007). Here, sewage of pharmaceutical production industry reached the WWTP. Further, extreme concentration could also be detected in the river in which the WWTP effluent is discharged. However, in a lake upstream of the outlet of this WWTP 6,500 µg/L were measured which is, globally, the highest concentration in surface water (liquid immission matrices, Fick et al. 2009).

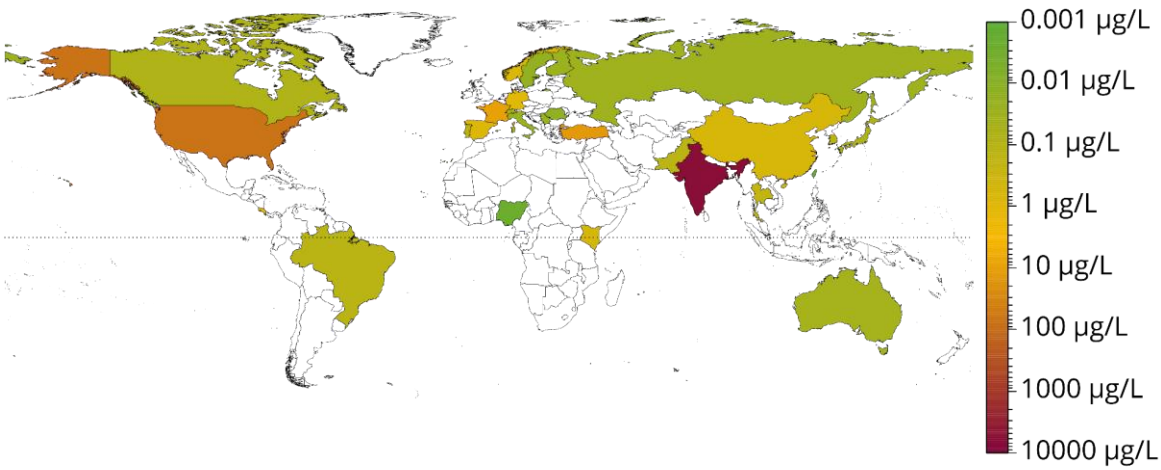
In Croatia, an extremely high emission value of 17,480 µg/L was detected as well, caused by untreated sewage of an industrial area. However, in comparison to the MEC of India, the sewage was untreated, whereas in India the concentration was determined in the treated effluent of a WWTP. The maximum emission concentration of Germany was much lower than the global and European maximum. It was measured in the untreated sewage of the hospital of Waldbröl with 38.691 µg/L (Pinnekamp et al. 2009).

Concerning the liquid immission on EU scale, the highest concentration was measured in the Arc River near Aix en Province in France (Feitosa-Felizzola & Chiron 2009) with 9.66 µg/L, which is much lower compared to the Indian MEC, but one order of magnitude higher compared to the highest German immission MEC of 1 µg/L (Weiss et al. 2007).

6.7.3 Specific distribution of ciprofloxacin

Global distribution of ciprofloxacin for liquid immission is shown in Figure 15.

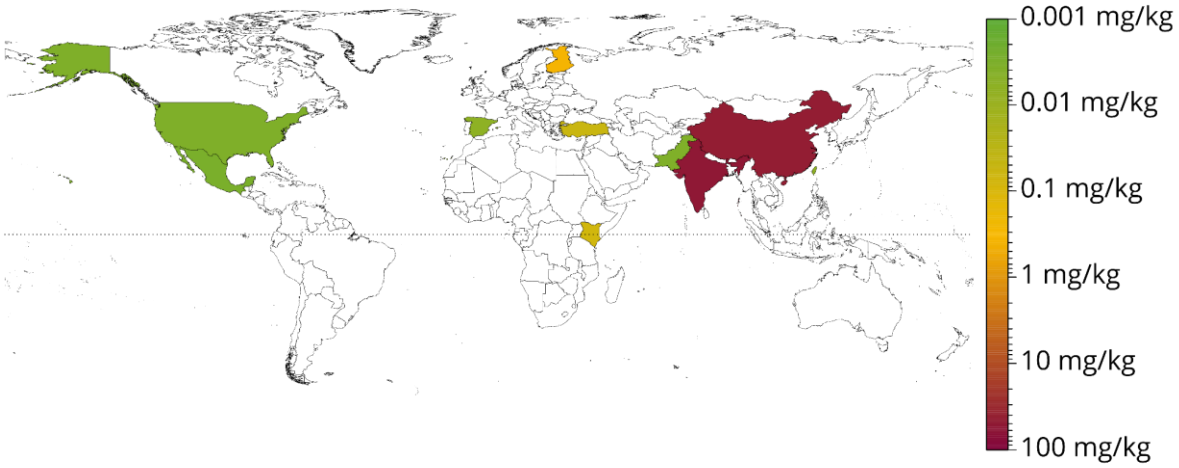
Figure 15: Maximum MECs for ciprofloxacin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

For ciprofloxacin in solid matrices 255 positively detected MECs were found. Globally, highest emitted load was found in manure with 45.59 mg/kg in China (Zhao, L., Y. H. Dong, et al. 2010). In the EU, high concentration of ciprofloxacin were detected in sludge of the WWTP Noorderhoek with 41.8 mg/kg (Netherlands; Butkovskyi et al. 2015). In Germany, the maximum MECs for solid emission matrices was 3.5 mg/kg in WWTP sludge (Giger 2005).

Figure 16: Maximum MECs for ciprofloxacin found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

As already described above, in the industrial area Patancheru (India) extremely high concentration of ciprofloxacin were detected in the crossing river and a lake due to the

pharmaceutic production. In crossing river, high loads of ciprofloxacin were also detected in the sediment of this river (54.248 mg/kg; Kristiansson et al. 2011; Figure 16). In comparison, the maximum MEC within the EU was 0.392 mg/kg and was detected in suspended particulate matter of a river close to the outlet of WWTP Jyväskylä (Finland; Lahti & Oikari 2011). In Germany no ciprofloxacin was detected in immission matrices.

6.8 Amoxicillin

Amoxicillin is a broad spectrum antibiotic and belongs to the antibiotic group of beta-lactams (Section 7.2).

6.8.1 General occurrence of amoxicillin

For amoxicillin, 51 publications reported MEC data resulting in 384 database entries. On a global scale, 134 MECs were found above the detection limit. In the EU, 48 of these MECs have been reported for an EU member state, whereas 18 measurements were positively detected within Germany (Table 19).

Table 19: Occurrence of amoxicillin on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**51**	**32**	**8**
MECs	**384**	**196**	**42**
Liquid emission (effluent/sewage)	140	68	11
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	148	71	17
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	6	1	0
Solid immission (sediment/soil/SPM)	1	1	0
Else	89	55	14
Positively detected MECs	**134**	**48**	**18**
Liquid emission (effluent/sewage)	59	17	4
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	36	14	6
Solid emission (manure/dung/sediment from aquaculture/SPM/biosolids/sludge)	2	0	0
Solid immission (sediment/soil/SPM)	0	0	0
Else	37	17	8

For amoxicillin, the number of data entries is much lower than for the previous substances. Most measurements have been reported for liquid immission matrices (Figure 17), whereas most positively detected MECs were found in matrices clustered within liquid emission.

6.8.2 Specific occurrence of amoxicillin

In the liquid emission matrices, highest MECs were detected in the WWTP effluent of Leon, Spain with 30 µg/L (Hijosa-Valsero et al. 2011). In Germany, the highest value for amoxicillin was detected in WWTP effluent of Dresden with 0.187 µg/L (Kaditz; Rossman et al. 2014, Table 20).

Table 20: Maximum MECs of amoxicillin on a global scale, in the EU and Germany

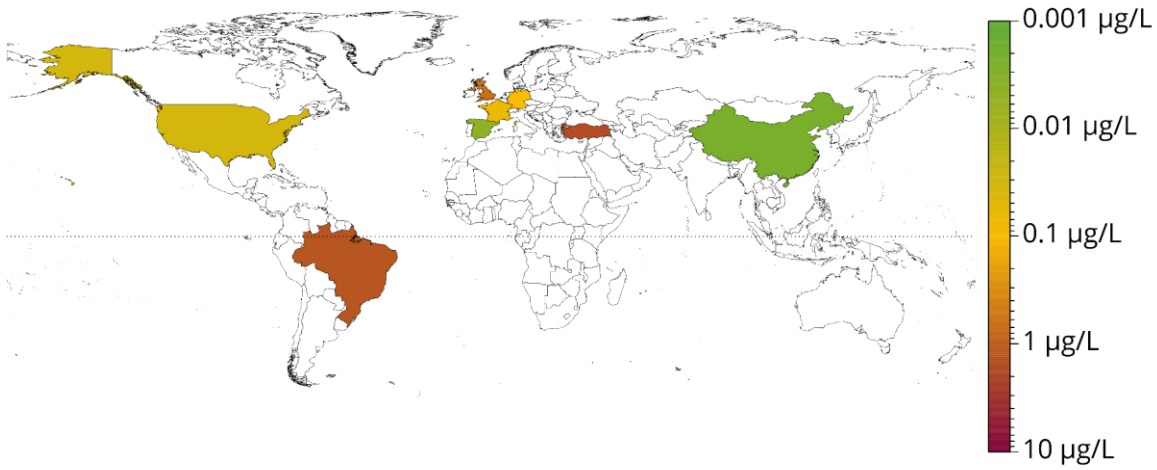
Maximum MEC	Global	European Union	Germany
Liquid emission (µg/L)	30 (Spain; WWTP effluent (treated); Hijosa-Valsero et al. 2011)	30 (Spain; WWTP effluent (treated); Hijosa-Valsero et al. 2011)	0.187 (WWTP effluent (treated); Rossmann et al. 2014)
Liquid immission (µg/L)	1.654 (Turkey; Surface Water - River/Stream; Aydin & Talinli 2013)	0.622 (UK; Surface Water - River/Stream; Kasprzyk-Hordern et al. 2008)	0.1 (Groundwater; Sadezky et al. 2008)
Solid emission (mg/kg)	0.079 (Kenya; WWTP sludge; Kimosop et al. 2016)	-	-
Solid immission (mg/kg)	-	-	-

The highest immission concentration was found in the Ahlat River, Turkey with 1.654 µg/L (Aydin & Talinli 2013). Within the EU, highest concentration could be detected in the Taff River, Wales, UK (Kasprzyk-Hordern et al. 2008).

6.8.3 Specific distribution of amoxicillin

Global distribution of amoxicillin is shown in Figure 17 for liquid immission. In eight countries, positively detected MEC have been reported for liquid immission matrices (Figure 17).

Figure 17: Maximum MECs for amoxicillin found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

Only two MECs above the detection limit were found for solid emission matrices and none for solid immission matrices (Table 19). In Kenya, 0.079 mg/kg of amoxicillin were found in the sludge of the WWTP Bungoma and 0.055 mg/kg in sludge of the WWTP Mumias (Kimosop et al. 2016).

7 Occurrence of antibiotic groups

Antibiotics (AB) are an important group of pharmaceuticals in our modern medicine therapies. Beside this application, they are also used to treat but also prevent animal and plant infections (Hirsch et al. 1999, Kümmerer 2009a). Furthermore, they have been applied as growth promoter in livestock for a long time (Hirsch et al. 1999). As many ABs are not hydrolyzed or significantly reduced during the wastewater treatment processes, high amounts of ABs are released into the environment (Kümmerer 2009a; Michael et al. 2013). In the last years, ABs therefore became a new class of water contaminants of emerging concern with adverse effects on aquatic life (Kolpin et al. 2002, Kümmerer 2009b). Already, five ABs were therefore placed on the EU-Watch list for emerging water pollutants. (Section 6).

Antibiotics cause raising problems, as the resistances even against new generations of ABs are permanently increasing in hospitals but also in the environment (Kümmerer 2009b).

Due to the high number of available ABs, the present report focuses on the following main AB groups: Aminoglycoside, macrolides, quinolones and fluorquinolones, tetracyclines, beta-lactams, sulfonamides and chloramphenicol and its relative substances as well as trimethoprim as only member of the group diaminopyrimidines.

Members of the specific group, which were measured and therefore included into the database, are represented for every single group. Substances, which are written in bold, were already presented in section 6 and substances, which are written in parentheses, are transformation products of a specific AB. Global distribution of the AB groups will be represented based on the number of MECs per country. We are aware that the number of MECs depend on the number of analysis, sampling campaign and publications and differ between countries. For many AB groups, most MECs have been reported for China, which might not only be related to the high contamination of different environmental matrices with the respective substances compared to other countries, but also to the high number of analysis, monitoring campaign and publications available. However, to get an overview on the distribution, we took the number of MECs as dimension.

7.1 Aminoglycosides

Aminoglycoside belong to ABs, which inhibit the protein biosynthesis of gram-negative bacteria. Their usage is mostly limited to veterinary drugs, due to adverse effects and high toxic potential in human therapy (Carvalho et al. 2016). Their main emission source should therefore be via wastewater of animal breeding, aquacultures or manure (Michael et al. 2013).

The following aminoglycosides were included in the database: amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, dihydrostreptomicin, apramycine, spectinomycin, ribostamycin, dibekacin.

7.1.1 General occurrence of aminoglycoside

Generally, the number of data entries of aminoglycosides is much lower compared to the following other antibiotic groups. Only two publications reported positive detections. On a global scale, 53 MECs were detected wherefrom only 21 MECs were above the detection limit. None of these MECs have been reported for an EU member state.

Table 21: Occurrence of aminoglycosides on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**4**	**1**	**1**
MECs	**116**	**6**	**6**
Human liquid emission (effluent/sewage)	38	2	2
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	0	0	0
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	5	4	4
Human solid emission (biosolids/sludge/SPM)	0	0	0
Veterinary solid emission (dung/manure/sediment from aquaculture)	0	0	0
Solid immission (sediment/soil/SPM)	10	0	0
Else	63	0	0
Positively detected MECs	**65**	**0**	**0**
Human liquid emission (effluent/sewage)	16	0	0
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	0	0	0
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	0	0	0
Human solid emission (biosolids/sludge/SPM)	0	0	0
Veterinary solid emission (dung/manure/sediment from aquaculture)	0	0	0
Solid immission (sediment/soil/SPM)	5	0	0
Else	44	0	0

For liquid emission matrices, 38 measurements were reported and 16 of these MECs were above the respective detection limit. For solid immission matrices, 10 measurements were reported, wherefrom five of these were found above the detection limit. For the EU, in total six MECs were reported, but none of these was above the detection limit.

7.2 Beta-lactams

Antibiotics of the beta-lactam group mainly inhibit the transpeptidases and, hence, the membrane synthesis of bacteria. A prominent intramolecular structure, the beta-lactam ring characterizes this antibiotic group (Carvalho et al. 2016).

The following beta-lactams are included in the database: imipenem, meropenem, loracarbef, ertapenem, cefaclor, cefadroxil, cefalexin, cefalonium, cefalotin, cefapirin, cefatrizine, cefazolin, cefdinir, cefepime, cefixime, cefoperazone, cefotaxime, cefotetan, cefovecin, cefoxitin, cefpodoxime, cefprozil, cefquinome, cefradine, ceftazidime, ceftezole, ceftibuten, ceftiofur, ceftriaxone, cefuroxime, aztreonam, **amoxicillin**, ampicillin, pivampicillin, bacampicillin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, benzylpenicillin, dicloxacillin, flucloxacillin, meticillin, mezlocillin, phenoxymethylpenicillin, piperacillin, ticarcillin, oxacillin, cloxacillin, mecillinam, nafcillin, penethamate, procaine benzylpenicillin, propicillin, clavulanic acid, sulbactam, sultamicillin, pivmecillinam.

7.2.1 General occurrence of beta-lactams

For beta-lactams, 106 publications reported MEC data resulting in 3,082 database entries. On a global scale, 667 MECs were found above the detection limit. In Germany, 74 positive detections have been reported.

Table 22: Occurrence of beta-lactams on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**106**	**51**	**13**
MECs	**3,082**	**1,679**	**343**
Human liquid emission (effluent/sewage)	829	307	81
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	30	2	0
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	1,541	1,104	144
Human solid emission (biosolids/sludge/SPM)	47	6	0
Veterinary solid emission (dung/manure/sediment from aquaculture)	2	0	0
Solid immission (sediment/soil/SPM)	21	4	0
Else	612	256	118
Positively detected MECs	**667**	**186**	**74**
Human liquid emission (effluent/sewage)	296	82	24
Veterinary liquid emission	5	0	0

Number of	Global	European Union	Germany
(manure/sewage from livestock/aquaculture)			
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	87	37	20
Human solid emission (biosolids/sludge/SPM)	17	0	0
Veterinary solid emission (dung/manure/sediment from aquaculture)	2	0	0
Solid immission (sediment/soil/SPM)	11	0	0
Else	249	67	30

Beta-lactams are regularly addressed during environmental monitoring campaigns, as indicated by the high number of available MECs. However, the amount of positive detections was smaller compared to the total MEC number (Table 22). The easy hydrolysis of the prominent chemical structure, the beta-lactam ring, makes these pharmaceuticals vulnerable to degradation, especially during changes of ambient conditions (Carvalho et al. 2016). Hence, beta-lactams should be significantly removed during wastewater treatment processes (Watkinson et al. 2007, 2009).

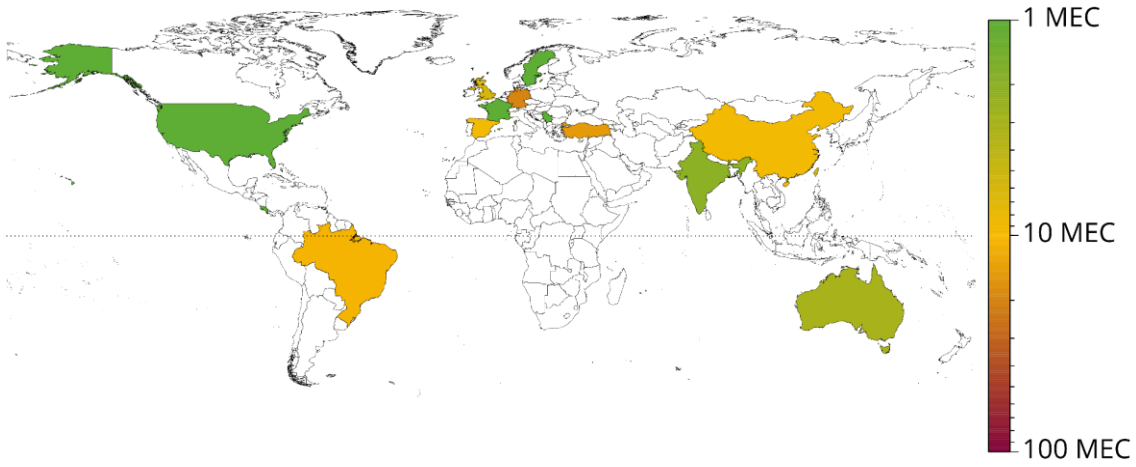
Most measurements have been reported for liquid immission matrices, whereas the number of positively detected MECs for liquid immission matrices is much lower. In contrast, a higher number of positive detections was found in matrices clustered within liquid emission (Table 22).

In solid matrices, 70 measurements have been reported, 30 of these were above the detection limit. Most of these positively detected measurements were found in solid emission matrices. No positive detections have been reported for EU member states (Table 22).

7.2.2 Specific distribution of beta-lactams

Globally, beta-lactams were positively detected in 14 countries. Interestingly, most MECs have been reported for Germany (20 MECs). For liquid immission matrices, this global distribution of beta-lactams is shown in Figure 18. Here, low numbers of MECs are represented in green, whereas high numbers are marked in red.

Figure 18: Number of positively detected MECs for the antibiotic group beta-lactams found in liquid immission matrices (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

For solid immission matrices, MECs were only available for China with 6 MECs and Kenya with 5 MECs. A map for solid immission matrices is therefore not presented.

7.3 Macrolides

Macrolides are considered as the most important antibacterial agents used in modern human medicine. Macrolide inhibit the protein biosynthesis and can be used to treat infections with a wide variety of Gram-negative and Gram-positive bacteria.

Carvalho and colleagues argued that macrolides should actually be considered at low concentration in the environment as they have a low water solubility and high sorption capacity to sludge in typical wastewater treatment processes (Carvalho et al. 2016). However, macrolides are regularly detected in different environmental matrices and due to their high consumption rate and high (and unexpected) stability, they may also have a strongly input on aquatic environment. Three macrolide antibiotics were already presented in section 5 as they are part of the WL.

The following macrolides and their respective transformation products (in parentheses) were included in the database: **azithromycin**, **clarithromycin**, **erythromycin** (anhydro-erythromycin, erythromycin-a dehydrate, erythromycin-h_2o), josamycin, kitasamycin, midecamycin, oleandomycin, roxithromycin, spiramycin, tilmicosin, tulathromycin, tylosin, tylosin tartrate, gamithromycin, miocamycin.

7.3.1 General occurrence of macrolides

For macrolides, 11,256 database entries have been generated from 394 publications. On a global scale, 4,372 MECs were above the detected limit. For EU member states, 1,721 MECs above the detection limit have been reported and 603 of these in Germany (

Table 23).

Table 23: Occurrence of macrolides on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**394**	**182**	**64**
MECs	**11,256**	**4,678**	**849**
Human liquid emission (effluent/sewage)	1,975	921	198
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	342	6	2
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	6,367	2,961	470
Human solid emission (biosolids/sludge/SPM)	234	110	17
Veterinary solid emission (dung/manure/sediment from aquaculture)	208	7	2
Solid immission (sediment/soil/SPM)	446	151	3
Else	1,684	522	157
Positively detected MECs	**4,372**	**1,721**	**603**
Human liquid emission (effluent/sewage)	1,249	600	186
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	86	5	2
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	1,634	639	285
Human solid emission (biosolids/sludge/SPM)	169	84	17
Veterinary solid emission (dung/manure/sediment from aquaculture)	61	4	1
Solid immission (sediment/soil/SPM)	128	23	3
Else	1,045	366	109

Even if their chemical characteristic should not allow a high water solubility (Carvalhos et al. 2016), macrolides were regularly detected above their respective detection limit (

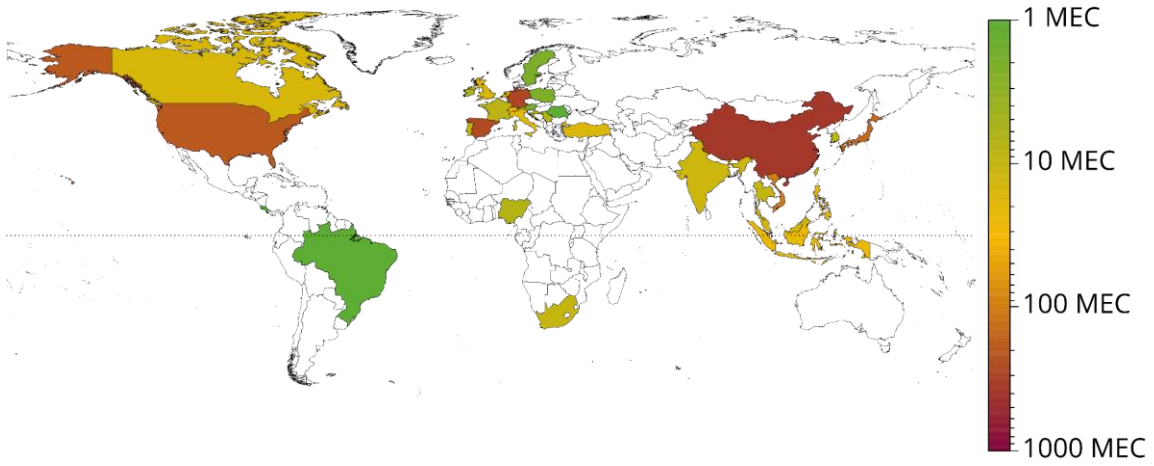
Table 23). Most measurements above the respective detection limit have been reported for liquid immission matrices including ground-, drinking and tap water as well as surface water.

In solid matrices, 358 positive detections have been reported. Most of these MECs were found in solid emission matrices.

7.3.2 Specific distribution of macrolides

In liquid immission matrices, macrolides were positively detected in 32 countries worldwide. Highest number of positive MECs were found in China with 376 MECs. Within the EU, most measurement above detection limit have been reported for Germany (285 MECs). The global distribution of the macrolides is shown in Figure 19 for liquid immission matrices. Here, low numbers of MECs are represented in green, whereas high numbers in red.

Figure 19: Number of positively detected MECs for the antibiotic group macrolides found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)

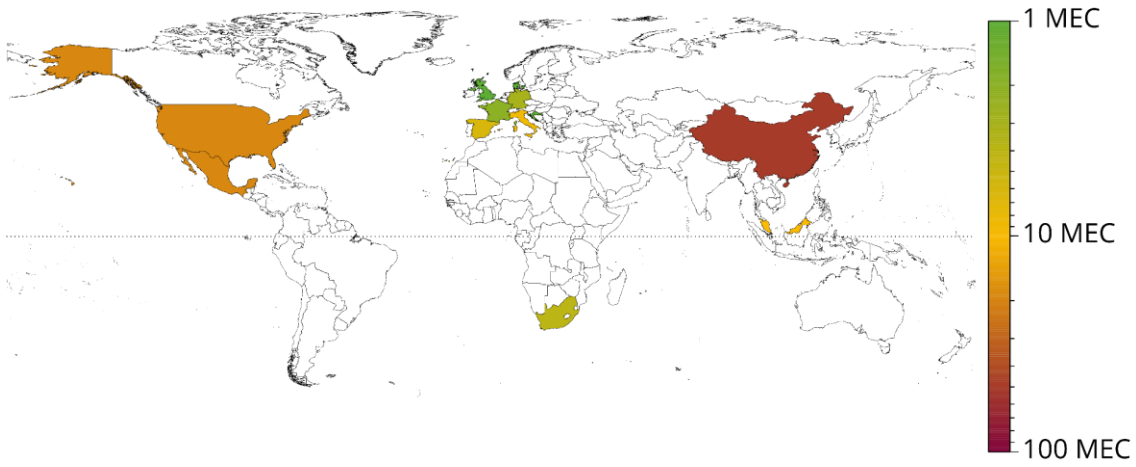


Source: own illustration, GWT-TUD GmbH

In solid immission matrices, the number of positively detected MEC is much lower (128 MECs;

Table 23). Macrolides could be found above their respective detection limit in 12 countries (Figure 20). As for the liquid immission, most MECs have been reported for China (50 MECs; Figure 20).

Figure 20: Number of positively detected MECs for the antibiotic group macrolides found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

7.4 Quinolones/Fluoroquinolones

Quinolones/Fluoroquinolones are a relatively new group of antibiotics (Carvalho et al. 2016) and were summarized in this report. They are effective against both gram-positive and gram-negative bacteria.

The following quinolones and fluoroquinolones were included in the database: sparfloxacin, norfloxacin, ofloxacin, nalidixic acid, moxifloxacin, lomefloxacin, levofloxacin, gatifloxacin, enoxacin, **ciprofloxacin,** sarafloxacin, diflofloxacin, difloxacin, cinoxacin, clinafloxacin, enrofloxacin, ibafloxacin, marbofloxacin, orbifloxacin, danofloxacin, fleroxacin, flumequine, fluorquinolone, oxolinic acid, pefloxacin.

7.4.1 General occurrence of quinolones and fluoroquinolones

For quinolones and fluoroquinolones, 354 publications reported MEC data resulting in 8,285 database entries. On a global scale, 4,626 MECs were found above the detection limit.

Table 24: Occurrence of quinolones and fluoroquinolones on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**354**	**152**	**25**
MECs	**8,285**	**2,724**	**183**
Human liquid emission (effluent/sewage)	1,833	774	63
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	176	8	5
Liquid immission	3,229	1,091	60

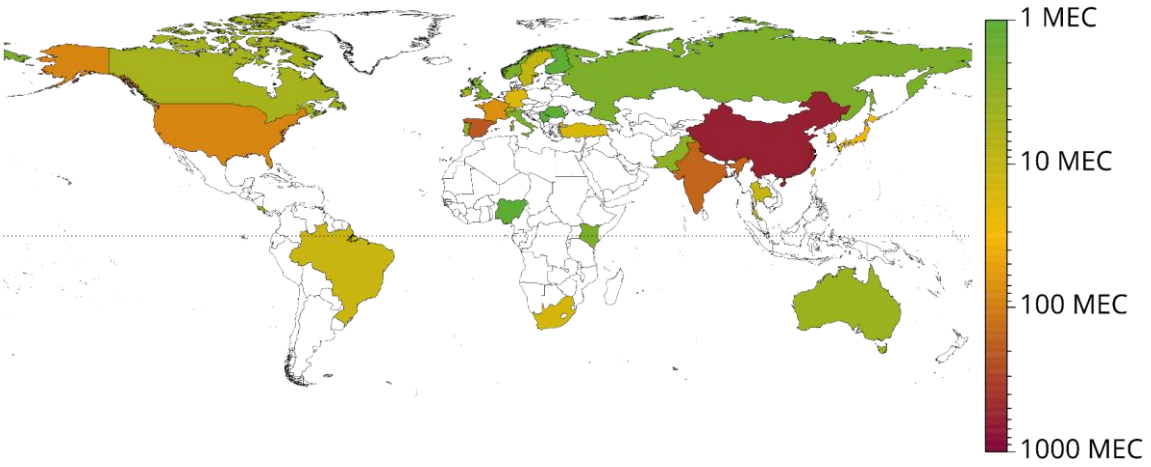
Number of	Global	European Union	Germany
(surface water/groundwater/bank filtrate/drinking and tap water)			
Human solid emission (biosolids/sludge/SPM)	309	151	14
Veterinary solid emission (dung/manure/sediment from aquaculture)	342	9	6
Solid immission (sediment/soil/SPM)	802	244	3
Else	1,594	447	32
Positively detected MECs	**4,626**	**1,402**	**123**
Human liquid emission (effluent/sewage)	1,299	542	53
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	89	5	5
Liquid immission (surface water/groundwater/bank filtrate/drinking and tap water)	1,295	312	16
Human solid emission (biosolids/sludge/SPM)	278	138	14
Veterinary solid emission (dung/manure/sediment from aquaculture)	240	8	5
Solid immission (sediment/soil/SPM)	332	58	3
Else	1,093	339	27

In general, most measurements have been reported for liquid immission matrices, whereas most positively detected MECs were found in liquid emission matrices (Table 24). In groundwater, surface and drinking water (grouped in liquid immission), 1,295 MECS (Table 24) within 31 countries were detected above the detection limit.

7.4.2 Specific distribution of quinolones and fluoroquinolones

For liquid immission matrices, quinolone and fluoroquinolone could be positive detected in 31 countries, whereas the highest number of positive MECs within this matrix group were found in China with 586 MECs. Within the EU, most measurement above detection limit have been reported for Spain (202 MECs). The global distribution of quinolones and fluoroquinolones is shown for liquid immission matrices in Figure 21. Here, the low number of MECs are represented in green, whereas high numbers are marked in red.

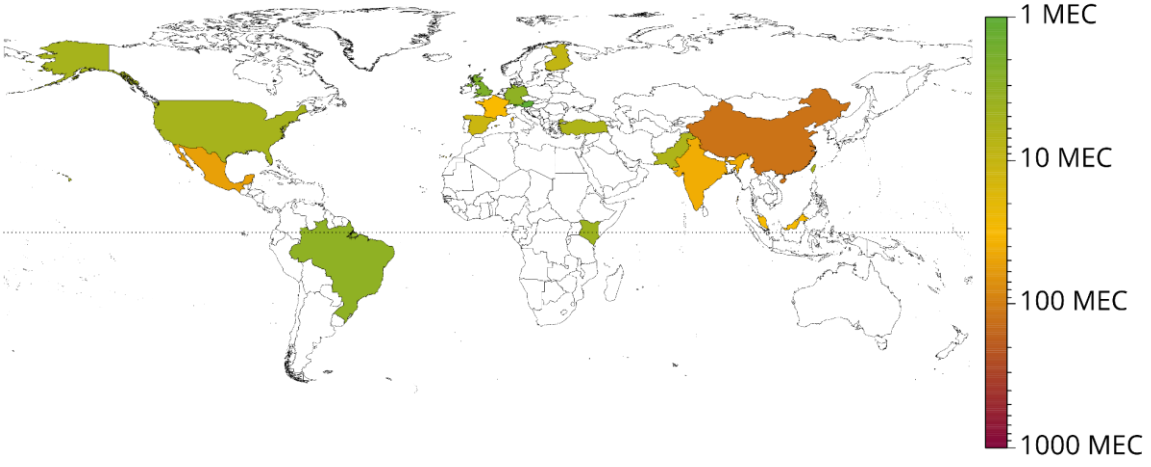
Figure 21: Number of positively detected MECs for the antibiotic group quinolones and fluoroquinolones found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

In solid immission matrices, the number of MECs is smaller than for liquid immission matrices. Quinolones and fluoroquinolones were found above their respective detection limit in 16 countries. As for liquid immission matrices, most positively detected MECs have been reported for China (123 MECs; Figure 22). Within the EU, 32 MECs above the detection limit were found in France, whereas only three positive MECs have been reported for Germany.

Figure 22: Number of positively detected MECs for the antibiotic group quinolones and fluoroquinolones found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

7.5 Sulfonamides

Sulfonamides is one of the oldest groups of ABs in medicine (Hruska and Franek 2012). Sulfonamides are used in human and in veterinarian medicine. High number of resistances against sulfonamides already exist (Carvalho et al. 2016).

The following sulphonamides and their respective transformation products (in parentheses) were included in the database: sulfabenzamide, sulfacetamide, sulfachloropyridazine, sulfaclozine, sulfadiazine (N-acetyl-sulfadiazine), sulfadicramide, sulfadimethoxine (N4-acetyl-sulfadimethoxine), sulfadoxine, sulfaguanidine, sulfamerazine (n-acetyl-sulfamerazine), sulfamethazine or *sulfadimidine* (N4-acetyl-sulfamethazine), sulfamethizole, sulfamethoxazole (N4-acetyl-sulfamethoxazole, N-acetyl-sulfamethoxazole, acetyl-sulfamethoxazole), sulfamethoxine, sulfamethoxypyridazine, sulfamethylthiazole, sulfametomidine, sulfametopyrazine, sulfametoxydiazine, sulfametrole, sulfamonomethoxine, sulfamoxole, sulfanilamide, sulfanitrin, sulfaphenazole, sulfapyridine, sulfaquinoxaline, sulfathiazole (N4-acetyl-sulfathiazole), sulfathiourea, sulfatroxazole, sulfisomidine, sulfisoxazole, sulfonamide, succinylsulfathiazole (acetyl-sulfadimidine).

7.5.1 General occurrence of sulfonamides

For sulfonamides, 21,742 database entries have been generated from 571 publications. More than half of these measurements have been reported for an EU member state. On a global scale, 7,552 MECs were found above the detection limit and 2,954 in the EU. Sulfonamides are therefore the most detected AB-group.

Table 25: Occurrence of sulfonamides on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**571**	**254**	**82**
MECs	**21,742**	**10,890**	**6,073**
Human liquid emission (effluent/sewage)	2,574	920	94
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	580	25	16
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	13,594	8,140	5,390
Human solid emission (biosolids/sludge/SPM)	548	295	1
Veterinary solid emission (dung/manure/sediment from aquaculture)	630	225	211
Solid immission (sediment/soil/SPM)	1,023	92	54
Else	2,793	945	307
Positively detected MECs	**7,552**	**2,954**	**824**
Human liquid emission (effluent/sewage)	1,484	599	75
Veterinary liquid emission	210	14	11

Number of	Global	European Union	Germany
(manure/sewage from livestock/aquaculture)			
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	3,457	1,519	547
Human solid emission (biosolids/sludge/SPM)	316	181	1
Veterinary solid emission (dung/manure/sediment from aquaculture)	265	50	40
Solid immission (sediment/soil/SPM)	350	92	46
Else	1,470	499	104

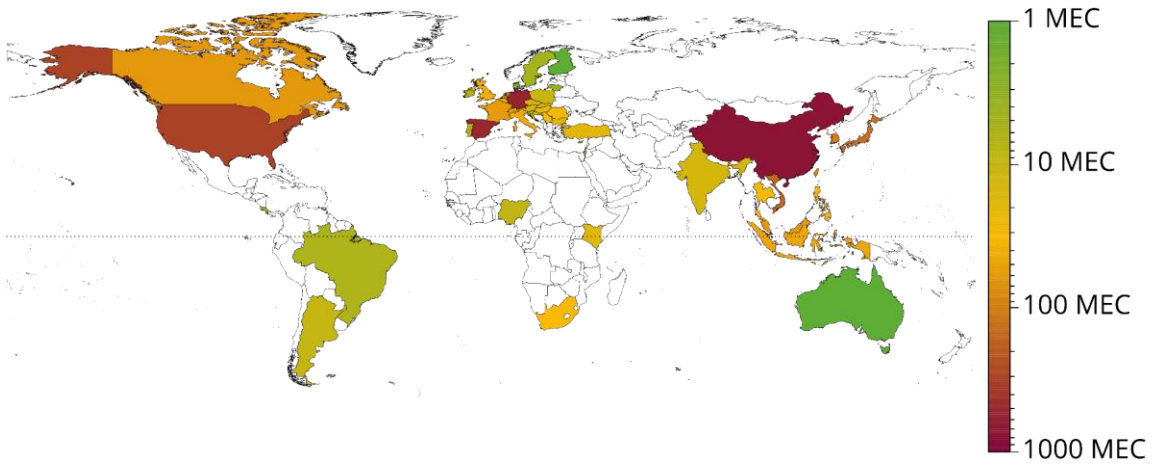
In general, most measurements above the respective detection limit have been reported for liquid immission matrices. This matrix group includes measurements in ground-, drinking and tap water as well as surface water.

In solid matrices, 2,201 positive detections have been reported. Most of these MECs were found in solid emission matrices (veterinarian origin: 630 MECs and human origin: 548 MECs;Table 25).

7.5.2 Specific distribution of sulfonamides

The global distribution of sulfonamides is shown for liquid immission matrices in Figure 23. Here, the low number of MECs are represented in green, whereas high numbers in red.

Figure 23: Number of positively detected MECs for the antibiotic group sulfonamides found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)

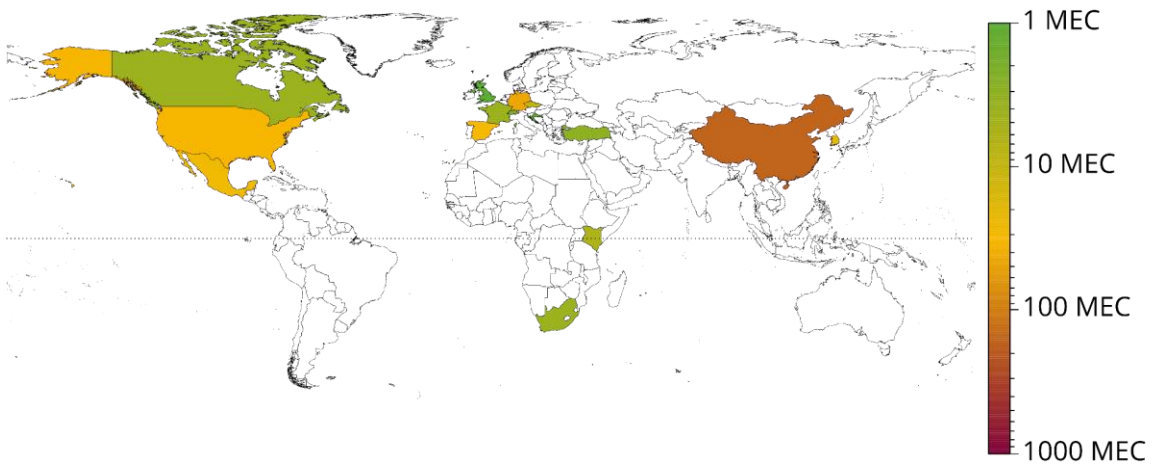


Source: own illustration, GWT-TUD GmbH

For sulfonamides, not only the highest number of measurements for all AB-groups have been reported, they also have the broadest distribution. In total, sulfonamides were positively detected in 51 countries in solid and liquid immission matrices. For liquid immission matrices, highest number of positive MECs were found in China with 750 MECs, followed by Germany with 547 MECs.

As for liquid immission matrices, the highest MECs number for solid immission matrices was found for China with 159 MECs, followed by Germany again (46 positively detected MECs).

Figure 24: Number of positively detected MECs for the antibiotic group sulfonamides found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

7.6 Tetracyclines

Tetracyclines are broad-spectrum antibacterial drugs that are used in human, but mainly in veterinarian medicine (Sarmah et al. 2006). Interestingly, their occurrence in water bodies is controversely described (Carvalho et al. 2016). For liquid matrices, tetracyclines were often not found about their respective detection limit (e.g. Verlicchi et al. 2012, Watkinson et al. 2007, Sadezky et al. 2008) which can be explained by the capability of complex formation with bi- or trivalent cations (Carvalho et al. 2016). Therefore, tetracyclines are more likely to be expected in soil or suspended particles because of this capability. On the other hand, the number of publications reporting positively detected MECs is respectable (e.g. Rossman et al. 2014, Opris et al. 2013). Subsequently, we will present their occurrence in the different defined matrix groups.

The following tetracyclines and their respective transformation products (in parentheses) were included in the database: anhydrochlortetracycline, chlortetracycline (epi-iso-chlorotetracycline, isochlortetracycline), demeclocycline, doxycycline, minocycline, oxytetracycline (alpha-apo-oxytetracycline, beta-apo-oxytetracycline), tetracycline (4-epianhydrochlortetracycline, 4-epianhydrotetracycline, 4-epichlortetracycline, 4-epioxytetracycline, 4-epitetracycline, anhydrotetracycline), lymecycline, meclocycline (methacycline hydrochloride).

7.6.1 General occurrence of tetracyclines

On a global scale, 253 publications reported MEC data resulting in 5,877 database entries. Nearly 50% of these MECs (2,509, Table 26) were found above the detection limit. However, only 537 of these positively detected MECs have been reported for EU member states.

Table 26: Occurrence of tetracyclines on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**253**	**110**	**36**
MECs	**5,877**	**1,458**	**294**
Human liquid emission (effluent/sewage)	1,131	368	32
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	270	8	0
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	2,304	468	83
Human solid emission (biosolids/sludge/SPM)	206	61	0
Veterinary solid emission (dung/manure/sediment from aquaculture)	442	82	48
Solid immission (sediment/soil/SPM)	341	242	80
Else	939	229	51
Positively detected MECs	**2,509**	**537**	**137**
Human liquid emission (effluent/sewage)	503	137	7
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	133	1	0
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	597	79	9
Human solid emission (biosolids/sludge/SPM)	136	33	0
Veterinary solid emission (dung/manure/sediment from aquaculture)	345	70	41
Solid immission (sediment/soil/SPM)	341	114	58
Else	454	103	22

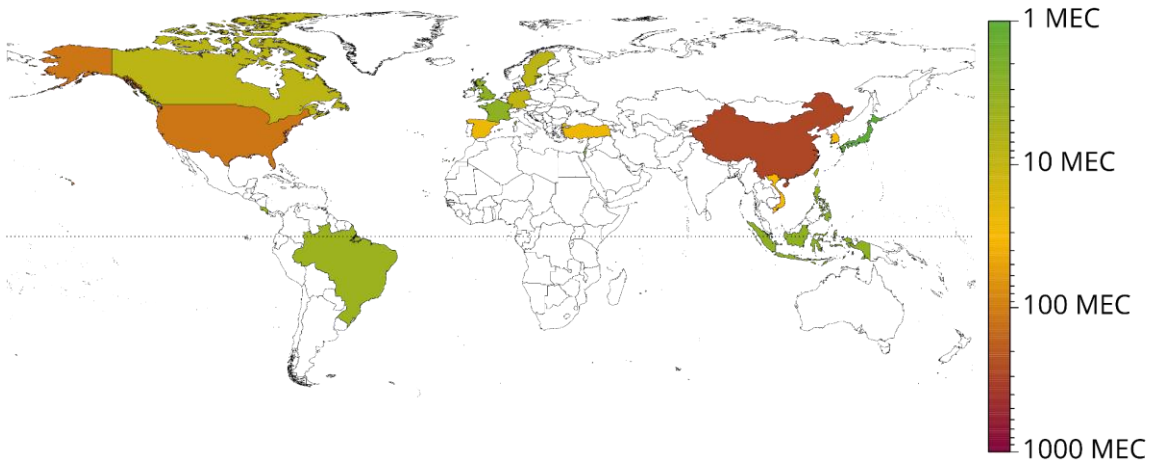
Globally, most measurements have been reported for liquid immission matrices, whereas most positively detected MECs were found in liquid emission matrices (veterinarian origin: 133 MECs and human origin: 503 MECs; Table 26).

In comparison to the other AB groups, high number of MECs were also detected for solid matrices. For solid matrices, 822 MECs above their detection limits (Table 26) have been reported for 14 countries, whereas most positively detected MECs were found in solid emission matrices (veterinarian origin: 345 MECs and human origin: 136 MECs; Table 26).

7.6.2 Specific distribution of tetracyclines

For liquid immission matrices, tetracyclines were positively detected in 19 countries. As for sulfonamides and quinolones, the highest number of positive detections were found in China with 282 MECs, followed by USA with 117 MECs. Within the EU, most positively detected measurements have been reported for Luxembourg (32 MECs). The global distribution for this matrix group is shown in Figure 25. Here, the low number of MECs are represented in green, whereas high numbers in red.

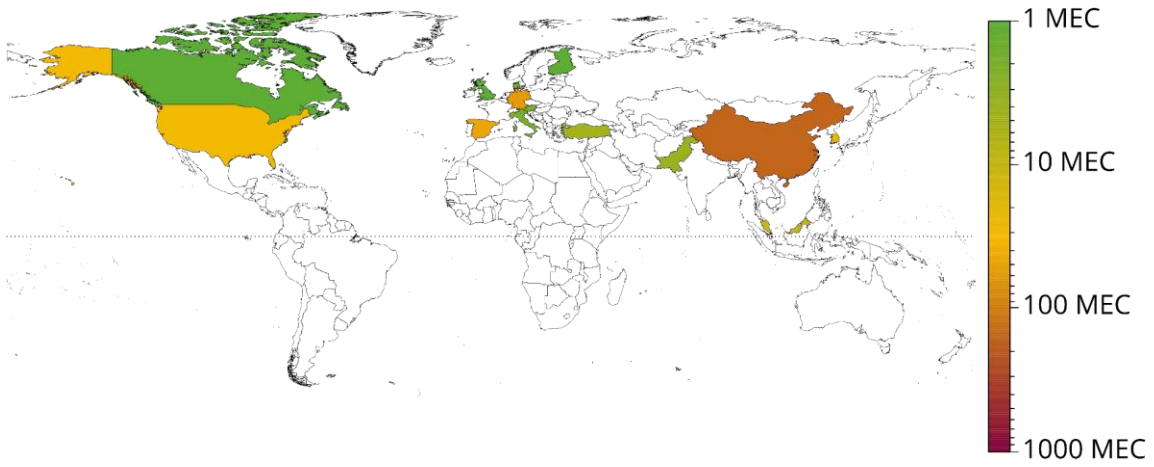
Figure 25: Number of positively detected MECs for the antibiotic group tetracyclines found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

In solid immission matrices, tetracyclines were found above their respective detection limit in 14 countries. As for liquid immission matrices, most positively detected MECs have been reported for China (158 MECs; Figure 26). Within the EU, 58 positively detected MECs were found in Germany, which represents the highest number within the EU.

Figure 26: Number of positively detected MECs for the antibiotic group tetracyclines found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

7.7 Chloramphenicol and related substances

Chloramphenicol and the related substances thiamphenicol and florfenicol were considered. These three pharmaceuticals are broad-spectrum antibiotics which inhibit the protein biosynthesis. According to Carvalho and colleagues, this group of AB is not frequently detected in the environment. (Carvalho et al. 2016)

7.7.1 General occurrence of chloramphenicol and related substances

For chloramphenicol and its related substances, 1,195 database entries have been generated from 88 publications. On a global scale, about 20% of these MECs were found above the detection limit.

Table 27: Occurrence of chloramphenicol, thiamphenicol and florfenicol on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**88**	**40**	**12**
MECs	**1,195**	**661**	**57**
Human liquid emission (effluent/sewage)	245	100	14
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	14	0	0
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	680	480	24
Human solid emission	20	7	0

Number of	Global	European Union	Germany
(biosolids/sludge/SPM)			
Veterinary solid emission (dung/manure/sediment from aquaculture)	2	0	0
Solid immission (sediment/soil/SPM)	50	38	0
Else	184	36	19
Positively detected MECs	**280**	**56**	**13**
Human liquid emission (effluent/sewage)	92	15	6
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	6	0	0
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	75	18	1
Human solid emission (biosolids/sludge/SPM)	11	2	0
Veterinary solid emission (dung/manure/sediment from aquaculture)	2	0	0
Solid immission (sediment/soil/SPM)	11	5	0
Else	83	16	6

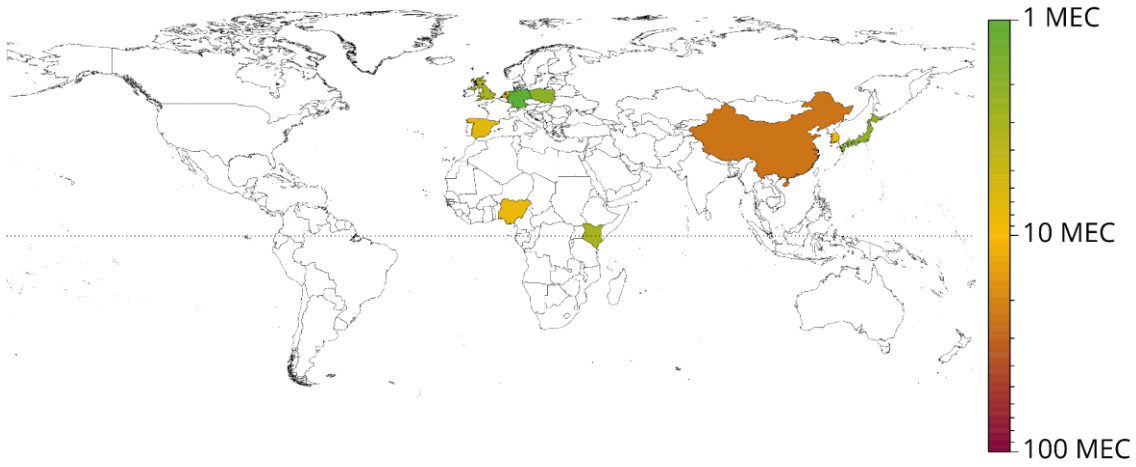
On a global scale, most MECs have been reported for liquid immission matrices, whereas most positively detected measurements were found in liquid emission matrices (veterinarian origin: 6 MECs and human origin: 92 MECs; Table 27).

For solid matrices, 24 MECs above the detection limits (Table 27) have been reported for 4 countries: 13 MECs for solid emission matrices and 11 for solid immission matrices.

7.7.2 Specific distribution of chloramphenicol and related substances

In total, chloramphenicol, thiamphenicol and florfenicol were positively detected in 11 countries. As for the previous antibiotic groups, the highest number of positive MECs were found in China with 24 MECs, followed by Singapore with 12 MECs. Within the EU, only low numbers of MECs have been reported. The global distribution for this matrix group is shown in Figure 27. Here, the low number of MECs are marked in green, whereas high numbers are presented in red.

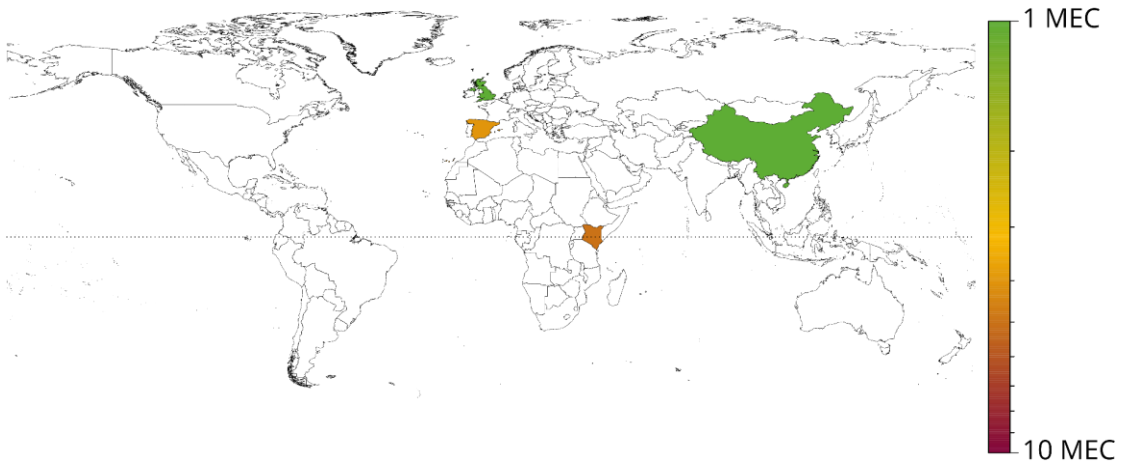
Figure 27: Number of positively detected MECs for chloramphenicol and related substances found in liquid immission media (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

In solid immission matrices, chloramphenicol, thiamphenicol and florfenicol were found above their respective detection limit in four countries: 1 MECs for China and the UK, 4 MECs for Spain and 5 MECs for Kenya.

Figure 28: Number of positively detected MECs for chloramphenicol and related substances found in solid immission media (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

Interestingly, chloramphenicol and its related substances have not been reported for North or South American countries until now.

7.8 Trimethoprim

The only detected member of the group diaminopyrimidines is trimethoprim and in the following, we therefore refer to trimethoprim instead of the AB-group. Trimethoprim has a

bactericidal effect if it is used alone and in combination with sulfonamides a synergistic bactericidal effect (Carvalho et al. 2016).

7.8.1 General occurrence of trimethoprim

For trimethoprim, 377 publications reported MEC data resulting in 3,976 database entries. On a global scale, 2,000 MECs were found above the detection limit. More than 75% of these MECs have been reported for an EU member state, whereas 157 positive detections were reported for Germany.

Table 28: Occurrence of trimethoprim on a global scale, in the EU and Germany

Number of	Global	European Union	Germany
Publications	**377**	**165**	**44**
MECs	**3,976**	**1,914**	**650**
Human liquid emission (effluent/sewage)	739	347	41
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	73	3	0
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	2,094	1,159	549
Human solid emission (biosolids/sludge/SPM)	105	61	5
Veterinary solid emission (dung/manure/sediment from aquaculture)	69	9	5
Solid immission (sediment/soil/SPM)	162	32	1
Else	734	303	49
Positively detected MECs	**2,000**	**739**	**157**
Human liquid emission (effluent/sewage)	591	255	40
Veterinary liquid emission (manure/sewage from livestock/aquaculture)	50	1	0
Liquid immission (surface water/ groundwater/bank filtrate/drinking and tap water)	685	262	78
Human solid emission (biosolids/sludge/SPM)	53	24	5
Veterinary solid emission	43	6	3

Number of	Global	European Union	Germany
(dung/manure/sediment from aquaculture)			
Solid immission (sediment/soil/SPM)	85	7	1
Else	503	184	30

For trimethoprim, most measurements and most positively detected MECs have been reported for liquid immission matrices. Only 182 positively detected MECs were found for solid matrices (Table 28).

7.8.2 Specific occurrence of trimethoprim

As trimethoprim is the only member of the antibiotic group diaminopyrimidines, we present concentrations and loads in the following.

Highest global concentration was found in an untreated industrial sewage of the WWTP Kalinovica, Croatia with 27,680 µg/L (Dolar et al. 2012; Table 29). Trimethoprim was positively detected in only nine EU member states. Highest concentration in liquid immission matrices was found in Xiaoqing River near the Laizhou Bay, China with 62.5 µg/L (Zhang et al. 2012; Table 29). In Germany, the highest MECs for liquid immission matrices within the EU was measured in groundwater close to the municipality Bösel with 0.89 µg/L (Hannappel et al. 2017; Table 29).

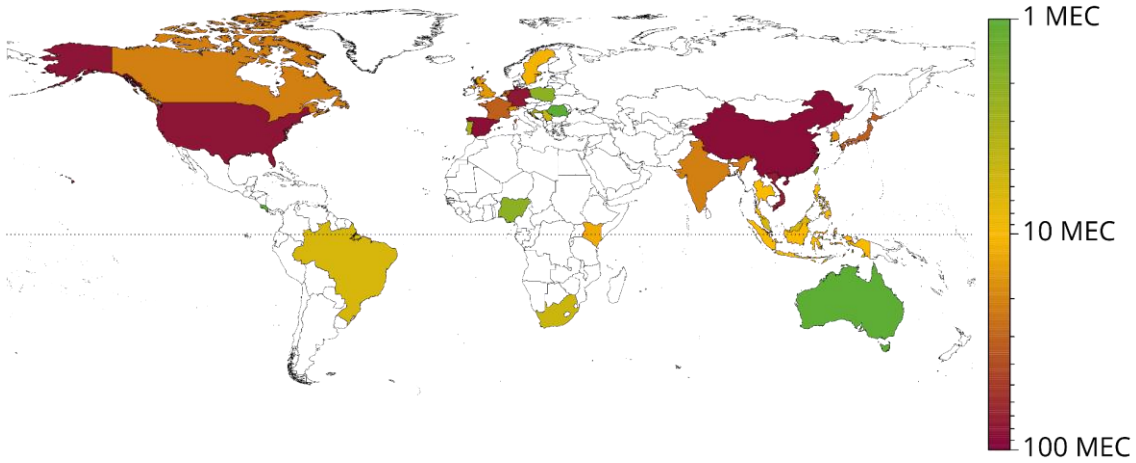
Table 29: Maximum MECs of trimethoprim on a global scale, in the EU and Germany

Maximum MEC	Global	European Union	Germany
Liquid emission (µg/L)	27,680 (Croatia; Sewage industrial (untreated); Dolar et al. 2012)	27,680 (Croatia; Sewage industrial (untreated); Dolar et al. 2012)	1.5 (WWTP effluent (treated); Bund/Länderausschuss für Chemikaliensicherheit (BLAC) 2003)
Liquid immission (µg/L)	62.5 (China; Surface Water - River/Stream; Zhang et al. 2012)	0.89 (Germany; Groundwater; Hannappel et al. 2017)	0.89 (Germany; Groundwater; Hannappel et al. 2017)
Solid emission (mg/kg)	17 (Austria, Germany, Manure, Martinez-Carballo et al. 2007 & Sattelberger et al. 2005)	17 (Austria, Germany, Manure, Martinez-Carballo et al. 2007 & Sattelberger et al. 2005)	17 (Austria, Germany, Manure, Sattelberger et al. 2005)
Solid immission (mg/kg)	87.55 (South Africa; Sediment - River/Stream; Matongo et al. 2015)	0.1 (Austria; Soil; Martinez-Carballo et al. 2007)	0.1 (Soil; Sattelberger et al. 2005)

7.8.3 Specific distribution of trimethoprim

For liquid immission matrices, concentrations above the detection limit have been reported for 31 countries (Figure 29). The highest number of positive MECs was found in China with 89 MECs, followed by Spain with 87 MECs. The global distribution of trimethoprim for this matrix group is shown in Figure 29.

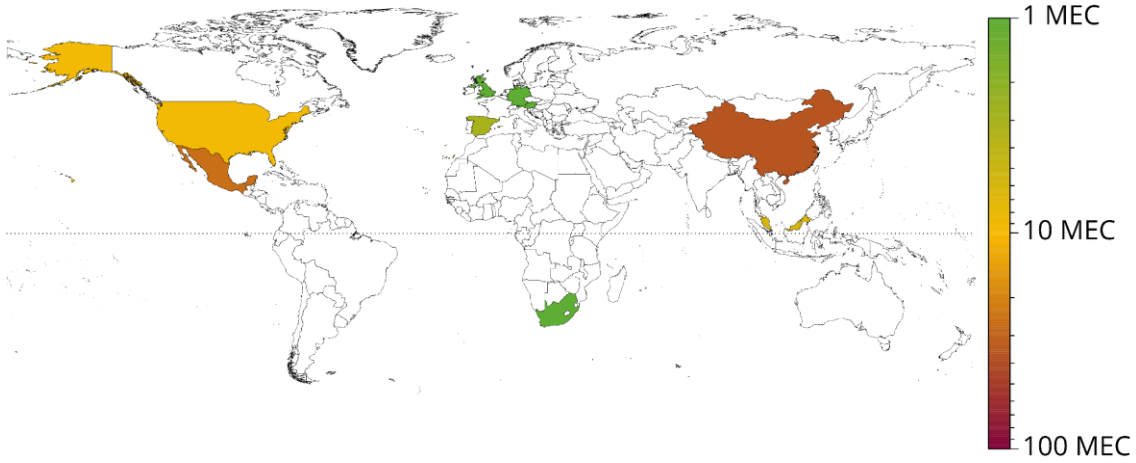
Figure 29: Number of positively detected MECs for trimethoprim in all liquid media/ immission (surface water/groundwater/bank filtrate/drinking and tap water)



Source: own illustration, GWT-TUD GmbH

For solid immission matrices, positively detected MECs were found in nine countries (Figure 30).

Figure 30: Number of positively detected MECs for trimethoprim in all solid media/ immission (sediment/soil/SPM)



Source: own illustration, GWT-TUD GmbH

Global maximum MECs have been reported for the sediment of the Henley dam outlet in South Africa with 87.55 mg/kg (Matongo et al. 2015).

7.9 Reserve antibiotics

We further analysed the occurrence of the following reserve antibiotics in the environment.

- Oxazolidinone e.g. linezolid (no entry in the database)
- Cephalosporine 4th generation
  - Cefquinome (no entry in the database)
  - Cefepime (no entry in the database)
- Cephalosporine 5th generation (no entry in the database)
- Polymyxine e.g. polymycin B, colistin (no entry in the database)
- Aztreonam (no entry in the database)
- Daptomycin (no entry in the database)
- Fosfomycin (no entry in the database)
- Tigecyclin (no entry in the database)

Within the database, there are no entry for any of these antibiotics until 2016. Measurements may have been performed in the last two years but were not part of this report and database update.

8 Cytostatic drugs

We further focused on the occurrence of cytostatic drugs. The following substance were of interest: afatinib, axitinib, azacitidin, bosutinib, cabazitaxel, ceritinib, cediranib, cobimetinib, crizotinib, dabrafenib, dasatinib, erlotinib, gefitinib, ibrutinib, imatinib, lapatinib, nilotinib, nintedanib, olaparib, palbociclib, panobinostat, pazopanib, pemetrexed-disodium, regorafenib, sorafenib, sunitinib, trametinib, vandetanib, vemurafenib, venetoclax, vismodegib.

None of these substances listed above is represented in the database. These pharmaceuticals are a new generation and may therefore not have been measured in the time period we focused on during the database update.

9 Conclusion and outlook

The main aim of the project was an update of the MEC DB in order to include scientific publications and reports released in the period 2010 to 2016. We successfully performed an intense literature survey, which results in 1,200 publications to be screened in detail. Finally, 504 publications contained 54,947 new MEC entries, which were entered to the DB.

As the DB is thought to be updated and further used for many years, we kindly suggest to perform specific optimizations in order to keep and further increase the consistency and integrity of the DB. As described in Section 4.1 in detail the original schema do not use the advantages of a relational and normalized DB scheme. Hence, different attributes, e.g. the CAS number, occur independently in different tables, which easily hampers the integrity of the entered data and subsequently leads to incomplete or even false search results. The same is true for repeatedly used entries of specific attributes, which are currently saved as text in every single MEC entry. To overcome the described problems a first optimization approach was performed in order to enable a consistent update of the DB in the present project.

A second big issue is the management of the literature and its linkage to the MEC DB. The literature is currently managed using the commercial EndNote software. However, the once major distribution of EndNote within the scientific community is steadily decreasing, due to free or OpenSource based alternatives. Moreover, the export capabilities of EndNote libraries are currently not state of the art, which hampers the exchange within a diversifying scientific community. A further problem is the limited linkage of the literature DB with the MEC DB, which results in double data maintenance regarding the literature data in both DBs. We therefore suggest to change the literature management to ZOTERO as described in Section 3. This should further enable the usage of Weblinks in the MEC DB to directly link to publicly shared and available ZOTERO libraries.

Further, access for some publications was limited during the review process. We therefore contacted authors via mail and researchgate.com, but the return was low. Publications with potential MECs data were stored in an extra depot within ZOTERO. Data returning after finalization of this project will be transferred to the UBA for a later update of the DB.

One big goal of the present study was the visualization of the data in terms of specific topic maps. Whereas the former project utilized ArcGIS for the creation of the maps, the present project used a script based approach utilizing R. However, current web technologies already enable the dynamic creation of maps, which is a more advanced approach for a developing DB. In our understanding, the implementation of dynamic maps e.g. utilizing a webGIS approach or dynamic webpage frameworks like R-Shiny would also foster the public awareness and accessibility of the data. However, these approaches require a DB optimization as mentioned before.

Finally, the high diversity of the published MEC data regarding the sampling procedure and presentation of results need to be addressed. Given the fact that different operators will continue to update the MEC and literature DB within the upcoming years, we kindly suggest to develop a manual how to enter data into the DB and which data in general should be entered. The MEC DB currently consists of 11 different statistical parameters for MECs, which further increases the already high fragmentation of the data. Therefore, it should be critically evaluated, which parameters are relevant or not. As mentioned in Section 4.1 a revision of the analytical attributes within the DB and a clear definition of “positive detection” and “below detection” is highly recommended. One aim of the next project may be the development of a guideline for a standardized data input into the DB.

List of references

Monographs:

Andersson, J., Woldegiorgis, A., Remberger, M., Kaj, L., Ekheden, Y., Dusan, B., Svenson, A., Brorström-Lundén, E. Dye, C., Schlabach, M. (2006). Results from the Swedish National Screening Programme 2005. Stockholm, Sweden. 100 pp.

aus der Beek, T. aus, Weber, F.-A., Bergmann, A., Grüttner, G., Carius, A. (2016): Pharmaceuticals in the environment: Global occurrence and potential cooperative action under the Strategic Approach to International Chemicals Management (SAICM). UBA Texte 67, Umweltbundesamt Dessau, Deutschland https://www.umweltbundesamt.de/sites/default/files/medien/1968/publikationen/iww_abschlussbericht_saicm_arzneimittel_final.pdf

Bayerisches Landesamt für Umwelt (LfU) (2009). Arzneimittelwirkstoffe und ausgewählte Metaboliten. Untersuchungen in bayerischen Gewässern 2004 - 2008. Augsburg, Germany. 63 pp.

Bergmann, A., Fohrmann, R., Weber, F.-A. (2011). Zusammenstellung von Monitoringdaten zu Umweltkonzentrationen von Arzneimitteln. UBA Texte 66, Umweltbundesamt Dessau, Deutschland, p.14 https://www.umweltbundesamt.de/sites/default/files/medien/461/publikationen/4188.pdf

Fick, J., Lindberg, R. H., Kaj, L., Brorström-Lundén, E. (2011). Results from the Swedish National Screening Programme 2010. Stockholm, Sweden. 56 pp.

Ivashechkin, P. (2005). Literaturauswertung zum Vorkommen gefährlicher Stoffe im Abwasser und in Gewässern. Aachen, Germany. RWTH Aachen. 172 pp.

Machado, K. S. (2010). Determinacao de hormonios sexuais femininos na bacia do alto iguacu, regiao metropolitana de Curitiba-PR. Universidade Federal do Paraná. Programa de Pós Graduação em Engenharia de Recursos Hídricos e Ambiental. Master-Thesis. 116 pp.

Pinnekamp, J., Beier, S., Cramer, C., Schröder, H., Mauer, C., Selke, D. (2009). Eliminierung von Spurenstoffen aus Krankenhausabwässern mit Membrantechnik und weitergehenden Behandlungsverfahren – Pilotprojekt Kreiskrankenhaus Waldbröl. Aachen, Germany. RWTH Aachen. 232 pp.

Robakowski, H. (2000). Arzneimittelrückstände und endokrin wirkende Stoffe in der aquatischen Umwelt. Karlsruhe, Germany. 104 pp.

Sadezky, A., Löffler, D., Ternes, T. (2008). KNAPPE (Knowlegde and Need Assessment on Pharmaceutical Products in Environmental Waters) - Deliverable number: D1.2: "Proposal of an environmental indicator and classification system of pharmaceutical product residues for environmental management". 92 pp.

Weiss, K. (2008). Austrag von Tierarzneimitteln aus Wirtschaftsdünger in Sickerwasser, Grundwasser und oberirdische Gewässer. Augsburg. Bayerisches Landesamt für Umwelt. 56 pp.

Bookchapter:

Kümmerer, K., (2004): Pharmaceuticals in the Environment — Scope of the Book and Introduction, in: Kümmerer, K. (Ed.), Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks. Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 3–11. https://doi.org/10.1007/978-3-662-09259-0_1

Articles taken from journals:

Albero, B., Sanchez-Brunete, C., Miguel, E., Aznar, R., Tadeo, J.L., (2014): Determination of selected pharmaceutical compounds in biosolids by supported liquid extraction and gas chromatography-tandem mass spectrometry. Journal of Chromatography A 1336, 52–58. https://doi.org/10.1016/j.chroma.2014.02.020

Al-Rajab, A.J., Sabourin, L., Lapen, D.R., Topp, E., (2010): The non-steroidal anti-inflammatory drug diclofenac is readily biodegradable in agricultural soils. Science of the Total Environment 409, 78–82. https://doi.org/10.1016/j.scitotenv.2010.09.020

Aris, A.Z., Shamsuddin, A.S., Praveena, S.M., (2014): Occurrence of 17α-ethynylestradiol (EE2) in the environment and effect on exposed biota: a review. Environment International 69, 104–119. https://doi.org/10.1016/j.envint.2014.04.011

aus der Beek, T. aus, Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., (2016): Pharmaceuticals in the environment—Global occurrences and perspectives. Environmental Toxicology and Chemistry 35, 823–835. https://doi.org/10.1002/etc.3339

Aydin, E., Talinli, I., (2013): Analysis, occurrence and fate of commonly used pharmaceuticals and hormones in the Buyukcekmece Watershed, Turkey. Chemosphere 90, 2004–2012. https://doi.org/10.1016/j.chemosphere.2012.10.074

Bernot, M.J., Becker, J.C., Doll, J., Lauer, T.E., (2016): A national reconnaissance of trace organic compounds (TOCs) in United States lotic ecosystems. Science of the Total Environment 572, 422–433. https://doi.org/10.1016/j.scitotenv.2016.08.060

Boxall, A.B.A., Fogg, L.A., Blackwell, P.A., Kay, P., Pemberton, E.J., Croxford, A., (2004): Veterinary medicines in the environment. Reviews of Environmental Contamination and Toxicology 180, 1–91.

Brausch, J.M., Connors, K.A., Brooks, B.W., Rand, G.M., (2012): Human Pharmaceuticals in the Aquatic Environment: A Review of Recent Toxicological Studies and Considerations for Toxicity Testing, in: Whitacre, DM (Ed.), Reviews of Environmental Contamination and Toxicology 218, 1–99. https://doi.org/10.1007/978-1-4614-3137-4_1

Butkovskyi, A., Hernandez Leal, L., Rijnaarts, H.H.M., Zeeman, G., (2015): Fate of pharmaceuticals in full-scale source separated sanitation system. Water Research 85, 384–392. https://doi.org/10.1016/j.watres.2015.08.045

Camacho-Muñoz, D., Martín, J., Santos, J.L., Alonso, E., Aparicio, I., Torre, T.D. la, Rodriguez, C., Malfeito, J.J., (2012): Effectiveness of three configurations of membrane bioreactors on the removal of priority and emergent organic compounds from wastewater: comparison with conventional wastewater treatments. Journal of Environmental Monitoring 14, 1428–1436. https://doi.org/10.1039/C2EM00007E

Carvalho, I.T., Santos, L., (2016): Antibiotics in the aquatic environments: A review of the European scenario. Environment International 94, 736–757. https://doi.org/10.1016/j.envint.2016.06.025

Clouzot, L., Marrot, B., Doumenq, P., Roche, N., (2008): 17α-Ethinylestradiol: An endocrine disrupter of great concern. Analytical methods and removal processes applied to water purification. A review. Environmental Progress 27, 383–396. https://doi.org/10.1002/ep.10291

Darwano, H., Duy, S.V., Sauve, S., (2014): A New Protocol for the Analysis of Pharmaceuticals, Pesticides, and Hormones in Sediments and Suspended Particulate Matter From Rivers and Municipal Wastewaters. Archives of Environmental Contamination and Toxicology 66, 582–593. https://doi.org/10.1007/s00244-014-0007-9

Dolar, D., Ignjatić Zokić, T., Ašperger, D., Košutić, K., Mutavdžić Pavlović, D., (2012): RO/NF membrane treatment of veterinary pharmaceutical wastewater: comparison of results obtained on a laboratory and a pilot scale. Environmental Science and Pollution Research International 19, 1033–1042. https://doi.org/10.1007/s11356-012-0782-7

Fatta-Kassinos, D., Hapeshi, E., Achilleos, A., Meric, S., Gros, M., Petrovic, M., Barcelo, D., (2011): Existence of Pharmaceutical Compounds in Tertiary Treated Urban Wastewater that is Utilized for Reuse Applications. Water Resource Management 25, 1183–1193. https://doi.org/10.1007/s11269-010-9646-4

Feitosa-Felizzola, J., Chiron, S., (2009): Occurrence and distribution of selected antibiotics in a small Mediterranean stream (Arc River, Southern France). Journal of Hydrology (Amsterdam) 364, 50–57.

Feitosa-Felizzola, J., Temime, B., Chiron, S., (2007): Evaluating on-line solid-phase extraction coupled to liquid chromatography–ion trap mass spectrometry for reliable quantification and confirmation of several classes of antibiotics in urban wastewaters. Journal of Chromatography A 1164, 95–104. https://doi.org/10.1016/j.chroma.2007.06.071

Ferrari, B., Paxéus, N., Giudice, R.L., Pollio, A., Garric, J., (2003): Ecotoxicological impact of pharmaceuticals found in treated wastewaters: Study of carbamazepine, clofibric acid, and diclofenac. Ecotoxicology and Environmental Safety 55, 359–370. https://doi.org/10.1016/S0147-6513(02)00082-9

Ferreira da Silva, B., Jelic, A., Lopez-Serna, R., Mozeto, A.A., Petrovic, M., Barcelo, D., (2011): Occurrence and distribution of pharmaceuticals in surface water, suspended solids and sediments of the Ebro river basin, Spain. Chemosphere 85, 1331–1339. https://doi.org/10.1016/j.chemosphere.2011.07.051

Gadd, J.B., Tremblay, L.A., Northcott, G.L., (2010): Steroid estrogens, conjugated estrogens and estrogenic activity in farm dairy shed effluents. Environmental Pollution 158, 730–736. https://doi.org/10.1016/j.envpol.2009.10.015

Ginebreda, A., Muñoz, I., de Alda, M.L., Brix, R., López-Doval, J., Barceló, D., (2010): Environmental risk assessment of pharmaceuticals in rivers: Relationships between hazard indexes and aquatic macroinvertebrate diversity indexes in the Llobregat River (NE Spain). Environment International 36, 153–162. https://doi.org/10.1016/j.envint.2009.10.003

Hannappel, S., Köpp, C., Rejman-Rasinska, (2017): Regionaler Themenbericht Ermittlung der Ursachen des Eintrages von Tierarzneimitteln in das oberflächennahe Grundwasser Datenauswertung 2012 bis 2016 (Themenbericht des Landes Niedersachsen No. Band 29), Grundwasser. Niedersächsischer Landesbetrieb für Wasserwirtschaft, Küsten- und Naturschutz (NLWKN), 49661 Cloppenburg.

Heberer, T., (2002): Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicology Letters 131, 5–17. https://doi.org/10.1016/S0378-4274(02)00041-3

Hijosa-Valsero, M., Matamoros, V., Sidrach-Cardona, R., Martín-Villacorta, J., Bécares, E., Bayona, J.M., (2010): Comprehensive assessment of the design configuration of constructed wetlands for the removal of pharmaceuticals and personal care products from urban wastewaters. Water Research 44, 3669–3678. https://doi.org/10.1016/j.watres.2010.04.022

Hirsch, R., Ternes, T., Haberer, K., Kratz, K.-L., (1999):. Occurrence of antibiotics in the aquatic environment. Science of the Total Environment 225, 109–118. https://doi.org/10.1016/S0048-9697(98)00337-4

Hruska, K., Franek, M., (2012): Sulfonamides in the environment: a review and a case report. Veterinarni Medicina 57, 1–35.

Hug, C., Zhang, X., Guan, M., Krauss, M., Bloch, R., Schulze, T., Reinecke, T., Hollert, H., Brack, W., (2015): Microbial reporter gene assay as a diagnostic and early warning tool for the detection and characterization of toxic pollution in surface waters. Environmental Toxicology and Chemistry 34, 2523–2532. https://doi.org/10.1002/etc.3083

Jones-Lepp, T.L., Sanchez, C., Alvarez, D.A., Wilson, D.C., Taniguchi-Fu, R.-L., (2012): Point sources of emerging contaminants along the Colorado River Basin: Source water for the arid Southwestern United States. Science of the Total Environment 430, 237–245. https://doi.org/10.1016/j.scitotenv.2012.04.053

Jux, U., Baginski, R.M., Arnold, H.G., Krönke, M., Seng, P.N., (2002): Detection of pharmaceutical contaminations of river, pond, and tap water from Cologne (Germany) and surroundings. International Journal of Hygiene and Environmental Health 205, 393–398. https://doi.org/10.1078/1438-4639-00166

Karnjanapiboonwong, A., Suski, J.G., Shah, A.A., Cai, Q., Morse, A.N., Anderson, T.A., (2011): Occurrence of PPCPs at a Wastewater Treatment Plant and in Soil and Groundwater at a Land Application Site. Water Air Soil Pollut 216, 257–273. https://doi.org/10.1007/s11270-010-0532-8

Kasprzyk-Hordern, B., Dabrowska, A., Vieno, N., Kronberg, L., Nawrocki, J., (2008): Occurrence of acidic pharmaceuticals in the Warta River in Poland. Chemia Analityczna 53, 289–303.

Kidd, K.A., Blanchfield, P.J., Mills, K.H., Palace, V.P., Evans, R.E., Lazorchak, J.M., Flick, R.W., (2007): Collapse of a fish population after exposure to a synthetic estrogen. PNAS 104, 8897–8901. https://doi.org/10.1073/pnas.0609568104

Kim, M.-K., Zoh, K.-D., (2016): Occurrence and removals of micropollutants in water environment. Environmental Engineering Research 21, 319–332. https://doi.org/2016.21.4.319

Kimosop, S.J., Getenga, Z.M., Orata, F., Okello, V.A., Cheruiyot, J.K., (2016): Residue levels and discharge loads of antibiotics in wastewater treatment plants (WWTPs), hospital lagoons, and rivers within Lake Victoria Basin, Kenya. . Environmental Monitoring and Assessment 188, 532. https://doi.org/10.1007/s10661-016-5534-6

Kolpin, D.W., Furlong, E.T., Meyer, M.T., Thurman, E.M., Zaugg, S.D., Barber, L.B., Buxton, H.T., (2002): Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999−2000: A National Reconnaissance. Environmental Science and Technology 36, 1202–1211. https://doi.org/10.1021/es011055j

Kot-Wasik, A., Jakimska, A., Śliwka-Kaszyńska, M., (2016): Occurrence and seasonal variations of 25 pharmaceutical residues in wastewater and drinking water treatment plants. Environmental Monitoring and Assessment 188, 661. https://doi.org/10.1007/s10661-016-5637-0

Kristiansson, E., Fick, J., Janzon, A., Grabic, R., Rutgersson, C., Weijdegård, B., Söderström, H., Larsson, D.G.J., (2011): Pyrosequencing of Antibiotic-Contaminated River Sediments Reveals High Levels of Resistance and Gene Transfer Elements. PLOS ONE 6, e17038. https://doi.org/10.1371/journal.pone.0017038

Kümmerer, K., (2009a): Antibiotics in the aquatic environment – A review – Part I. Chemosphere 75, 417–434. https://doi.org/10.1016/j.chemosphere.2008.11.086

Kümmerer, K., (2009b): Antibiotics in the aquatic environment – A review – Part II. Chemosphere 75, 435–441. https://doi.org/10.1016/j.chemosphere.2008.12.006

Kümmerer, K., (2009c): The presence of pharmaceuticals in the environment due to human use – present knowledge and future challenges. Journal of Environmental Management 90, 2354–2366. https://doi.org/10.1016/j.jenvman.2009.01.023

Kunz, P.Y., Kienle, C., Carere, M., Homazava, N., Kase, R., (2015): In vitro bioassays to screen for endocrine active pharmaceuticals in surface and waste waters. Journal of Pharmaceutical and Biomedical Analysis, SI: Analytical approaches 106, 107–115. https://doi.org/10.1016/j.jpba.2014.11.018

Küster, A., Adler, N., (2014): Pharmaceuticals in the environment: scientific evidence of risks and its regulation. Philosophical Transactions of the Royal Society London B Biological Science 369. https://doi.org/10.1098/rstb.2013.0587

Larsson, D.G.J., de Pedro, C., Paxeus, N., (2007): Effluent from drug manufactures contains extremely high levels of pharmaceuticals. Journal of Hazardous Materials 148, 751–755. https://doi.org/10.1016/j.jhazmat.2007.07.008

Layton, A.C., Gregory, B.W., Seward, J.R., Schultz, T.W., Sayler, G.S., (2000): Mineralization of Steroidal Hormones by Biosolids in Wastewater Treatment Systems in Tennessee U.S.A. Environmental Science and Technology 34, 3925–3931. https://doi.org/10.1021/es9914487

Li, W., Shi, Y., Gao, L., Liu, J., Cai, Y., (2012): Occurrence of antibiotics in water, sediments, aquatic plants, and animals from Baiyangdian Lake in North China. Chemosphere 89, 1307–1315. https://doi.org/10.1016/j.chemosphere.2012.05.079

Li, Z., Xiang, X., Li, M., Ma, Y., Wang, J., Liu, X., (2015): Occurrence and risk assessment of pharmaceuticals and personal care products and endocrine disrupting chemicals in reclaimed water and receiving groundwater in China. Ecotoxicology and Environmental Safety 119, 74–80. https://doi.org/10.1016/j.ecoenv.2015.04.031

Lonappan, L., Brar, S.K., Das, R.K., Verma, M., Surampalli, R.Y., (2016): Diclofenac and its transformation products: Environmental occurrence and toxicity - A review. Environment International 96, 127–138. https://doi.org/10.1016/j.envint.2016.09.014

Loos, R., Marinov, D., Sanseverino, I., Napierska, D., Lettieri, T., (2018): Review of the 1st Watch List under the Water Framework Directive and recommendations for the 2nd Watch List - EU Science Hub - European Commission (No. 10.2760/614367), ISBN 978-92-79-81839-4, doi:10.2760/614367

Luo, Y., Xu, L., Rysz, M., Wang, Y., Zhang, H., Alvarez, P.J.J., (2011): Occurrence and Transport of Tetracycline, Sulfonamide, Quinolone, and Macrolide Antibiotics in the Haihe River Basin, China. Environmental Science and Technology 45, 1827–1833. https://doi.org/10.1021/es104009s

Martínez-Carballo, E., González-Barreiro, C., Scharf, S., Gans, O., (2007): Environmental monitoring study of selected veterinary antibiotics in animal manure and soils in Austria. Environmental Pollution 148, 570–579. https://doi.org/10.1016/j.envpol.2006.11.035

Matongo, S., Birungi, G., Moodley, B., Ndungu, P., (2015): Occurrence of selected pharmaceuticals in water and sediment of Umgeni River, KwaZulu-Natal, South Africa. Environmental Science and Pollution Research 22, 10298–10308. https://doi.org/10.1007/s11356-015-4217-0

McArdell, C.S., Molnar, E., Suter, M.J.-F., Giger, W., (2003): Occurrence and Fate of Macrolide Antibiotics in Wastewater Treatment Plants and in the Glatt Valley Watershed, Switzerland. Environmental Science and Technology 37, 5479–5486. https://doi.org/10.1021/es034368i

Michael, I., Rizzo, L., McArdell, C.S., Manaia, C.M., Merlin, C., Schwartz, T., Dagot, C., Fatta-Kassinos, D., (2013): Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: A review. Water Research 47, 957–995. https://doi.org/10.1016/j.watres.2012.11.027

Michalova, E., Vyzkumny U.V.L., Novotna, P. (2013). Tetracyclines in veterinary medicine and bacterial resistance to them. A review. Veterinarni Medicina - UZPI (Czech Republic).

Moreno-Gonzalez, R., Rodriguez-Mozaz, S., Gros, M., Perez-Canovas, E., Barcelo, D., Leon, V.M., (2014): Input of pharmaceuticals through coastal surface watercourses into a Mediterranean lagoon (Mar Menor, SE Spain): Sources and seasonal variations. Science of the Total Environment 490, 59–72. https://doi.org/10.1016/j.scitotenv.2014.04.097

Oaks, J.L., Gilbert, M., Virani, M.Z., Watson, R.T., Meteyer, C.U., Rideout, B.A., Shivaprasad, H.L., Ahmed, S., Iqbal Chaudhry, M.J., Arshad, M., Mahmood, S., Ali, A., Ahmed Khan, A., (2004): Diclofenac residues as the cause of vulture population decline in Pakistan. Nature 427, 630–633. https://doi.org/10.1038/nature02317

Rossmann, J., Schubert, S., Gurke, R., Oertel, R., Kirch, W., (2014): Simultaneous determination of most prescribed antibiotics in multiple urban wastewater by SPE-LC–MS/MS. Journal of Chromatography B 969, 162–170. https://doi.org/10.1016/j.jchromb.2014.08.008

Ruhí, A., Acuña, V., Barceló, D., Huerta, B., Mor, J.-R., Rodríguez-Mozaz, S., Sabater, S., (2016): Bioaccumulation and trophic magnification of pharmaceuticals and endocrine disruptors in a Mediterranean river food web. Science of The Total Environment, 5th Special Issue SCARCE: River Conservation under Multiple stressors: Integration of ecological status, pollution and hydrological variability 540, 250–259. https://doi.org/10.1016/j.scitotenv.2015.06.009

Santos, L.H.M.L.M., Gros, M., Rodriguez-Mozaz, S., Delerue-Matos, C., Pena, A., Barceló, D., Montenegro, M.C.B.S.M., (2013): Contribution of hospital effluents to the load of pharmaceuticals in urban wastewaters: Identification of ecologically relevant pharmaceuticals. Science of the Total Environment 461–462, 302–316. https://doi.org/10.1016/j.scitotenv.2013.04.077

Sarmah, A.K., Meyer, M.T., Boxall, A.B.A., (2006): A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. Chemosphere 65, 725–759. https://doi.org/10.1016/j.chemosphere.2006.03.026

Senta, I., Terzić, S., Ahel, M., (2013): Occurrence and fate of dissolved and particulate antimicrobials in municipal wastewater treatment. Water Research 47 (2), 463-956. https://doi.org/10.1016/j.watres.2017.12.029

Smital, T., Terzic, S., Loncar, J., Senta, I., Zaja, R., Popovic, M., Mikac, I., Tollefsen, K.-E., Thomas, K.V., Ahel, M., (2013): Prioritisation of organic contaminants in a river basin using chemical analyses and bioassays. Environmental Science and Pollution Research 20, 1384–1395. https://doi.org/10.1007/s11356-012-1059-x

Ternes, T.A., (2001): Analytical methods for the determination of pharmaceuticals in aqueous environmental samples. Trends in Analytical Chemistry 20, 419–434. https://doi.org/10.1016/S0165-9936(01)00078-4

Ternes, T.A., (1998): Occurrence of drugs in German sewage treatment plants and rivers1Dedicated to Professor Dr. Klaus Haberer on the occasion of his 70th birthday.1. Water Research 32, 3245–3260. https://doi.org/10.1016/S0043-1354(98)00099-2

Tiedeken, E.J., Tahar, A., McHugh, B., Rowan, N.J., (2017): Monitoring, sources, receptors, and control measures for three European Union watch list substances of emerging concern in receiving waters – A 20year systematic review. Science of the Total Environment 574, 1140–1163. https://doi.org/10.1016/j.scitotenv.2016.09.084

Triebskorn, R., Hetzenauer, H., (2012): Micropollutants in three tributaries of Lake Constance, Argen, Schussen and Seefelder Aach: a literature review. Environmental Sciences Europe 24, 8. https://doi.org/10.1186/2190-4715-24-8

Vallejo, A., Prieto, A., Moeder, M., Usobiaga, A., Zuloaga, O., Etxebarria, N., Paschke, A., (2013): Calibration and field test of the Polar Organic Chemical Integrative Samplers for the determination of 15 endocrine disrupting compounds in wastewater and river water with special focus on performance reference compounds (PRC). Water Research 47, 2851–2862. https://doi.org/10.1016/j.watres.2013.02.049

Verlicchi, P., Al Aukidy, M., Zambello, E., (2012): Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment-A review. Sceince of the total Environment 429, 123–155. https://doi.org/10.1016/j.scitotenv.2012.04.028

Vieno, N., Sillanpää, M., (2014): Fate of diclofenac in municipal wastewater treatment plant — A review. Environment International 69, 28–39. https://doi.org/10.1016/j.envint.2014.03.021

Wise, A., O'Brien, K., Woodruff, T., (2011): Are Oral Contraceptives a Significant Contributor to the Estrogenicity of Drinking Water? Environmental Sciences and Technology 45, 51–60. https://doi.org/10.1021/es1014482

Xu, J., Wu, L., Chang, A.C., (2009): Degradation and adsorption of selected pharmaceuticals and personal care products (PPCPs) in agricultural soils. Chemosphere 77, 1299–1305. https://doi.org/10.1016/j.chemosphere.2009.09.063

Yuan, X., Qiang, Z., Ben, W., Zhu, B., Qu, J., (2015): Distribution, mass load and environmental impact of multiple-class pharmaceuticals in conventional and upgraded municipal wastewater treatment plants in East China. Environmental Science: Processes & Impacts 17, 596–605. https://doi.org/10.1039/C4EM00596A

Zhang, R.J., Zhang, G., Zheng, Q., Tang, J.H., Chen, Y.J., Xu, W.H., Zou, Y.D., Chen, X.X., (2012): Occurrence and risks of antibiotics in the Laizhou Bay, China: Impacts of river discharge. Ecotoxicology and Environmental Safety 80, 208–215. https://doi.org/10.1016/j.ecoenv.2012.03.002

Zhang, X., Oakes, K.D., Luong, D., Metcalfe, C.D., Pawliszyn, J., Servos, M.R., (2011): Kinetically-Calibrated Solid-Phase Microextraction Using Label-Free Standards and Its Application for Pharmaceutical Analysis. Analytical Chemistry 83, 2371–2377. https://doi.org/10.1021/ac200032k

Zhang, Y., Geißen, S.-U., Gal, C., (2008): Carbamazepine and diclofenac: Removal in wastewater treatment plants and occurrence in water bodies. Chemosphere 73, 1151–1161. https://doi.org/10.1016/j.chemosphere.2008.07.086

Zhao, L., Dong, Y.H., Wang, H., (2010): Residues of veterinary antibiotics in manures from feedlot livestock in eight provinces of China. Science of the Total Environment 408, 1069–1075. https://doi.org/10.1016/j.scitotenv.2009.11.014

Zhao, W., Guo, Y., Lu, S., Yan, P., Sui, Q., (2016): Recent advances in pharmaceuticals and personal care products in the surface water and sediments in China. Frontiers of Environmental Sciences Eng. 10, 2. https://doi.org/10.1007/s11783-016-0868-4

Zuo, Y., Zhang, K., Zhou, S., (2013): Determination of estrogenic steroids and microbial and photochemical degradation of 17α-ethinylestradiol (EE2) in lake surface water, a case study. Environmental Science: Processes & Impacts 15, 1529–1535. https://doi.org/10.1039/C3EM00239J

Conference contributions:

Hirsch, R. (1998): Antibiotika in der Umwelt. Arzneimittel in Gewässern - Risiko für Mensch, Tier und Umwelt? Fachtagung. Wiesbaden, Germany. Hessisches Landesamt für Umwelt und Geologie.

Internet addresses:

NORMAN (2012). EMPODAT Database of the Network of reference laboratories for monitoring of emerging environmental pollutants (NORMAN). http://www.normandata.eu/empodat_index.php accessed between November 2012 and June 2013.

Manuals:

Bivand R. and Lewin-Koh N. (2017). maptools: Tools for Reading and Handling Spatial Objects. R package version 0.9-2. https://CRAN.R-project.org/package=maptools

Bivand R., Keitt T. and Rowlingson B. (2018). rgdal: Bindings for the 'Geospatial' Data Abstraction Library. R package version 1.2-18. https://CRAN.R-project.org/package=rgdal

Bivand R. and Rundel C. (2017). rgeos: Interface to Geometry Engine - Open Source ('GEOS'). R package version 0.3-26. https://CRAN.R-project.org/package=rgeos

Neuwirth E. (2014). RColorBrewer: ColorBrewer Palettes. R package version 1.1-2. https://CRAN.R-project.org/package=RColorBrewer

Ooms J., James D., DebRoy S., Wickham H. and Horner J. (2018). RMySQL: Database Interface and 'MySQL' Driver for R. R package version 0.10.14. https://CRAN.R-project.org/package=RMySQL

R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Ripley B. and Lapsley M. (2017). RODBC: ODBC Database Access. R package version 1.3-15. https://CRAN.R-project.org/package=RODBC

A Appendix

Figure 31: Maximum MECs for azithromycin found in solid immission media

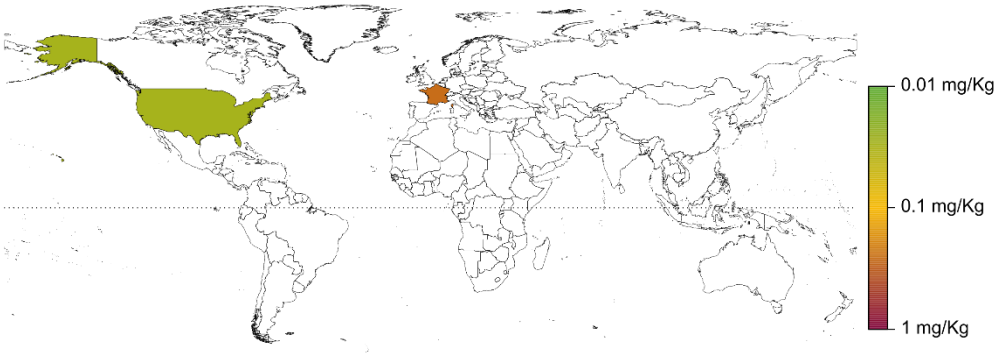


Figure 32: Maximum MECs for clarithromycin found in solid immission media

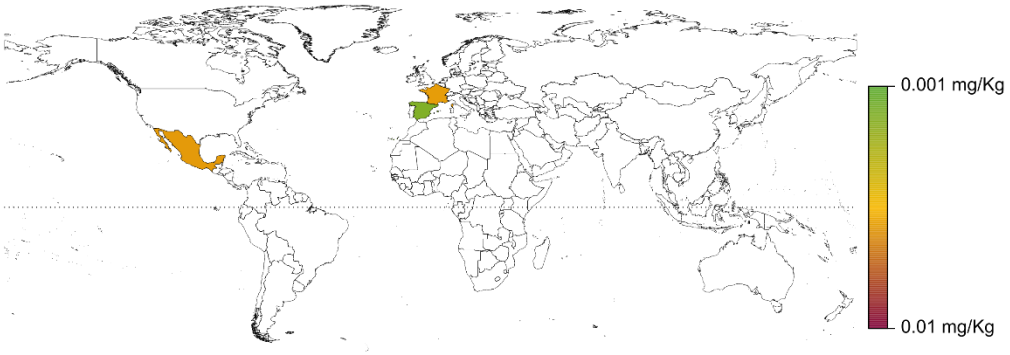


Figure 33: Number of positively detected MECs for the antibiotic group beta-lactams found in solid immission media