Umweltforschungsplan des
Bundesministeriums für Umwelt,
Naturschutz, Bau und Reaktorsicherheit

Forschungskennzahl 3712 65 408

Pharmaceuticals in the environment: Global occurrence and potential cooperative action under the Strategic Approach to International Chemicals Management (SAICM)

von

Tim aus der Beek, Frank-Andreas Weber, Axel Bergmann
IWW Rheinisch-Westfälisches Institut für Wasser
Beratungs- und Entwicklungsgesellschaft mbH, Mülheim an der Ruhr

Gregor Grüttner, Alexander Carius
adelphi consult GmbH, Berlin

IWW Rheinisch-Westfälisches Institut für Wasser
Beratungs- und Entwicklungsgesellschaft mbH
Moritzstr. 26
45476 Mülheim an der Ruhr
Germany

Im Auftrag des Umweltbundesamtes

November 2015

Berichtskennblatt

Berichtsnummer	UBA-FB 00
Titel des Berichts	Pharmaceuticals in the environment: Global occurrence and potential cooperative action under the Strategic Approach to International Chemicals Management (SAICM)
Autor(en) (Name, Vorname)	aus der Beek, Tim Weber, Frank-Andreas Bergmann, Axel Grüttner, Gregor Carius, Alexander
Durchführende Institution (Name, Anschrift)	IWW Rheinisch-Westfälisches Institut für Wasser Beratungs- und Entwicklungsgesellschaft mbH Moritzstr. 26 45476 Mülheim an der Ruhr Deutschland
Fördernde Institution	Umweltbundesamt Postfach 14 06 06813 Dessau-Roßlau
Abschlussjahr	2015
Forschungskennzahl (FKZ)	3712 65 408
Seitenzahl des Berichts	94
Zusätzliche Angaben	Folgender separater Anhang steht zum Download bereit: - - Zusammenfassung eines Workshops zum Thema „Arzneimittel in der Umwelt – globales Vorkommen, Effekte und Handlungsoptionen“ im April 2014 in Genf
Schlagwörter	Pharmazeutika, Umwelt, Handlungsoptionen, Verbrauch, globales Vorkommen, Messungen, Datenbank

Report Cover Sheet

Report No.	UBA-FB 00
Report Title	Pharmaceuticals in the environment: Global occurrence and potential cooperative action under the Strategic Approach to International Chemicals Management (SAICM)
Author(s) (Family Name, First Name)	aus der Beek, Tim Weber, Frank-Andreas Bergmann, Axel Gruettner, Gregor Carius, Alexander
Performing Organisation (Name, Address)	IWW Rheinisch-Westfälisches Institut für Wasser Beratungs- und Entwicklungsgesellschaft mbH Moritzstr. 26 45476 Mülheim an der Ruhr Germany
Funding Agency	Umweltbundesamt Postfach 14 06 06813 Dessau-Roßlau
Report Date (Year)	2015
Project No. (FKZ)	3712 65 408
No. of Pages	94
Supplementary Notes	The following supplements are available for download: - Chair's Conclusions of the workshop "Pharmaceuticals in the Environment - Global occurrence, effects, and options for action from April 2014 in Geneva
Keywords	Pharmaceuticals, Environment, Mitigation Options, Consumption, Global occurrences, Measurements, Database

Abstract

Pharmaceuticals are known to occur widely in the environment of industrialized countries. In developing countries, more monitoring results have recently become available, but a concise picture on the prevailing concentrations is still elusive. In a comprehensive literature review of 1016 original publications and 150 review articles, we compiled measured environmental concentrations of human and veterinary pharmaceutical substances reported worldwide in surface water, groundwater, tap/drinking water, manure, soil, and other environmental matrices in a systematic database. As result, 123,761 database entries have been made. Pharmaceuticals or their transformation products have been detected in the environment of 71 countries covering all five UN regions. In total, 631 different pharmaceuticals have been found above the detection limits of the analytical methods employed, revealing regional patterns. 17 substances have been detected in all five UN regions. For example, the anti-inflammatory drug diclofenac has been detected in the environment of 50 countries, in several locations at ecotoxicologically relevant concentrations. Urban wastewater seems to be the dominant emission pathway of pharmaceuticals globally, whereas emissions from industrial production, hospitals, agriculture, and aquaculture are important locally. We conclude that pharmaceuticals in the environment are a global challenge calling for multi-stakeholder and multi-sector approaches to prevent, reduce, and manage pharmaceuticals entering the environment, such as the recently adopted new emerging policy issue under the Strategic Approach to International Chemicals Management (SAICM). We provide an overview of strategies for action proposed in the literature and examine them with respect to their effectiveness in terms of mitigating the entry and occurrence of pharmaceuticals in the environment and their potential to be addressed under SAICM.

Kurzbeschreibung

Der ansteigende Verbrauch von Arzneimitteln und die Verbesserung der Messmethoden hat in den letzten Jahrzehnten hat dazu geführt, dass diese mittlerweile vermehrt in der Umwelt von Industrienationen detektiert werden. In Entwicklungs- und Schwellenländern existiert eine geringere, jedoch ansteigende Anzahl von Messwerten. Ziel der hier vorliegenden Studie war die globale Analyse des Vorkommens von Arzneimitteln in der Umwelt. Insgesamt 1.016 Publikationen und Datenquellen, basierend auf publizierten Daten, wurden im Rahmen der Studie ausgewertet. Hieraus konnten 123.761 Messwerte von Arzneimitteln in unterschiedlichen Umweltkompartimenten in eine Datenbank übertragen werden. Im Ergebnis wurden für 71 Länder Messungen mit Arzneimittelpositivbefunden in der Umwelt nachgewiesen. Insgesamt wurde deutlich, dass in der Literatur insgesamt Umweltproben auf 713 verschiedene Wirkstoffe untersucht wurden, wovon 631 in Konzentrationen über dem Detektionslimit nachgewiesen wurden. 16 Wirkstoffe wurden in allen Regionen der Welt im Oberflächen-, Grund- und Trinkwasser nachgewiesen. Am häufigsten, in insgesamt 50 Ländern, wurde der Schmerzmittel-Wirkstoff Diclofenac in der Umwelt aufgefunden, oftmals in ökotoxikologisch relevanten Konzentrationen. Bei den am häufigsten genannten Eintragsquellen der Arzneimittel handelt es sich um urbanes Abwasser, gefolgt von Krankenhäusern, Landwirtschaft, Aquakultur und Produktionsstätten von Arzneimitteln. Diese Studie hat gezeigt, dass Arzneimittel in der Umwelt ein globales Problem darstellen, d.h. dass sie nicht nur in Industrieländern, sondern auch in Entwicklungs- und Schwellenländern in der Umwelt zu finden sind. Zahlreiche Akteure aus verschiedenen Bereichen müssen involviert werden um den Eintrag in die Umwelt zu vermindern. Einen vielversprechenden Ansatz stellt hier das internationale SAICM-Programm dar (Strategischer Ansatz zum

internationalen Chemikalienmanagement). In der hier vorliegenden Studie wird eine Übersicht über in der Literatur diskutierte Verminderungsstrategien gegeben; diese wird hinsichtlich von Möglichkeiten zur globalen Verminderung von Arzneimitteleinträgen in die Umwelt im Kontext von SAICM diskutiert.

Table of Content

List of Figures

List of Tables

Abbreviations

BAT	Best Available Technique
BEP	Best Environmental Practice
BMP	Best Manufacturing Practice
EDC	Endocrine Disrupting Compound
CAS	Chemical Abstracts Service
DDD	Defined Daily Dose
EE2	17-alpha Ethinylestradiol
EEG	Eastern Europe Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPPP	Environmentally Persistent Pharmaceutical Pollutants
ERA	Environmental Risk Assessment
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (U.S.A.)
GPA	Global Plan of Action
GRULAC	Group of Latin American and Caribbean States
GMP	Good Manufacturing Practice
ICCM	International Conference on Chemicals Management
ICH	International Conference on Harmonization
iIATT-SPHS	Informal UN Interagency Task Team on Green Procurement in the Health Sector
ILO	International Labour Organization of the United Nations
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
ISDE	International Society of Doctors for the Environment
ISO	International Organization for Standardization
IWW	IWW Water Centre (Germany)
LIF	Läkemedelsindustriföreningen (Swedish research-based pharmaceutical industry)
MEC	Measured Environmental Concentration
NGO	Non-Governmental Organization
NORMAN	Network of Reference Laboratories, Research Centres and Related Organisations for Monitoring of Emerging Environmental Substances
OECD	Organization for Economic Co-operation and Development

OEWG	Open-ended Working Group
OPS	Overarching Policy Strategy (SAICM)
PAR	Public Assessment Report
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentration
SAICM	Strategic Approach to International Chemicals Management
SPM	Suspended Particulate Matter
UBA	Umweltbundesamt (German Federal Environment Agency)
UN	United Nations
UNDP	United Nations Development Programme
UNEP	United Nations Environment Programme
UNIDO	United Nations Industrial Development Organization
UNITAR	United Nations Institute for Training and Research
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WEOG	Western Europe and Other Industrialized Countries Group
WHO	World Health Organization
WWTP	Wastewater Treatment Plant

English Summary

In recent decades, growing population numbers, changing population structures, better supply and marketing have led to an increase in the use of pharmaceuticals (e.g. Van Boeckel et al. 2014). At the same time, new analytic methods have been developed – and older methods refined – such that pharmaceuticals can be detected in environmental samples from ranges of µg/l to pg/l. Since the late 1990s, there has been a clear increase in the number of scientific publications on the occurrence of pharmaceuticals in the environment. The goal of the present study is the worldwide analysis – on the basis of published data – of the occurrence of pharmaceuticals in the environment.

The backdrop to this global study on the occurrence of pharmaceuticals in the environment is the United Nations' Strategic Approach to International Chemicals Management (SAICM). SAICM was developed with the needs of various interest groups in mind and assists in efforts to meet the goals of the Earth Summit 2002 in Johannesburg. In this regard, it should be ensured that by 2020, chemicals are produced and used in such a way that their impact on the environment and human health is reduced significantly.

In the past, it was found that no comprehensive data set on the worldwide occurrence of pharmaceuticals in the environment was available and that it would not be possible to conduct any potential analyses on the impacts on environmental organisms. It is thus the goal of this study to create a body of data and knowledge which attests to the importance and relevance of this issue on a global level. Findings from the study are intended to promote the topic of pharmaceuticals in the environment as a new emerging policy issue in SAICM, so that the topic can also be coordinated on a global scale.

Creating the database

Literature on this topic currently comprises around 150 reviews. However, most of these focus on specific countries such as China (Bu et al. 2013), or on special bodies of water such as the Llobregat river in Spain (Gonzales et al. 2012), groups of pharmaceuticals such as psychotropic drugs (Calisto & Esteves 2009), on individual active ingredients such as the antibiotic tetracycline (Daghrir & Drogui 2013), on environmental compartments such as groundwater (Lapwort et al. 2012), on sampling methods (Petrovic et al. 2005) or on local emissions sources such as hospitals (Orias & Perrofin 2013). Only a few summaries of scientific findings on pharmaceuticals in the environment (e.g. Hughes et al. 2012) operate on a continental or global scale. Here, data from national measurement programmes, university research reports and non-English language publications were not included, meaning that data from developing countries and emerging economies was often not taken into consideration. Alongside the sources of literature and data mentioned above, existing databases in Germany (Bergmann et al. 2011) and from European projects and networks such as NORMAN (www.norman.network.net), KNAPPE (Sadezky et al. 2008), FATE-SEES (JRC 2012) and POSEIDON (Ternes et al. 2004) were also used for data research purposes.

In addition to the survey of literature, 41 stakeholders from the fields of science and the environment – inclusive of scientists, NGOs and ministries in developing economies – from 18 countries were contacted in order to obtain data. A total of 1,016 publications and data sources with original data could thus be brought together in an Endnote© database. Measurements of pharmaceuticals occurring in the environment were transferred into a unified SQL database format, in which a large amount of additional information was also incorporated, including detection limits, location at which the measurement was taken, environmental compartments and a bibliography. An estimate as to the plausibility of the measured values was also made. A total of 123,761 entries were included in the

database. A database entry here does not necessarily represent a single value: many literature and data sources summarise values in statistical bulks such as averages, medians or percentages. Around 47% of the database entries relate to measured values for surface waters, rivers representing by far the largest part in this respect. Around 8% of the data relates to groundwater and drinking water. A further 40% were gained from measurements within the wastewater and sewage sector. 2% of the data relates to sediments and the remainder to soils, manure and suspended particles.

Global occurrence of pharmaceuticals

In total, measurements attesting to the presence of pharmaceuticals in the environment could be compiled for 71 countries. Although the majority of measurements relate to industrialised countries, recent years have seen a growing trend towards values from developing and emerging economies. It can be shown that in Asia in particular, a number of different pharmaceuticals have been measured in water, whilst the number of values for Africa is markedly lower. In general, it can be noted that in all continents, the amount of evidence attesting to the presence of pharmaceuticals in the environment correlates to the number of measurements taken. This means that in countries with a low number of positive finding such as Russia, there is also limited data available. Correspondingly, it is in the industrialised countries where most of the measurement data was compiled, such as in Germany, in which the most measurements attesting to the presence of pharmaceuticals in the environment could be found.

In total, environmental analyses were performed on 713 different active substances, including 142 transformations products. From this, 631 – inclusive of 127 transformations products – were detected in concentrations over the detections limit. 16 active substances were found in surface, ground and drinking waters in all regions of the world. The painkiller diclofenac was the pharmaceutical most commonly found in the environment, being present in around 50 countries. In at least 45 countries, carbamazepine, ibuprofen, sulfamethoxazole and naproxen were found. Alongside these antiepileptics, painkillers and antibiotics, hormones and antilipemics were also detected in all UN regions.

Occurence of diclofenac

On diclofenac, the most commonly observed pharmaceutical agent in the environment, further analysis of average observed concentrations and their potential ecotoxicological impacts were conducted. To this end, national weighted averages as to the observed diclofenac concentrations were calculated based on the number of measured values. In this respect, it was only possible to use database values which related to single measurements or to averages with which the total number of samples was known. The highest average concentration – 1.55 µg/l – was observed in Pakistan. In general, every UN region had at least one country with an average concentration of at least 0.1 µg/l. In this respect, it must be taken into account that in each country, the basis of the available data was different and that the measured values are thus not directly comparable. By way of an example, the higher value of 0.164 µg/l for Germany can be seen as reliable, as this was gained from 4,137 measurements. A similarly high value of 0.117 µg/l in Malaysia was gained from just two measurements, meaning that the statistical significance of this average value remains low. To evaluate the environmental risks, the observed concentrations of diclofenac were compared with the predicted-no-effect-concentrations (PNECs). PNECs are derived from standardised laboratory experiments with organisms such as daphnia, fish or plants. The PNEC for diclofenac was determined to be 0.1 µg/l (European Commission 2013). In the comparison of the PNECs with the average national concentration in 50 countries, it can be seen that the PNEC was exceeded in 34 countries. This is clear evidence as to the likely ecotox-

icological dangers at the respective measurement locations. This underlines the importance of an urgently needed global approach to minimisation of pharmaceuticals in the environment, as for instance may be developed in the framework of SAICM. The example of diclofenac also shows that pharmaceuticals can cause effects on populations: due to the use of diclofenac as a veterinary pharmaceutical, a drastic reduction in the Indian vulture population has been observed since 1996 (Oaks et al. 2004, Green et al. 2006).

Entry paths

Alongside the global dissemination of pharmaceuticals in the environment, their various entry paths are also of interest. When it was present in the literature and data sources, this information was entered into the database. In total, entry paths could be allocated to 13% of the database entries. This low number can be explained by the large number of measurements taken in rivers and sewage plants, as it is rare that sources, which lay upstream, are known. The most commonly named entry sources relate to urban sewage. Due to the large part of the world population which is urban, and because the majority of pharmaceuticals are used in domestic context, this estimation appears to be realistic.

Hospitals were the second most important entry path named in the database. Here, a number of active substances can be found in often high concentrations, as clearly illustrated in Orias and Perrodin (2013). Hospitals are also mostly linked to municipal sewage plants and only rarely are equipped with customised sewage systems. Because municipal sewage systems were not designed for the removal of pharmaceutical micropollutants, the elimination rate is often low. Micropollutants from hospitals can thus often appear in surface waters. It must however be taken into account that active pharmaceutical agents can be clearly differentiated in terms of their behaviours in sewage systems and in the environment, as they have different sorption coefficients, transformations kinetics and half-lives.

Animal husbandry is the entry path named third most often. Pharmaceutical production sites are a further entry source capable of generating high local concentrations in the environment. In the database, multiple entries on the concentrations of active agents – antibiotics in particular – of a medium to high mg/l level in surface waters were recorded (Larsson et al. 2007, Fick et al. 2009). The highest values are recorded particularly in emerging and developing economies in which environment-related threshold values are seldom available or implemented. One further local entry path is aquaculture, which accounts for a particularly large number of database entries for Asia. Here, fish breeding in rivers is to be inspected particularly critically, as dilution, in comparison to oceans and seas, is low and ecosystems located downstream can be affected.

Measures

Uptake of the issue of pharmaceuticals in the environment as an emerging policy issue as part of the Strategic Approach to International Chemicals Management (SAICM) can also initiate cross-sector and multi-stakeholder strategies in emerging and developing economies, targeted towards voluntary minimisation and risk management in relation to pharmaceuticals in the environment. In this respect, options for further action should be set out so that the efficiency and availability of pharmaceuticals does not become an issue, especially in countries in which access to the health system is still limited. Cooperation between various stakeholders at the global and regional levels is thus necessary; this can include international organisations, national governments, pharmaceutical manufacturers, doctors, pharmacists, patients, vets, farmers, water treatment plant operators, development agencies, NGOs, health insurers, water suppliers and research institutes. Other potential op-

tions for further activity include information campaigns targeted at the general population and towards doctors, producers of pharmaceuticals and governments. It can be discussed whether it is possible to further reduce the amount of pharmaceuticals substances entering the environment; this can include packaging size, requiring prescription, official disposal sites, and development of environmentally friendly medications. These measures, which often are already being implemented at the source of entry into the environment, can also be supplemented with additional end-of-pipe technical solutions. As these solutions are expensive and require significant financing, they are currently primarily discussed for industrialised countries. In general, the technological measures which stand out in this context are those which improve elimination rates in water treatment facilities, in which case the use of ozone and (powdered) activated carbon achieves the best results (Joss et al. 2005), including in the cost-benefit analysis (Günthert & Rödel 2013). For instance, Switzerland is planning for this very reason to upgrade 100 of its 700 municipal wastewater treatment plants in the next 25 years, in order to be able to treat more than 50% of the total volume wastewater. It is predicted that the load of micropollutants will thus be cut in half, at the cost of 1.2 billion Swiss francs. In earlier studies, possible options for action were primarily researched with an eye to German (START 2008) or European relationships. The present study evaluated existing options for action in relation to their suitability to address the issue in the context of SAICM and on a global scale.

Conclusion

This study has shown that pharmaceuticals in the environment represent a global problem, as pharmaceuticals can be attested to in all continents. A total of 631 substances were found in 71 countries. The main paths of entry were identified as urban wastewater from wastewater treatment plants, agriculture, industry and hospitals. Measures for minimising the entry of pharmaceuticals into the environment include those such as information campaigns on the disposal of pharmaceuticals in addition to technical measures such as the expansion of wastewater treatment plants. The integration of the issue of pharmaceuticals in the environment as a emerging policy issues can also initiate cross-sector and multi-stakeholder strategies in emerging and developing economies.

In general, further data – especially on developing/emerging economies and Eastern Europe – is necessary if further reliable assertions on the occurrence of pharmaceuticals in the environment in this region are to be made and particularly impacted areas are to be identified.

Deutsche Zusammenfassung

Wachsende Bevölkerungszahlen, veränderte Bevölkerungsstrukturen, bessere Versorgung und Vermarktung führten in den vergangenen Jahrzehnten zu einem Anstieg des Verbrauchs von Arzneimitteln (z.B. Van Boeckel et al. 2014). Gleichzeitig wurden neue Analytikverfahren entwickelt oder bestehende verfeinert, so dass Arzneimittel in Umweltproben mittlerweile im µg/L bis pg/L Bereich detektiert werden können. Seit den späten 1990er Jahren ist ein deutlicher Anstieg von wissenschaftlichen Publikationen zum Vorkommen von Arzneimitteln in der Umwelt zu verzeichnen. Ziel der hier vorliegenden Studie ist die Analyse des weltweiten Vorkommens von Arzneimitteln in der Umwelt, basierend auf publizierten Daten.

Hintergrund dieser globalen Studie zum Vorkommen von Arzneimitteln in der Umwelt ist der Strategischen Ansatz zum Internationalen Chemikalienprogramm (SAICM) des Umweltprogramms der Vereinten Nationen (UNEP). SAICM wurde unter Berücksichtigung der Bedürfnisse unterschiedlicher Interessengruppen entwickelt und unterstützt die Erreichung der Ziele des 2002 Johannesburg Weltgipfels für nachhaltige Entwicklung. Hierbei soll sichergestellt werden, dass bis 2020 Chemikalien so produziert und verwendet werden, dass ihr Einfluss auf die Umwelt und menschliche Gesundheit signifikant reduziert wird.

In der Vergangenheit wurde festgestellt, dass zum globalen Vorkommen von Arzneimitteln in der Umwelt keine einheitliche Datengrundlage vorliegt und damit auch keine Potenzialanalyse zu Effekten und Auswirkungen auf Umweltorganismen durchgeführt werden kann. Somit ist das Ziel dieser Studie, eine globale Daten- und Wissensgrundlage zu schaffen, die die räumliche und inhaltliche Bedeutung und Relevanz des Themas belegt. Die Ergebnisse dieser Studie sollen die Aufnahme des Themas als neues politisches Entwicklungsthema in SAICM unterstützen, um das Thema „Arzneimittel in der Umwelt“ auch koordiniert global zu adressieren.

Datenbankerstellung

In der Literatur existieren bereits etwa 150 Reviews, jedoch fokussieren diese meist auf bestimmte Länder, wie beispielsweise China (Bu et al. 2013), auf spezielle Wasserkörper, wie den Llobregat Fluss in Spanien (Gonzalez et al. 2012), auf Arzneimittelgruppen, wie Psychopharmaka (Calisto & Esteves 2009), auf einzelne Wirkstoffe, wie das Antibiotikum Tetrazyklin (Daghrir & Drogui 2013), auf Umweltkompartimente, wie Grundwasser (Lapworth et al. 2012), auf Probenahmemethoden (Petrovic et al. 2005) oder auf lokale Emissionsquellen, wie Krankenhäuser (Orias & Perrodin 2013). Nur sehr wenige Zusammenfassungen wissenschaftlicher Ergebnisse zu Arzneimitteln in der Umwelt beziehen sich auf die kontinentale bis globale Skala wie z.B. Hughes et al. (2012). Hier wurde jedoch auf die Auswertung von Daten aus staatlichen Messprogrammen, universitären Forschungsberichten und nicht-englischen Veröffentlichungen verzichtet, so dass Daten aus Entwicklungs- und Schwellenländer oftmals nicht berücksichtigt wurden. Neben den oben beschriebenen Literatur- und Datenquellen wurden auch bestehende Datenbanken aus Deutschland (Bergmann et al. 2011) sowie aus europäischen Projekten und Netzwerken wie NORMAN (www.norman-network.net), KNAPPE (Sadezky et al. 2008), FATE-SEES (JRC 2012) und POSEIDON (Ternes et al. 2004) bei der Datenrecherche verwendet.

Zusätzlich zur Literaturrecherche wurden 41 Akteure aus den Bereichen Umwelt und Wissenschaft in 18 Ländern kontaktiert, z.B. Wissenschaftler, NGOs und Ministerien in Entwicklungsländern, um Daten zu beziehen. Es konnten auf diese Weise 1.016 Publikationen und Datenquellen mit Originaldaten in einer Endnote©-Datenbank zusammengetragen werden. Die Messwerte der in der Umwelt

vorkommenden Arzneimittel wurden aus allen Quellen in ein einheitliches SQL-Datenbankformat übertragen, wobei eine Vielzahl von Zusatzinformationen wie z.B. Detektionslimit, Ort der Messung, Kompartiment sowie ein Literaturverweis aufgenommen wurden. Eine Einschätzung der Plausibilität der Messwerte wurde ebenfalls vorgenommen. Insgesamt konnten 123.761 Einträge in der Datenbank vorgenommen werden. Ein Datenbankeintrag entspricht hierbei nicht unbedingt einem Einzel-Messwert, da viele Literatur- und Datenquellen Messwerte in statistischen Größen, wie z.B. einem Mittelwert, Median oder Perzentil zusammenfassen. Etwa 47% der Datenbankeinträge beziehen sich auf Messwerte in Oberflächengewässern, wobei Flüsse den weitaus größten Anteil ausmachen. Für Grund- und Trinkwasser standen knapp 8% der Gesamtdaten zur Verfügung. Weitere 40% der Daten wurden im Kläranlagenab- und –zulauf sowie im Klärschlamm gemessen. 2% der Datenbankeinträge beziehen sich auf Sedimente und die verbleibenden 3% auf Böden, Wirtschaftsdünger und Schwebstoffe.

Globales Vorkommen von Pharmazeutika

Insgesamt konnten Messungen mit Arzneimittelpositivbefunden in der Umwelt für 71 Länder nachgewiesen werden. Obwohl die Mehrheit der Messungen auf industrialisierte Länder entfällt, ist in den letzten Jahren ebenfalls ein ansteigender Trend von Messwerten in Entwicklungs- und Schwellenländern zu verzeichnen. Es zeigt sich, dass besonders in Asien viele verschiedene Arzneimittel im Wasser gemessen wurden, während die Anzahl der Messwerte in Afrika deutlich geringer ist. Generell kann vermerkt werde, dass auf allen Kontinenten die Anzahl der Positivbefunde mit der Anzahl der Messungen korreliert. Dies bedeutet, dass in den Ländern mit einer niedrigen Anzahl an Positivbefunden, z.B. Russland, auch immer wenige Messdaten vorliegen. In den industrialisierten Ländern, wo meist viele Messdaten erhoben werden, wie z.B. in Deutschland, liegen dementsprechend auch die meisten Positivbefunde vor.

Insgesamt wurden Umweltproben auf 713 verschiedene Wirkstoffe, inklusive 142 Transformationsprodukte, untersucht. Davon wurde 631, inklusive 127 Transformationsprodukte, in Konzentrationen über dem Detektionslimit nachgewiesen. 16 Wirkstoffe wurden in allen Regionen der Welt im Oberflächen-, Grund- und Trinkwasser nachgewiesen. Am häufigsten, in insgesamt 50 Ländern, wurde der Schmerzmittel-Wirkstoff Diclofenac in der Umwelt nachgewiesen. In mindestens 45 Ländern wurden die Wirkstoffe Carbamazepin, Ibuprofen, Sulfamtethoxazol und Naproxen nachgewiesen. Neben diesen Antiepileptika, Schmerzmitteln und Antibiotika wurden auch Hormone und Lipidsenker in allen UN Regionen detektiert.

Vorkommen von Diclofenac

Zu Diclofenac, dem am häufigsten in der Umwelt gemessenen pharmazeutischen Wirkstoff, wurden weitere Auswertungen zu mittleren gemessenen Konzentrationen und deren potenziell ökotoxikologischen Auswirkungen durchgeführt. Dazu wurden länderbasierte Mittelwerte der gemessenen Diclofenac-Konzentrationen berechnet und mit der Anzahl der Messwerte gewichtet. Hierbei konnten nur Werte aus der Datenbank verwendet werden, die sich auf Einzelmessungen oder Mittelwerte mit bekannter Gesamtprobenanzahl bezogen. Die höchste Durchschnittskonzentration wurde mit 1,55 µg/l für Pakistan berechnet. Generell wurde in jeder UN Region in mindestens einem Land eine Durchschnittskonzentration von mindestens 0,1 µg/l gefunden. Hierbei muss jedoch berücksichtigt werden, dass in jedem Land eine unterschiedliche Datengrundlage zur Verfügung stand und die Werte nicht direkt vergleichbar sind. So kann beispielsweise der hohe Wert von 0,164 µg/l für Deutschland als belastbar angesehen werden, da er auf 4.137 Messungen beruht. Ein ähnlicher hoher Wert von 0,117 µg/l in Malaysia bezieht sich hingegen nur auf zwei Messwerte, wodurch die statistische Aus-

sagekraft dieses Durchschnittswerts gering bleibt. Um die Umweltrisiken zu bewerten, wurden die gemessenen Konzentrationen von Diclofenac mit den sogenannten Predicted-No-Effect-Concentrations (PNECs) verglichen, die aus standardisierten Laborexperimenten mit Organismen wie z.B. Daphnien, Fischen oder Pflanzen abgeleitet werden. Der PNEC für Diclofenac wurde auf 0,1 µg/l festgelegt (European Commission 2013). Beim Vergleich des PNECs mit den mittleren länderbasierten Konzentrationen aus 50 Ländern fällt auf, dass der PNEC in 34 Ländern überschritten wird. Dies ist ein deutlicher Hinweis auf wahrscheinliche ökotoxikologische Gefährdungspotenziale an den jeweiligen Messstellen. Dies unterstreicht die Bedeutung eines dringend benötigten globalen Ansatzes zur Eintragsminderung von Arzneimitteln in die Umwelt, wie er beispielsweise in SAICM entwickelt werden könnte. Am Beispiel von Diclofenac zeigt sich auch, dass Arzneimittel Effekte auf Populationsebene verursachen können. Aufgrund des Einsatzes von Diclofenac als Tierarzneimittel ist es seit 1996 zu einem drastischen Rückgang der indischen Geierpopulationen gekommen (Oaks et al. (2004), Green et al. (2006)).

Eintragspfade

Neben der globalen Verbreitung der Arzneimittel in der Umwelt sind ebenfalls die verschiedenen Eintragspfade von Interesse. Soweit es in den Literatur- und Datenquellen angegeben wurde, wurden diese Informationen ebenfalls in die Datenbank übertragen. Insgesamt konnten so für 13% der Datenbankeinträge Eintragspfade zugewiesen werden. Dieser geringe Wert kann durch die große Anzahl von Messungen in Flüssen und Kläranlagen begründet werden, da selten sämtliche Eintragsquellen, die fluss- bzw. kanalaufwärts der Messstelle liegen, bekannt sind. Bei den am häufigsten genannten Eintragsquellen handelt es sich um urbanes Abwasser. Aufgrund des großen urbanen Anteils an der Weltbevölkerung und da die meisten Arzneimittel im häuslichen Umfeld verwendet werden, erscheint diese Einschätzung realistisch.

Der zweithäufigste Eintragspfad, der in der Datenbank genannt wird, sind Krankenhäuser. Hier kann eine Vielzahl von Wirkstoffe in oftmals hohen Konzentrationen gefunden werden, was in Orias & Perrodin (2013) übersichtlich dargestellt wird. Krankenhäuser sind meist an die öffentliche Kanalisation angeschlossen und verfügen nur selten über eine eigene angepasste Kläranlage. Da kommunale Kläranlagen nicht für die Entfernung von pharmazeutischen Mikroschadstoffen konzipiert wurden, sind die Reinigungsraten oftmals gering. So können Mikroschadstoffe aus Krankenhäusern in Oberflächengewässer gelangen. Hierbei muss jedoch berücksichtigt werden, dass sich Arzneimittelwirkstoffe bezüglich ihres Verhaltens in Kläranlagen und in der Umwelt deutlich voneinander unterscheiden, da sie unterschiedliche Sorptionskoeffizienten, Transformationskinetiken und Halbwertszeiten aufweisen.

Der am dritthäufigsten genannte Eintragspfad ist die Tierzucht. Eine weitere Eintragsquelle, die lokal hohe Konzentrationen in der Umwelt erzeugen kann, sind pharmazeutische Produktionsstätten. In der Datenbank sind multiple Einträge zu Konzentrationen von Wirkstoffen, insbesondere Antibiotika, im mittleren bis hohen mg/L Bereich in Oberflächengewässern erfasst (z.B. Larsson et al. (2007) und Fick et al. (2009)). Insbesondere in Entwicklungs- und Schwellenländern, in denen umweltbezogene Grenzwerte nur selten vorhanden oder durchgesetzt werden, wird über die höchsten Werte berichtet. Ein weiterer lokaler Eintragspfad ist die Aquakultur, für die insbesondere aus Asien viele Datenbankeinträge vorliegen. Hierbei wird die Fischzucht in Flüssen als besonders kritisch angesehen, da die Verdünnung, im Gegensatz zu Seen und Meeren, gering ist und flussabwärts gelegene Ökosysteme beeinträchtigt werden können.

Maßnahmen

Eine Aufnahme von „Arzneimittel in der Umwelt“ als prioritäres Politikthema (emerging policy issues) im strategischen Ansatz für ein Internationales Chemikalienmanagement (SAICM) des Umweltprogramms der Vereinten Nationen (UNEP) könnte Akteur- und Sektor-übergreifende Handlungsstrategien auch in Schwellen- und Entwicklungsländern initiieren, die auf die freiwillige Verminderung und das Risikomanagement von Arzneistoffen in der Umwelt ausgerichtet sind. Dabei sind Handlungsoptionen derart auszugestalten, dass die Wirksamkeit und Verfügbarkeit und Arzneistoffen nicht in Frage gestellt wird, insbesondere in Ländern, in denen der Zugang zum Gesundheitssystem noch unzureichend ist. Dazu ist eine Zusammenarbeit verschiedener Akteure auf der globalen und der regionalen Ebene notwendig, u.a. internationaler Organisationen, nationaler Regierungen, Zulassungsbehörden, Arzneimittelhersteller, Ärzte, Apotheker, Patienten, Veterinärmediziner, Landwirte, Kläranlagenbetreiber, Entwicklungsdienste, Nichtregierungsorganisationen, Krankenversicherer, Wasserversorger und Forschungsinstitute. Zu den potenziellen Handlungsoptionen gehören Informationskampagnen für die Bevölkerung, aber auch für Ärzte, Pharmaproduzenten und Regierungen. Des Weiteren wird diskutiert ob über Verpackungsgröße, Verschreibungspflicht, offizielle Entsorgungsstellen, Entwicklung umweltfreundlicher Medikamente und viele weitere Möglichkeiten der Eintrag von Arzneimittelwirkstoffen in die Umwelt verringert werden kann. Diese Maßnahmen, die oftmals bereits an der Quelle des Eintrags einsetzen, können zudem durch technische *end of pipe* Lösungen ergänzt werden. Da diese Lösungen sehr aufwendig sind und einen hohen Finanzierungsbedarf aufweisen, werden sie primär in Industrieländern eingesetzt. Generell stehen hierbei technologische Maßnahmen im Vordergrund, welche die Eliminationsraten in den Kläranlagen verbessern, wobei die Verwendung von Ozon und (Pulver-)Aktivkohle die besten Ergebnisse erzielt (Joss et al. 2005), auch hinsichtlich der Kosten-Nutzen Rechnung (Günthert & Rödel 2013). Beispielsweise plant die Schweiz aus diesem Grund ca. 100 ihrer 700 kommunalen Kläranlagen in den nächsten 25 Jahren aufzurüsten, um so mehr als 50% des Gesamtabwasser-aufkommens zu behandeln. Es wird prognostiziert, dass sich die Mikroschadstofffracht dadurch halbiert, bei einem Kostenaufwand von 1,2 Milliarden Schweizer Franken. In vorausgegangenen Studien wurden mögliche Handlungsoptionen vor allem im Hinblick auf die deutschen (START 2008) und europäischen Verhältnisse (BIO-IS 2013) untersucht. Im hier vorliegenden Projekt wurden existierende Handlungsoptionen bezüglich ihrer Eignung bewertet, das Thema global im Rahmen von SAICM zu adressieren.

Fazit

Diese Studie hat gezeigt, dass Arzneimittel in der Umwelt ein globales Problem sind, da auf allen Kontinenten Arzneimittel nachgewiesen wurden. Insgesamt wurden 631 Stoffe in 71 Ländern gefunden. Am häufigsten wurde hierbei das Schmerzmittel Diclofenac gefunden. Als Haupteintragspfad wurde urbanes Abwasser aus Kläranlagen, Landwirtschaft, Industrie und Krankenhäusern identifiziert. Maßnahmen zur Verminderung des Eintrags von Arzneimitteln in die Umwelt beinhalten z. B. Informationskamapgnen zur Entsorgung von Arzneimitteln, aber auch technische Maßnahmen, wie z.B. der Ausbau von Kläranlagen. Die Integration von Arzneimitteln in der Umwelt als prioritäres Politikthema (emerging policy issues) im strategischen Ansatz für ein Internationales Chemikalienmanagement (SAICM) des Umweltprogramms der Vereinten Nationen (UNEP) könnte Akteur- und Sektor-übergreifende Handlungsstrategien auch in Schwellen- und Entwicklungsländern initiieren.

Generell sind weitere Daten, insbesondere aus Entwicklungs- und Schwellenländern sowie Osteuropa nötig um weitere belastbare Aussagen zum Vorkommen von Arzneimitteln in der Umwelt in diesem Regionen zu treffen um besonders belastete Standorte zu identifizieren

1 Introduction

The Strategic Approach to International Chemicals Management (SAICM, see textbox below) has identified "Environmentally Persistent Pharmaceutical Pollutants" (EPPP, see textbox below on terminology) as an emerging policy issue (see textbox on emerging policy issues) at the fourth session of the International Conference on Chemicals Management (ICCM4). An extended nomination dossier (SAICM/ICCM.4/7) has been developed by the Ministry of Environment of Peru, the Ministry of Housing, Land Planning and Environment of Uruguay and the International Society of Doctors for the Environment (SAICM 2015).

Strategic Approach to International Chemicals Management (SAICM)

Adopted by the International Conference on Chemicals Management (ICCM) on 6 February 2006 in Dubai, United Arab Emirates, the Strategic Approach to International Chemicals Management (SAICM) is a policy framework to foster the sound management of chemicals around the world. SAICM has as its overall objective the achievement of the sound management of chemicals throughout their life cycle so that, by 2020, chemicals are produced and used in ways that minimize significant adverse impacts on human health and the environment. This "2020 goal" was adopted by the World Summit on Sustainable Development in 2002 as part of the Johannesburg Plan of Implementation.

SAICM comprises the Dubai Declaration on International Chemicals Management, expressing high-level political commitment to SAICM, and an Overarching Policy Strategy (OPS) which sets out its scope, needs, objectives, financial considerations underlying principles and approaches and implementation and review arrangements. Objectives are grouped under five themes: risk reduction; knowledge and information; governance; capacity-building and technical cooperation; and illegal international traffic.

The Declaration and Strategy are accompanied by a Global Plan of Action (GPA) that serves as a working tool and guidance document to support implementation of SAICM and other relevant international instruments and initiatives. Activities in the plan are to be implemented, as appropriate, by stakeholders, according to their applicability.
(Text from www.saicm.org)

In 2011 at OEWG1, a first nomination of pharmaceuticals in the environment as an emerging policy issue in SAICM was postponed as the scope of the problem was still not evident (For further information see textbox on the process of nomination at the end of this chapter). This study has been initiated and conducted in order to investigate and provide a global data and knowledge database about the occurrences of pharmaceuticals in the environment and their related potential effects. The results of this study was used to support the extended nomination dossier for a new emerging policy issue in SAICM, which has been developed by the Ministry of Environment of Peru, the Ministry of Housing, Land Planning and Environment of Uruguay and the International Society of Doctors for the Environment (ISDE) for consideration at OEWG2. Here, all participating countries agreed on moving the application of pharmaceuticals in the environment on to ICCM4, where the final decision on adding it as a new emerging policy in SAICM was made. More details on the nomination procedures and history can be found in the textbox below. Cooperative action under SAICM could initiate a multi-sectoral,

multi-stakeholder, life-cycle approach to preventing, reducing, and managing pharmaceuticals in the environment.

Current efforts to address the occurrence and effects of pharmaceuticals in the environment under SAICM demand for an up-to-date review of the current state of knowledge on the global relevance and prevailing concentrations of pharmaceuticals in the environment.

This study thus aims at providing a comprehensive review of measured environmental concentrations (MEC) of both human and veterinary pharmaceutical substances on the global scale. Published MEC in sewage, surface water, groundwater, tap/drinking water, sediment, manure, soil, and other environmental matrices were compiled in a global database for systematic analyses of the global occurrence of pharmaceuticals in the environment. For selected cases, the prevailing concentrations were used to assess ecotoxicological risks based on predicted no-effect concentrations (PNEC), derived from effect studies. Furthermore, the database was analysed regarding regional patterns, trends, and the relevance of different emission pathways as basis for deriving effective global strategies of action. Additionally, data on annual pharmaceutical consumption was compiled from publicly available publications to assess regional differences with regard to e. g. the availability of medicines and the active pharmaceutical substance used and the design effective monitoring strategies.

This study also provides an overview of options for action to minimize the entry of pharmaceuticals into the environment and evaluates their suitability for inclusion into the SAICM Global Plan for Action.

Terminology "Pharmaceuticals in the Environment" instead of EPPP

In this report, we prefer the term "Pharmaceuticals in the Environment" instead of "Environmentally Persistent Pharmaceutical Pollutants" (EPPP) used in the nomination dossier, because in the latter the word "persistent" is used inconsistently to established definitions (e.g., Stockholm Convention on Persistent Organic Pollutants or criteria used for PBT assessment). Human pharmaceuticals may prevail pseudo-persistently in the environment due to the continuous emission, even if they do not fulfil the criteria for persistence.

Modern medicine cannot be imagined without pharmaceuticals. Pharmaceuticals are a crucial element of modern medicine and confer significant benefits to society. More than 3,000 active pharmaceutical substances are being administered worldwide in prescription medicines, over-the-counter therapeutic drugs, and veterinary drugs. Their active ingredients comprise a variety of synthetic chemicals produced by pharmaceutical companies in both the industrialized and the developing world at a rate of 100,000 tons per year (WHO 2014). While pharmaceuticals are stringently regulated for efficacy and patient safety, the adverse side effects they may have in the natural environment have not yet been sufficiently studied and are not covered by an international agreement or arrangement. Growing world population, investments in the health care sector, advances in research and development, high global market availability, and aging societies in industrialized countries have led to a strong increase of pharmaceutical consumption in the last decades (Van Boeckel et al. 2014).

Emerging Policy Issue under SAICM

In accordance with the SAICM Overarching Policy Strategy (paragragh 24.j), one of the functions of the International Conference on Chemicals Management (ICCM) is to call for appropriate action on emerging policy issues as they arise and to forge consensus on priorities for cooperative action (www.saicm.org).

The following criteria for an emerging policy issue within the SAICM framework must be met:

- It involves each life-cycle phase;
- It is insufficiently addressed by any other global regulation;
- It has clearly emerged from the current level of scientific understanding.

So far resolutions have been adopted on the following issues:

- Lead in Paint
- Chemicals in Products
- Hazardous substances within the life cycle of electrical and electronic products
- Nanotechnology and manufactured nanomaterials
- Endocrine-disrupting chemicals
- Perfluorinated chemicals and the transition to safer alternatives

An open and transparent procedure is available for those wishing to nominate emerging policy issues for consideration by the Conference.

At the same time, laboratory instruments and analytical methods have further advanced, enabling the detection of certain pharmaceutical substances in the aquatic and terrestrial environment down to the pg/L to µg/L range (e.g. Zrnčić et al. 2014). It also explains the increase in scientific publications since the late 1990s (Boxall et al. 2012). Parallel to monitoring studies, ecotoxicological effects pharmaceutical substances in the environment exert on non-target organisms have been demonstrated in a growing number of laboratory (Triebskorn et al. 2007, Foster et al. 2010, Brodin et al. 2013, Ebert et al. 2011), field-scale (Kidd et al. 2007, Michelini et al. 2012, Liebig et al. 2010), and wildlife studies (Oaks et al. 2004).

Even though there are about 150 review articles on pharmaceuticals in the environment, these often refer to specific countries, e.g. China (Bu et al. 2013) or Sweden (Falas et al. 2012), to specific water bodies, e.g. the Spanish Llobregat River (Gonzalez et al. 2012) or the North American Great Lakes (Klecka et al. 2010), to specific therapeutical groups, e.g. psychiatric substances (Calisto & Esteves 2009) or cytostatics (Besse et al. 2012), to specific substances, e.g. the antibiotic tetracycline (Daghrir & Drogui 2013) or the anti-epileptic carbamazepine, to specific targets, e.g. livestock (Kemper 2008), to specific sampling matrices, e.g. treated wastewater (Aguayo et al. 2010) or groundwater (Lapworth et al. 2012), to specific sampling methods (e.g. Petrovic 2014 or Buchberger 2011), to specific emission sources, e.g. pharmaceutical factories (Cardoso et al. 2014; Fick et al. 2009) or hospitals (Orias & Perrodin 2013), or to transformation products (Fatta-Kassinos et al. 2011).

Few publications provide a semi-global review focusing on peer-reviewed publications in international journals (Miege et al. (2009), Li (2014), Hughes et al. (2012)). But these reviews often potentially miss other quality data published in governmental reports, water body authorities, university research, and other publications, especially in developing and emerging countries. Due to the focus on industrialized countries, so far no concise picture on the global situation has been provided. For example, Hughes et al. (2012) who reviewed literature for 41 countries, state in their Abstract "... [there is] little work outside North America, Europe, and China, and no work within Africa".

Process of Nomination of EPPP as Emerging Policy Issue under SAICM

- In 2011, "Environmentally Persistent Pharmaceutical Pollutants" (EPPP) was first proposed for nomination as an emerging policy issue under SAICM by the International Society of Doctors for the Environment (ISDE).
- The Open-ended Working Group (OEWG), at its first meeting in Belgrade, Serbia in November 2011, considered that some of the activities set out in this proposal did not meet the criteria for the issue to be considered to be an emerging policy issue, but recognizes the merit of further consideration of the issue by ICCM, following its third session, and encourages the proponent to develop the proposal further (Decision OEWG.1/4)[1].
- In 2014, in line with the modality for nominating new emerging policy issues under SAICM, an extended nomination dossier (SAICM/OEWG.2/INF/15)[2] has been developed by the Ministry of Environment of Peru, the Ministry of Housing, Land Planning and Environment of Uruguay and the International Society of Doctors for the Environment (ISDE) for consideration at OEWG2.
- In accordance with SAICM Resolution II/4, the secretariat invited comments on the nomination dossier by 11 July 2014 and published received comments on the SAICM website.
- The revised submission was presented to the second meeting of the Open-ended Working Group (OEWG2) held in Geneva on 14-17 December 2014. A summary of the proposal was provided by the Secretariat (SAICM/OEWG.2/7). Following its discussion the Working Group agreed that the proposal should be revised in a contact group. The Working Group endorsed the proposal amended in the contact group for consideration by ICCM4.
- The proposal was presented for final adoption at ICCM4, held in Geneva from 28 September to 2 October 2015 (SAICM/ICCM.4/7). ICCM4 adopted an omnibus resolution on emerging policy issues. The resolution will be published at www.saicm.org. It recognises the potential adverse effects associated with exposure to environmentally persistent pharmaceutical pollutants on human health and the environment, and the need to protect humans and ecosystems and their constituent parts that are especially vulnerable.
- The Conference
    - agrees that international cooperation is crucial to build awareness and understanding and promote action on EPPPs as an EPI;
    - decides to implement cooperative action on EPPPs with the overall objective of increasing awareness and understanding among policymakers and other stakeholders;
    - invites governments and other stakeholders to generate and share information to fill identified knowledge gaps;
    - invites relevant IOMC[3] participating organizations, within their respective mandate as part of their work programme, to lead and facilitate cooperative action to develop an EPPP work plan;
    - requests all interested stakeholders and organizations to provide support on a voluntary basis, for such cooperative action; and

1 http://www.saicm.org/images/saicm_documents/OEWG/Meeting%20documents/OEWG1%2019_OEWG1%20Report%20E.pdf)

2 http://www.saicm.org/images/saicm_documents/OEWG2/Meetingdocs/FINAL/INFDOCS/k1402830%20saicm-eowg2-inf%2015.pdf

3 IOMC: Inter-Organization Programme for the Sound Management of Chemicals

- invites relevant IOMC participating organizations and other SAICM stakeholders to report on cooperative action to ICCM5 or any other session as decided upon by the Conference.

(cited from ENB report Vol. 15 No. 236, p.7)

2 Project Aim

Pharmaceuticals are known to occur widely in the aquatic environment of industrialized countries. In developing and emerging countries, more information on the occurrence of pharmaceuticals in the environment has become available in recent years, but a concise picture on the prevailing concentrations and potential effects on human and ecosystem health in these countries was still elusive.

As the basis for further considerations, the goal of the current project is to define the state of knowledge on the global relevance of pharmaceuticals in the environment by

- compiling Measured Environmental Concentrations (MEC) of human and veterinary pharmaceuticals from all five UN regional groups,
- comparing regional consumption data and future trends,
- assessing the relevance of different emission pathways (production, use, disposal),
- assessing the role of infrastructure, population, pharmaceutical availability, agricultural practice, etc. on the emissions of pharmaceuticals into the environment,
- providing databases and maps to illustrate the global relevance of pharmaceuticals in the environment as an emerging issue, and
- preparing possible activities for inclusion into the Global Plan of Action.

3 Literature Review and Database Compilation

3.1 Defining pharmaceutical substances

Within this study, pharmaceuticals have been defined as substances that are primarily being used for therapeutic purposes. Therefore, recreational drugs, such as cocaine and caffeine, have been excluded from the analysis. Also, homeopathic drugs, natural substances, etc. have not been considered.

3.2 Bibliographic database

A systematic literature review has been conducted as of October 2013 using multiple search strategies: (i) peer-reviewed publications were identified using scientific search engines including Web of Science (www.webofknowledge.com) and Science Direct (www.sciencedirect.com) and by tracing down original publications cited in review articles, (ii) non-peer reviewed articles, books, university research, and governmental reports in different languages were identified using internet search engines and library catalogues, (iii) existing databases, e.g. created in projects financed by the European commission, such as KNAPPE (Sadezky et al. 2008), FATE-SEES (JRC 2012), or POSEIDON (Ternes et al. 2004), international networks, such as NORMAN (www.norman-network.net), and a predecessor database compiled by Bergmann et al. (2011) on behalf of the German Environment Protection Agency, (iv) 41 stakeholders from local governments, universities, and others were contacted in order to gather additional regional information, mainly in Africa, Asia, and Latin America.

All identified publications were categorized in a bibliographic database (Endnote©, Thomson Reuters, Toronto) according to the country the data was measured in. If a publication included data for more than one country, the literature citation was assigned to each of the countries. Most of the compiled publications were written in English language, whereas publications in Chinese, Dutch, French, German, Portuguese, Russian, Slovenian, Spanish, and Swedish languages were also evaluated.

Due to time constraints, not all available literature could be analysed, especially from countries such as the U.S.A, Germany, and China, which are already dominating the database.

3.3 Database of Measured Environmental Concentrations

Reported data was transferred from each publication, report, and other data sources to the new database (MEC database), which is organized in a Microsoft Access© environment. Each database entry comprises 32 fields, including the name of the pharmaceutical substance, its CAS number, the environmental matrix the substance was measured in, geographical location, sampling period, number of measurements, measured concentration in original and standardized units, detection limit of the analytical method employed, pollution source (if stated in publication), literature citation, publication language and type, and quality flag.

Regarding the environmental matrices investigated, surface water, riverbank filtration, groundwater, well water, tap/drinking water, sewage and wastewater treatment plant (WWTP) streams, WWTP sludge, manure, soil, sediments, suspended particulate matter, and other environmental matrices were distinguished with multiple sub-categories. No differentiation was made between tap water and drinking water, because the distinction between countries in which tap water is drinking water and others in which tap water is not suitable or not commonly used for drinking was not always clear in several publications.

The geographical sampling location (including geographical name, region, and country) were categorized according to the United Nations regional group (Africa Group; Asia-Pacific Group; Eastern Europe Group (EEG); Group of Latin American and Caribbean States (GRULAC); Western Europe and Others Group (WEOG), including North America, Australia, and New Zealand).

Most publication reports aggregated MEC data of a specific number of measurements (e.g., average, median, 90th percentile, minimum or maximum of a monitoring campaign), rather than single observations. Aggregated data was compiled in one database entry stating the statistical type and the number of underlying measurements. Since the statistical distribution of the aggregated data is rarely known, only database entries reporting single or average values were considered in deriving weighted national average concentrations. The highest concentrations reported for a specific environmental matrix in each country was assigned as national maximum concentration for the respective matrix.

A quality flag of each database entry refers to the reliability, plausibility, and analytical standards applied in each publication. Since the quality assessment of a publication is difficult to measure and thus a matter of subjectivity, the quality flag serves as an indicator only. Generally, peer-reviewed publications have been considered verified sources of high quality. The quality of other publications including university theses is difficult to evaluate. Nevertheless, even though some of the methods and results published in these theses are difficult to verify, the majority of publications received a good quality flag.

Next to the measured pharmaceutical itself, the database provides further information for each entry on (also see Table 1 for a database example):

- PharmaCAS: CAS number (from the pharmaceutical compound database).
- Pharma Therapy Group: Therapeutical group of the pharmaceutical compound (from the pharmaceutical compound database).

- Pharma Target: Target of pharmaceutical compound: human, veterinary, human and veterinary (from the pharmaceutical compound database).
- Pharma Type: Defines if pharmaceutical compound is a parent or transformation product (from the pharmaceutical compound database).
- Matrices: Environmental matrix in which the pharmaceutical has been measured (sewage (urban, industrial, hospital), influent/sludge/effluent from wastewater treatment plants, surface water (rivers, lakes, estuaries, oceans, aquacultures, unspecific), riverbank infiltration, groundwater, well water, drinking water, tap water, sediment (rivers, lakes, estuaries, oceans, aquacultures, unspecific), suspended particulate matter (rivers, sewage, estuaries, oceans, unspecific), rain, soil, soil water, manure (liquid, dung), dust, unknown).
- Sampling Location: Location where sampling took place, e.g. river basin or name of the wastewater treatment plant.
- Sampling Description: More detailed information about the sampling location, e.g. the city next to the river or WWTP.
- Sampling Period: Defines start and end of the measuring campaign.
- Sampling Country: Includes the name of the country according to the United Nations (UN).
- Sampling Province: Name of the province, e.g. Nebraska or Baden-Württemberg.
- UN Region: Continental classification according to UN.
- Statistics: Statistical type of measurements (single value, maximum, minimum, median, average, fraction, P90, smaller/larger than, unknown).
- Number of Samples: Number of samples used to calculate MEC value.
- Detection: Positive or negative detection.
- MEC: Measured environmental concentration.
- Unit: The unit in which the MEC value is given.
- MEC standard: MEC value converted to standard units.
- Unit standard: Unit converted to standard units (µg/L or mg/L).
- Detection Limit: Detection limit of the applied method.
- Unit Detection Limit: Unit of the detection limit.
- Detection Limit standard: Detection limit converted to standard units.
- Unit Detection Limit standard: Detection Limit unit converted to standard units (µg/L or mg/L).
- Pollution Source: Given sources of pollution (production of pharmaceuticals, urban/hospital/industrial wastewater, aquaculture, animal farm, manure/sludge, irrigation, discharge of unused pharmaceuticals).
- Literature Citation: Name of the publication, which is linked to an Endnote database.

- Literature Author/Organisation: Further literature details, e.g. author of data entry in NORMAN.
- Literature Language: Language of publication cited.
- Literature Type: Type of the cited publication (university research, EU-project, governmental report, review, company publication).
- Literature Availability: Defines if cited publication is copyright protected, publicly available, or personal communication.
- Literature Credibility: Provides information about the reliability of the cited publication (good, questionable, unknown).
- Responsibility: This field relates to the person responsible for the database entry.

Table 1: Exemplary entry within the MEC database

Pharma Name	Trimethoprim
Pharma CAS	738-70-5
Pharma Therapy Group	Antibiotics
Pharma Target	Human and veterinary
Pharma Type	Parent
Matrix	Surface Water - River/Stream
Sampling Location	Dead Horse River
Sampling Description	Confluence Plum river
Sampling Period Start	2010
Sampling Period End	2010
Sampling Country	Canada
Sampling Province	Manitoba
UN Region	Western European and Others Group (WEOG)
Statistics	Max
Number Samples Analysed	4
Detection	positive detection
MEC	2.1
Unit	ng/l
MEC standard	0.0021
Unit standard	µg/L
Detection Limit	2
Unit Detection Limit	ng/l
Detection Limit standard	0.002
Unit Detection Limit standard	µg/L
Pollution Source	unknown
Literature Citation	Carlson et al. (2013)
Literature Author/Organisation	Carlson et al. (2013)
Literature Language	English
Literature Type	University Research
Literature Availability	copyright
Literature Credibility	good
Responsibility	adB

3.4 Consumption Database

The aim of analysing the consumption data base was to answer questions on the availability of pharmaceuticals in different countries and on differences in the active substances used. National data on pharmaceutical consumption or prescription patterns could be used to prioritize high-volume pharmaceuticals for monitoring campaigns and estimate MEC for countries in which monitoring campaigns are still missing. Unfortunately, existing commercial databases (e.g., IMS Health, Danbury) on regional pharmaceutical consumption/sale could not be acquired due to high service charg-

es. Commonly, commercial databases focus on industrialized and emerging countries and do not cover data of most developing countries. However, IMS Health data for Germany has been available for four years from the predecessor project. All other database entries have been found by studying relevant literature.

Consumption or prescription data of human and veterinary pharmaceuticals were compiled from publicly available literature using the search strategy outlined above. Only those data referring to country-wise yearly consumption (in units such as kg/a) have been compiled. Some publications report Defined Daily Doses (DDD) or other doses per patient, which could not be converted to country-wise consumption without additional information. The database fields specify the name of the pharmaceutical, the yearly amount consumed, reference period, country, and UN region, as well as literature citation and data quality flag. Another field specifies the underlying data source, since often no national sum of total consumption is reported, but a sectorial value only, such as consumption in hospitals, from outpatients, or for veterinary purposes.

4 Global Occurrence of Pharmaceuticals in the Environment

The literature review resulted in 1016 original publications reporting unique MEC data of human and/or veterinary pharmaceutical substances worldwide. In addition, 147 review articles were assessed. From all literature resources, published MEC data were compiled in the database, resulting in 123,761 database entries. Most entries refer to aggregated data of multiple measurements. Therefore, the number of underlying measurements in the database is expected to be much higher than the number of database entries. Since the number of underlying samples is missing for some aggregated data and some database entries refer to different statistical parameters of the same monitoring data (e.g., average, median, maximum, minimum), the total number of underlying measurements of the database cannot be specified. In the following, we thus refer to the number of database entries as an indicator of monitoring intensity. Most database entries were generated from data published in peer-reviewed journal articles, followed by existing databases (such as NORMAN). In comparison, fewer database entries were generated from governmental reports, books, and university theses.

The sampling period has been available for about 88% of all database entries. Only 1,281 database entries have been sampled before 2001.The first measurement included in the data base refers to antibiotics in pig farms from 1987 (Hamscher et al. 2003). Since 2001, a constant, almost exponential increase of measurements of pharmaceuticals in the environment can be noticed. The number of database entries increases from about 2,000 in the year 2001 to more than 24,000 in the year 2010. This increase originates on the one hand from technological advances in instrumental chemical analysis, such as advanced GC-MS procedures (Buchberger 2011), which allows for detecting pharmaceuticals in samples already in the pg/l range. On the other hand, scientific, governmental, and public awareness about this new emerging pollutant has caused an increase of parameters in environmental monitoring protocols. After 2010, the number of database entries drops down to 224 in 2013 (as per October 2013, when the literature research was stopped), which probably can be explained by the time period it takes to analyze the samples and to publish them in a sometimes protracted peer-review process. In the meantime, it can be expected that this number has grown substantially.

In the following sub-chapters, the database entries have been analysed in order to answer the following questions concerning pharmaceuticals in the environment:

- In which matrices have pharmaceutical been measured?
- In which countries have pharmaceuticals been found in the environment?
- How many and what kind of pharmaceutical substances have been found?
- Are the same pharmaceuticals detected in each UN regional group?
- Can pharmaceuticals have ecotoxicological effects at the concentrations found?
- What are the dominant emission pathways?
- Are monitoring programs affected by biases?
- Are consumption data available to provide information on availability of medicines and on regional consumption patterns? Can consumption data help to substitute MEC data?
- What are the conclusions on the global occurrence of pharmaceuticals in the Environment?

4.1 On a global scale, in which matrices have pharmaceuticals been measured?

Pharmaceutical substances have been analyzed in a variety of different environmental matrices (Table 2). Most measurements have been reported for surface waters (47% of total database entries), the majority referring to rivers and streams, followed by lakes and oceans. The groundwater to drinking-water scheme comprises 8% of the total database entries, with most measurements referring to groundwater and fewer to untreated well water, riverbank infiltration, or tap/drinking water. Wastewater (40% of total database entries) is dominated by measurements in the WWTP effluent, followed by WWTP influent, untreated hospital sewage, WWTP sludge, and untreated urban sewage. In comparison, the potential emission pathway of veterinary pharmaceuticals from manure and dung to soil comprises relatively few measurements (3% of total database entries) and the significance of pharmaceuticals sorbed to suspended particulate matter and contamination of sediments is hardly studied (2% of total database entries).

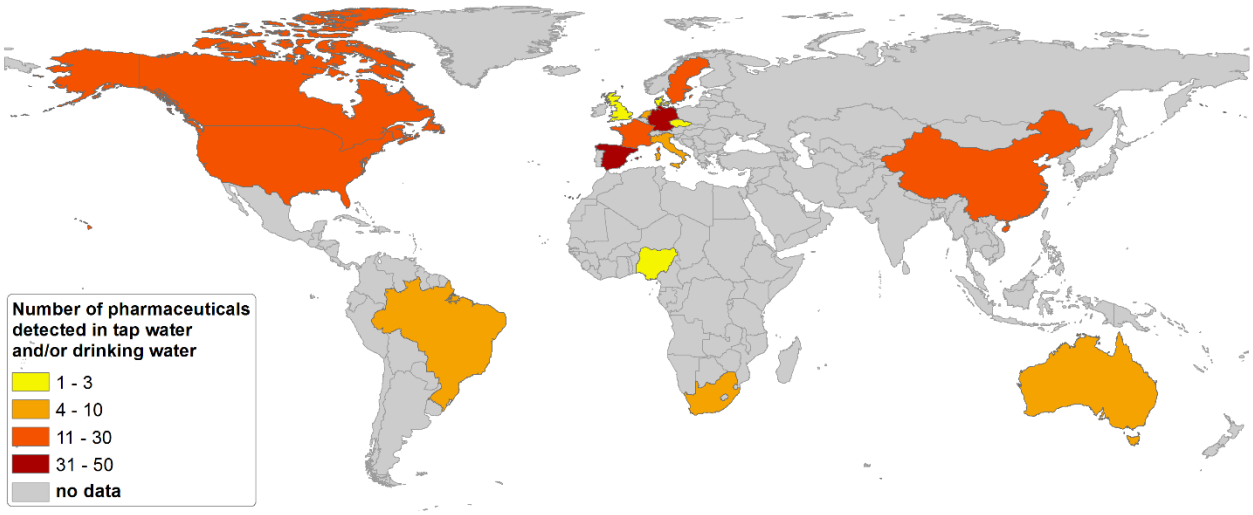
Table 2: MEC database-entries in each environmental matrix

Environmental matrix	MEC Database-Entries	Sum
Surface water - unspecific	3.245	67.987
Surface water - River/Stream	50.686	
Surface water - Lake	1.711	
Surface water - Sea or Ocean	1.420	
Surface water - Aquaculture	467	
Surface water - Estuary	743	
Riverbank filtration	485	
Groundwater	3.304	
Well water (untreated)	1.713	
Tap water/Drinking Water	4.213	
Sewage urban (untreated)	1.891	49.330
Sewage industrial (untreated)	729	
Sewage hospital (untreated)	2.889	
Sewage hospital (treated)	351	
WWTP inflow (untreated)	13.219	
WWTP effluent (treated)	27.579	
WWTP sludge	2.672	
Sediment - unspecific	283	3.070
Sediment - River/Stream	1.247	
Sediment - Lake	612	
Sediment - Sea or Ocean	55	
Sediment - Aquaculture	184	
Sediment - Estuary	155	
Suspended particulate matter - unspecific	9	
Suspended particulate matter - Estuary	5	
Suspended particulate matter - Sewage	146	
Suspended particulate matter - Sea or Ocean	12	
Suspended particulate matter - River/Stream	362	
Rain	15	3.374
Soil	1.295	
Soil Water	372	
Manure - liquid	999	
Manure - dung	580	
Dust	18	
Unknown	95	

Pharmaceutical substances in tap/drinking water

For drinking/tap water, less data is available compared to surface waters and wastewater, especially, for developing and emerging countries (Figure 1). In Spain and Germany, more than 30 pharmaceuticals have been detected and 11 to 30 in Canada, China, France, Sweden, and USA. Also in French bottled water some pharmaceuticals in trace concentrations ranges have been detected (Bruchet et al. 2005). These results contrast a report of WHO (2012), which includes considerably less data on pharmaceuticals in drinking water.

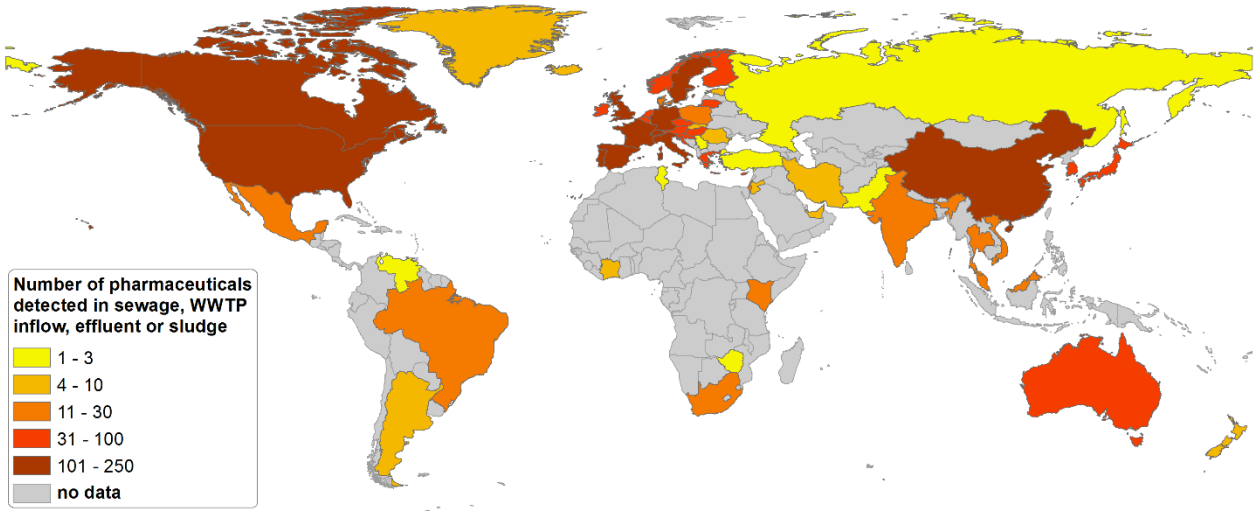
Figure 1: Number of pharmaceutical substances detected in tap/drinking water per country



Pharmaceutical substances in sewage and wastewater treatment plants

For the wastewater matrices sewage, WWTP influent, effluent, and sludge, in total 559 different pharmaceuticals have been detected globally. The number of pharmaceuticals detected in wastewater matrices in each country is illustrated in Figure 2. High numbers of pharmaceuticals detected in a region correlate with high numbers of measurements, for example in Canada and China. In general, a close relationship between occurrences in WWTP effluent and surface waters can be assumed, since most WWTP discharge directly into surface waters, such as rivers and lakes.

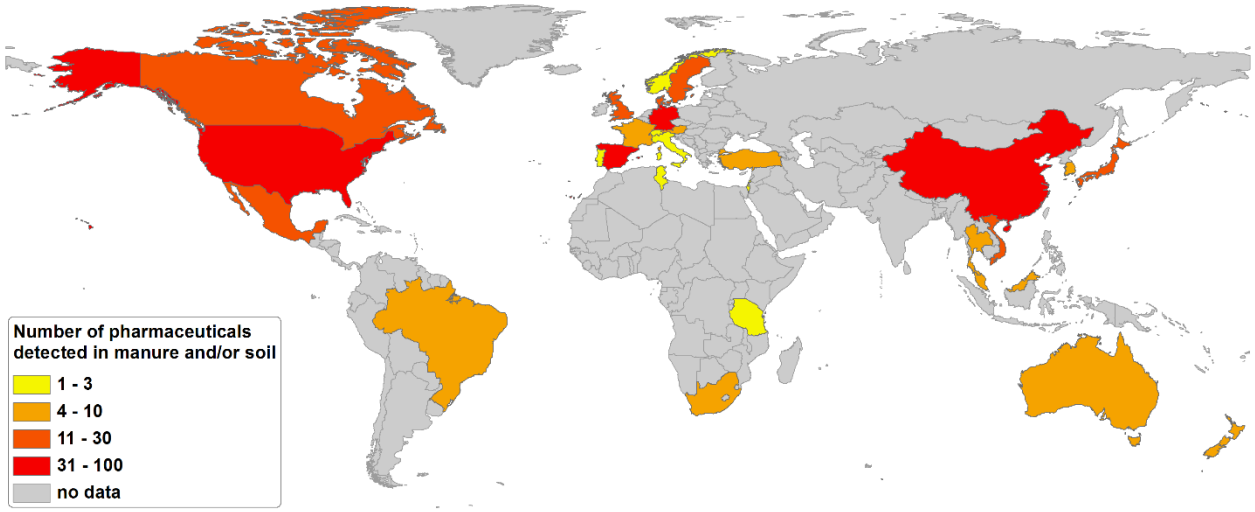
Figure 2: Number of pharmaceuticals detected in sewage, wastewater treatment plants inflow /effluent /sludge per country



Pharmaceutical substances in manure and soil

As shown in Table 2, only 3% of all database entries refer to measurements of pharmaceuticals in manure and soil. This is also well depicted in Figure 3, which features a global, country based map on the number of pharmaceuticals detected in manure and/or soil. Here, about 30 to 100 substances have been found in Europe, North America, and China. In many other regions, little research on this topic has been published and therefore, few data sets are available. However, in Brazil, Australia, Turkey, South Korea, and Malaysia, 4 to 10 different substances have been reported.

Figure 3: Number of pharmaceuticals detected in manure and/or soil per country



4.2 In which countries have pharmaceuticals been found in the environment?

According to the database, pharmaceutical substances have been found in 71 countries worldwide, in which at least one MEC of one pharmaceutical substance was reported in the literature at concentrations exceeding the detection limit of the analytical method employed. These 71 countries in which pharmaceutical substances have been detected in the environment cover all five UN regional groups.

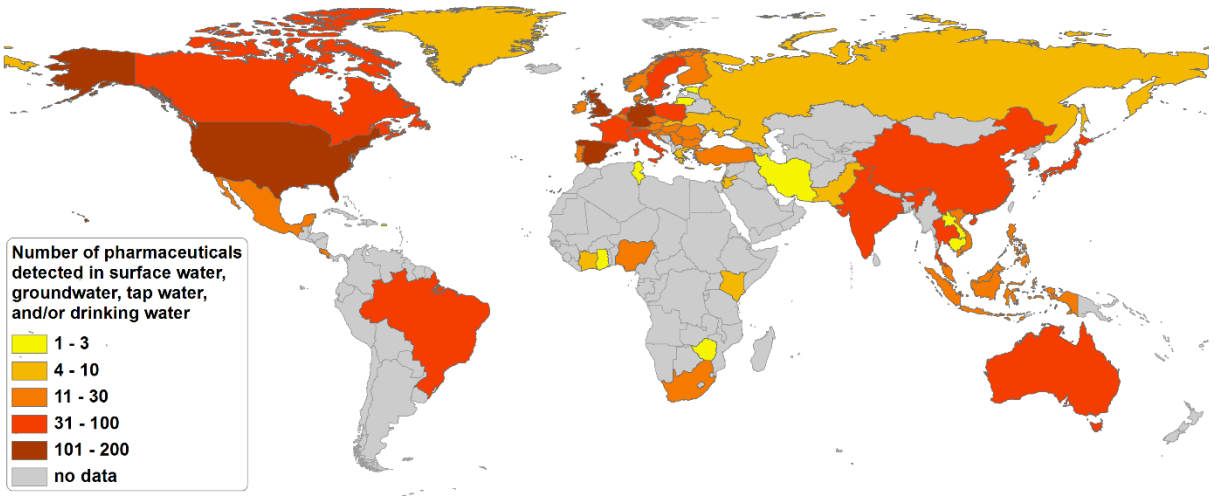
In each UN regional group, at least 38 different pharmaceutical substances have been found in surface water, groundwater or tap/drinking water. More than 100 different pharmaceutical substances have been found in several European countries and the USA in the aquatic environment (surface waters, groundwater and/or tap/drinking water) in concentrations exceeding the detection limit of the analytical method employed (see Figure 4). More than 30 different pharmaceutical substances have been found in other Western and Eastern European countries, Asia and the Pacific, and also in GRULAC countries. In most countries of the Pacific, Africa, and Eastern Europe less or equal than 30 pharmaceuticals have been detected.

It needs to be highlighted that for each country for which publications have been available, positive detections of pharmaceuticals in at least one matrix have been reported.

Despite global coverage, pronounced regional patterns in environmental monitoring prevail. Industrialized countries in the UN region WEOG (Western Europe and others group, including North America, Australia, and New Zealand) generally feature a good coverage. For WEOG countries, about 96,000 database entries have been generated from 730 publications, so that roughly three out of four database entries fall into this geographical group. Most database entries have been compiled for Germany (16,343 from 221 publications), followed by USA (9,515 from 143 publications) and Spain (13,092 from 83 publications). For Malta, Iceland, Greenland, and Faroe Islands only a single publication each has been available. In contrast, for African countries 23 publications were available resulting in 1,159 database entries (mainly South Africa, Nigeria, and Kenya).

Most publications added to the data base have been available for Germany (221 with 16,343 MECs), followed by USA (143 with 9,515 MECs) and Spain (83 with 13,092 MECs). For Malta, Iceland, Greenland, and Faroe Islands only a single publication has been available. Many single measurements for the Netherlands have been provided by the NORMAN-database, resulting in 17,547 MECs from only 16 publications. For Asia and the Pacific about 16,000 database entries have been compiled from 145 publications, whereas most data has been available for China (8239 MECs), followed by Vietnam (2144 MECs), South Korea (1629 MECs), and Japan (1286 MECs). For Laos, United Arab Emirates, Cambodia, and the Philippines only a single publication has been found. No data at all has been found for Central Asian countries, including Mongolia. The Eastern Europe group is represented with data for 13 countries, 8809 MECs, and 59 publications. Slovakia (2388 MECs), Czech Republic (1396 MECs), and Slovenia (1174 MECs) feature a good data coverage, whereas no data has been available for countries such as Belarus and Latvia. For GRULAC (group of Latin America and Caribbean States), 2247 MECs from 59 publications and 7 countries have been included in the database. However, Brazil (1234 MECs) and Mexico (868 MECS) contribute to 54 of the 59 publications.

Figure 4: Number of pharmaceuticals detected in surface waters, groundwater, tap water, and/or drinking water per country



Africa shows the lowest data coverage with 1159 MECs from 23 publications and 8 countries. Most data has been found for South Africa (713 MECs), Nigeria (231 MECs), and Kenya (96 MECs).

Some of these regional patterns described above are also evident in Figure 4, which visualizes country based numbers of pharmaceutical occurrences in surface waters, groundwater, tap water, and/or drinking water. More than 100 different pharmaceutical substances have been detected in several European countries and USA. More than 30 different pharmaceutical substances have been found in Western and Eastern Europe, Asia and the Pacific, and also in GRULAC. In most regions of the Pacific, Africa, and Eastern Europe less or equal than 30 substances have been detected.

However, lower occurrence numbers do not automatically mean that less pharmaceutical substances persist in the environment. For example, when comparing the sum of national MECs, e.g. for Spain, with Figure 4, it becomes evident that high correlations between the number of measurements and detection in the environment exist. Therefore, it can be stated that the more measurements are conducted, the more pharmaceutical substances will be found in the environment. Pharmaceuticals in the environment can thus be regarded a global problem, which also affects developing and emerging countries as similar patterns as in industrialized countries have been highlighted.

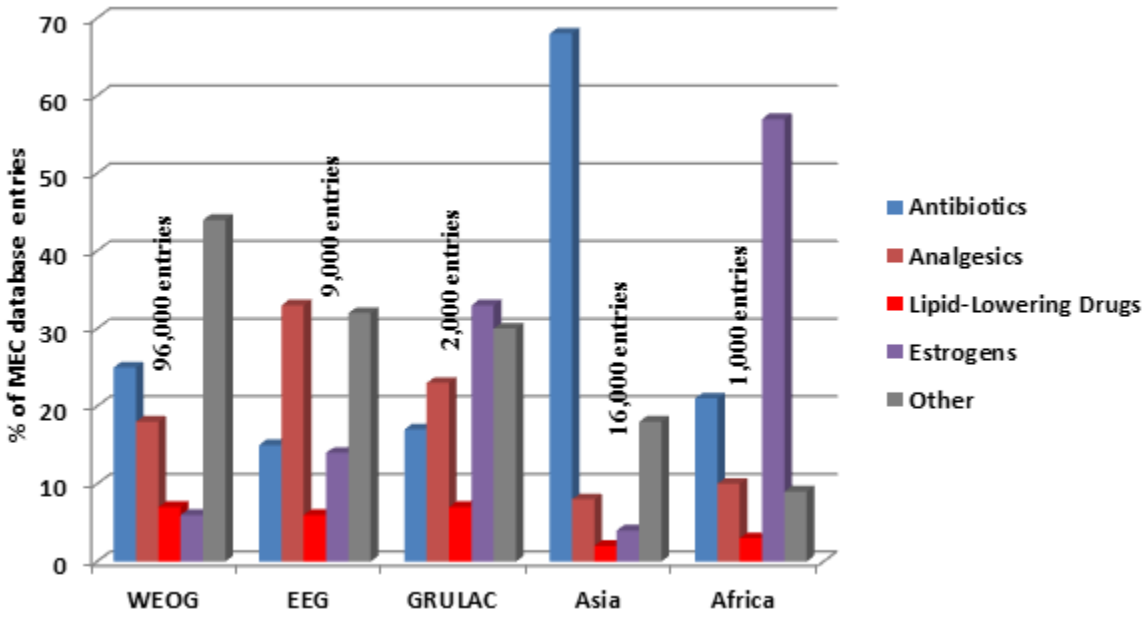
In summary, global maps for different environmental matrices have been created (see Figure 1 for drinking and tap water, Figure 2 for sewage, WWTP influent, effluent, sludge and Figure 3 for soil and manure). The largest amount of data has been available for the wastewater matrices. Here, 559 different pharmaceutical substances have been detected globally, whereas high regional occurrences correlate with high number of measurements, for example in Canada and China. In general, a close relationship between occurrences in wastewater and surface waters can be assumed, as most sewage measurements were conducted in WWTP effluents (see Table 2), which usually discharge directly into surface waters, such as rivers and lakes. For drinking and tap water, less data is available, especially, for developing and emerging countries, which is also apparent in the global map (Figure 1). In Spain and Germany more than 30 pharmaceuticals have been detected, and between 11 and 30 in Canada, China, France, Sweden, and USA. Even in bottled water some pharmaceuticals in trace concentrations ranges have been detected (Bruchet et al. 2005).

4.3 How many and what kind of pharmaceutical substances have been found?

In each UN regional group, at least 38 different pharmaceutical substances have been found in surface water, groundwater or tap/drinking water. More than 100 different pharmaceutical substances have been found in several European countries and USA in the aquatic environment (surface waters, groundwater and/or tap/drinking water) in concentrations exceeding the detection limit of the analytical method employed (Figure 4). In most regions of the Pacific, Africa, and Eastern Europe less or equal than 30 pharmaceuticals have been detected.

The most commonly found therapeutic groups are antibiotics, analgesics, and hormones. Regional differences are evident (see overview in Figure 5) as all UN regions emphasize different measurement priorities, for example antibiotics in Asia, hormones in Africa, analgesics in Eastern Europe, and a vast range of different pharmaceuticals groups in WEOG. However, it needs to be noted that all regions are subject to different main units, as e.g. in WEOG nearly a hundredfold of database entries are available, compared to Africa. Here, even though estrogens only are a minor contributor in WEOG, they still have been measured more often than in Africa, where estrogens are the dominantly measured group.

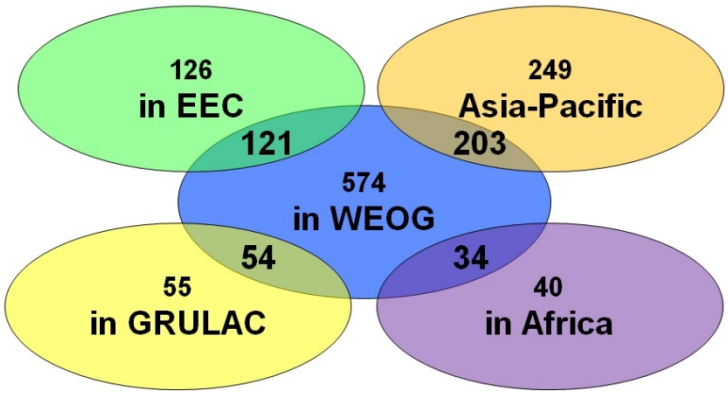
Figure 5: Distribution of therapeutic groups within the MEC-database according to UN regions in relation to the total number of regional MEC-database entries



4.4 Are the same pharmaceuticals detected in each UN regional group?

Globally, 713 different pharmaceutical substances have been analyzed in environmental water samples, of which 631 have positively been detected above the detection limits of the analytical method employed in the publication. This total number includes 127 transformation products out of 142 analyzed. Further analysis showed that in most UN regions very similar substances were found as in WEOG countries (WEOG: 574 out of 646 analyzed (89%); Asia: 249 out of 313 (80%); EEG: 126 out of 205 (61%); GRULAC: 55 out of 84 (65%); Africa: 40 out of 59 (68%)). However, some regional differences are notable, especially in Asia, where primarily in Europe relatively uncommon antibiotics were detected, and in Africa, where additional veterinary growth stimulants (de Jager et al. 2011) and antiviral substances (K'Oreje et al. 2012) were detected (Figure 6).

Figure 6: Number of pharmaceuticals found in the environment within each UN region and overlaps of pharmaceuticals with WEOG group



In total, 16 pharmaceutical substances have been detected in surface, drinking, and groundwater of each UN region (Table 3). Additionally, the antibiotic tetracycline has been measured in WWTP effluent in all UN regions. Diclofenac, which is a widely used analgesic for both human and veterinary application, is the most often pharmaceutical globally found in the environment. In total, it has been detected in surface, groundwater and/or tap/drinking water of 50 countries. In all UN regions, it belongs to the five most often detected pharmaceuticals in the environment. Another four pharmaceutical substances have been found in the environment nearly as often as diclofenac: carbamazepine (antiepileptics), sulfamethoxazole (antibiotics), ibuprofen, and naproxen (both analgesics). Other pharmaceutical substances which have been globally detected in the environment include hormones, such as estrone and ethinylestradiol, and clofibric acid (metabolite of lipid-lowering drug). The list of pharmaceutical substances found in all five UN regional groups is constrained by the low number of measurements in Africa and GRULAC. If the number of measurements in these two UN regions continues to increase, it can be expected that also the number of globally detected pharmaceuticals will increase.

Table 3: Number of countries with positive detection in surface, drinking, groundwater in each UN region

Pharmaceutical	Therapeutical group	Africa	Asia-Pacific	EEG	GRU-LAC	WEOG	Global
Diclofenac	Analgesics	3	8	13	3	23	**50**
Carbamazepine	Antiepileptics	3	6	13	2	24	**48**
Ibuprofen	Analgesics	3	8	10	2	24	**47**
Sulfamethoxazole	Antibiotics	5	9	10	2	21	**47**
Naproxen	Analgesics	2	8	10	2	23	**45**
Estrone	Estrogens	1	10	6	2	16	**35**
Estradiol	Estrogens	2	9	4	2	17	**34**
Ethinylestradiol	Estrogens	1	8	3	2	17	**31**
Trimethoprim	Antibiotics	2	9	3	2	13	**29**
Paracetamol	Analgesics	1	6	4	3	15	**29**
Clofibric acid	Lipid-lowering drug	1	3	5	2	12	**23**
Ciprofloxacin	Antibiotics	1	5	1	2	11	**20**
Ofloxacin	Antibiotics	1	4	1	1	9	**16**
Estriol	Estrogens	1	1	2	1	10	**15**
Norfloxacin	Antibiotics	1	4	1	2	7	**15**
Acetylsalicylic acid	Analgesics	1	4	1	2	7	**15**

4.5 Can pharmaceuticals have ecotoxicological effects at the concentrations found?

The most striking results of analyzing the global database are prevailing concentrations of several pharmaceutical substances reported for the aquatic environment that are within the range known to cause ecotoxic effects in aquatic systems. While similar conclusions have been drawn in other publications (Fent et al. 2006; Bergmann et al. 2011, Hughes et al. 2012, Triebkorn et al. 2014), the global perspective of the established database adds a new dimension to this emerging issue. An example of ecotoxicological effects of eight pharmaceutical substances is provided in Figure 7.

The non-steroid anti-inflammatory drug diclofenac has caused a near-extinction of vultures on the Indian subcontinent, which was caused by the birds' feeding on the carcasses of cattle treated with the anti-inflammatory drug diclofenac (Oaks et al. 2004). In aquatic systems, diclofenac is known to cause damage of inner organs in rainbow trout (Triebskorn et al. 2007). Assessing the compiled database MEC, the weighted-average diclofenac concentrations reported in surface waters exceeds the proposed PNEC of diclofenac of 0.1 µg/L (EC 2013) in 12 countries worldwide, indicating ecotoxicological risks at the examined locations. Further information are provided in the following case study sub-chapter.

EE2 at concentrations of 5-6 ng/L has been demonstrated to cause population collapse of fathead minnow (*Pimephales promelas*) due to feminization of male fish in a whole-lake experiment (Kidd et al. 2007). The feminization of fish due to estrogenic pollution of water bodies has already been reported for several countries worldwide (Harris et al. 2011). According to the database, the maximum EE2 concentrations reported in surface waters exceed the proposed PNEC of 0.01 ng/L (Caldwell et al. 2012) in 28 countries worldwide, also indicating ecotoxicological risks at these locations. The highest concentrations often occur downstream of urban sewage discharge in densely populated areas. Further information are provided in the following case study sub-chapter.

Figure 7: Some selected examples of adverse effects of pharmaceuticals on non-target organisms in laboratory, field, and environmental observations

				
Pharmaceutical	Diclofenac	17α-Ethinylestradiol	Diclofenac	Sulfonamide
Therapeutic group	Analgesics	Synthetic estrogen	Analgesics	Antibiotic
Non-target organism	Vulture (*Gyps bengalensis*)	Fathead minnow (*Pimephales promelas*)	Rainbow trout (*Oncorhynchus mykiss*)	Maize (*Zea mays*) Willow (*Salix fragilis*)
Effects	Population collapse due to renal failure	Population collapse due to feminization of male fish	Strong reactions of liver, kidney, and gills	Adverse effects on root growth. Death of maize at high conc.
Study type	Wildlife	Whole-lake experiment	Laboratory	Greenhouse
Reference	Oakes et al. 2004	Kidd et al. 2007	Triebskorn et al. 2007	Michelini et al. 2012
				
Pharmaceutical	Fluoxetine	Oxazepam	Ivermectin	Enrofloxacin, Ciprofloxacin
Therapeutic group	Antidepressant	Anxiolytics	Veterinary parasiticide	Antibiotics
Non-target organism	Leopard Frog (*Rana pipiens*)	European perch (*Perca fluviatilis*)	Dung fly and beetle	Cyanobacterium (*Anabaena flosaquae*) Duckweed (*Lemna minor*)
Effects	Delayed tadpole development	Altered behaviour and feeding rate	Mortality of eggs and larvae	Growth inhibition
Study type	Laboratory	Laboratory	Laboratory and field	Laboratory
Reference	Foster et al. 2010	Brodin et al. 2013	Liebig et al. 2010	Ebert et al. 2011

Despite these two examples, it must be noted that for most of the 631 different pharmaceutical substances detected in the environment, predicted no-effect concentrations have not yet been established (Fent et al. 2006; Bergmann et al. 2011, Boxall et al. 2012, Triebkorn et al. 2014), preventing

an assessment of the concentrations detected. In the European Union, an Environmental Risk Assessment (ERA) is mandatory for newly marketed drugs (EC 2001a, b), but most commonly used drugs were introduced before the regulation came into force and thus have not been assessed (Küster and Adler 2014).

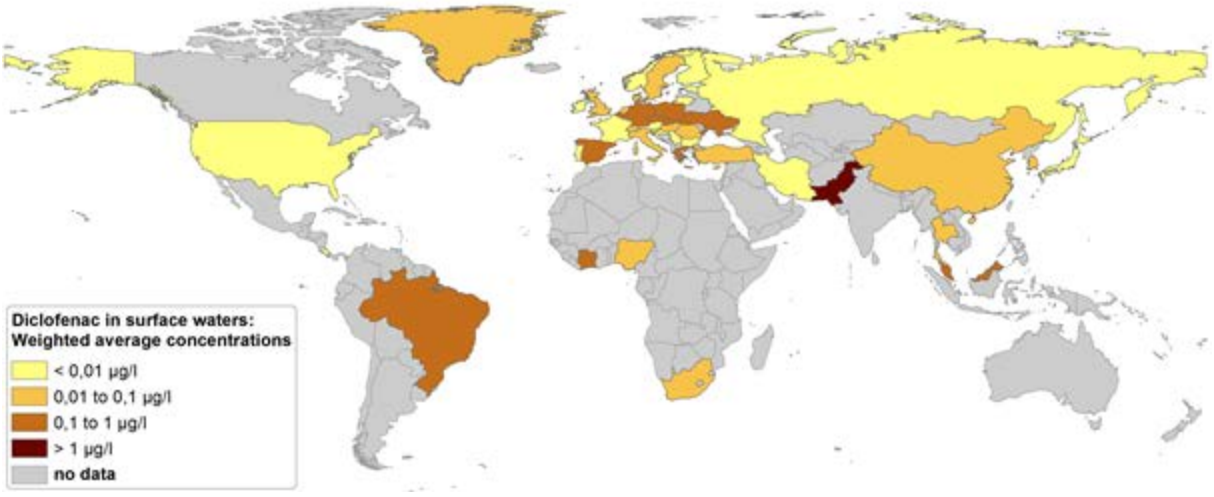
Moreover, the literature review suggests that in many locations several pharmaceuticals are simultaneously occurring in the environment, demanding for new methods to assess the ecotoxicological effects of long-term exposure to low concentrations of mixtures of pharmaceuticals with potential synergistic or antagonistic modes of action, also with respect to the potential presence of other chemical and nonchemical stressors (Boxall et al. 2012).

In addition, if pharmaceuticals are repeatedly detected in drinking water – even at concentrations below what is considered harmful – the public may lose confidence in the overall quality of their drinking water. The precautionary principle calls for actions to minimize the occurrence of pharmaceuticals in drinking water.

Case study: Diclofenac

As diclofenac is the most often detected pharmaceutical in the environment and due to its high ecotoxicological potential, a more detailed analysis of its global occurrence has been conducted. For each country where measurements of diclofenac in surface waters were available, weighted average concentrations have been calculated. As described in Chapter 3.3, only measurements which were defined as single values or average values with a published number of measurements have been considered. The results are illustrated in Figure 8, whereas Figure 9 includes maximum diclofenac concentrations within each country. Generally, a wide global coverage of diclofenac is given, with average concentrations up to 1.55 µg/l (Pakistan). High average concentrations of more than 0.1 µg/l have been found in at least one country of each UN region.

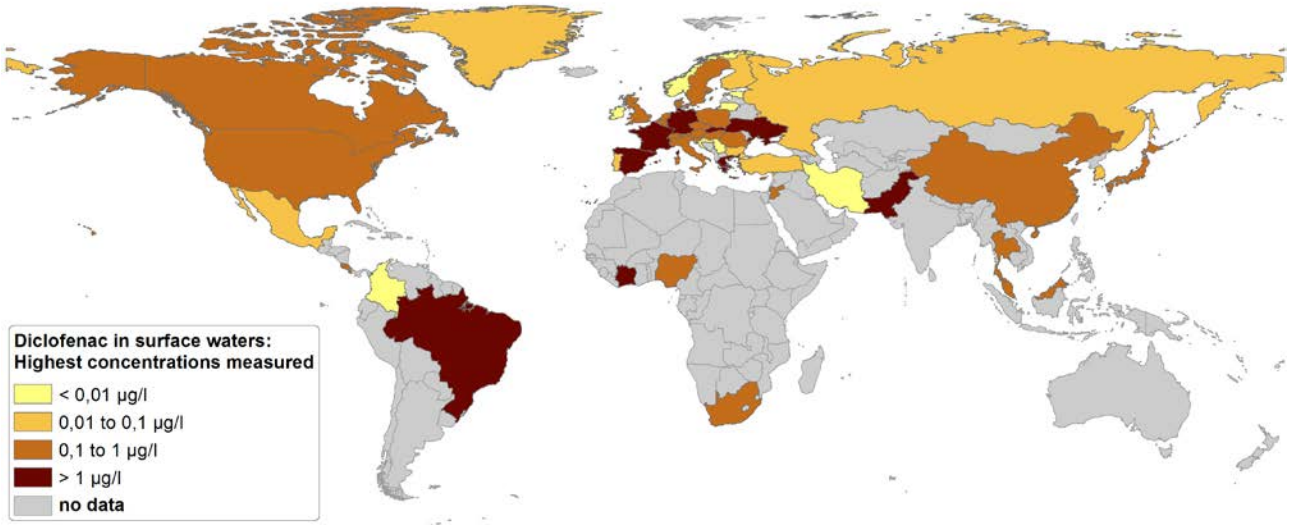
Figure 8: Average weighted diclofenac concentrations in surface water per country



Interestingly, average concentrations for diclofenac could not be calculated for Canadian and Australian surface waters, as for these two countries reported concentrations focused on maximum values and on measurements in wastewater. However, it needs to be noted that any assumptions derived

from these kinds of maps need to be evaluated carefully, as a different number of measurements have been available for each country. For example, average diclofenac concentrations of some countries, such as Germany (0.164 µg/l) can be considered reliable due to the large number of measurements (Germany: 4,137). For some other countries with the same concentration range the average value is based on a very low number of measurements and has to be interpreted carefully, e.g. Malaysia (0.117 µg/l, 2 samples). Therefore, a direct comparison of countries is not suitable and any global concentration map should rather be treated as a visual indicator of global occurrence of pharmaceutical micro pollutants. In general, the more often pharmaceuticals are being measured, the more often they are being detected in the environment. With the majority of measurements being conducted in WEOG (see Figure 84), these countries also feature the highest absolute detection numbers for diclofenac, which is also depicted in Figure 48.

Figure 9: Highest diclofenac concentration in surface water per country



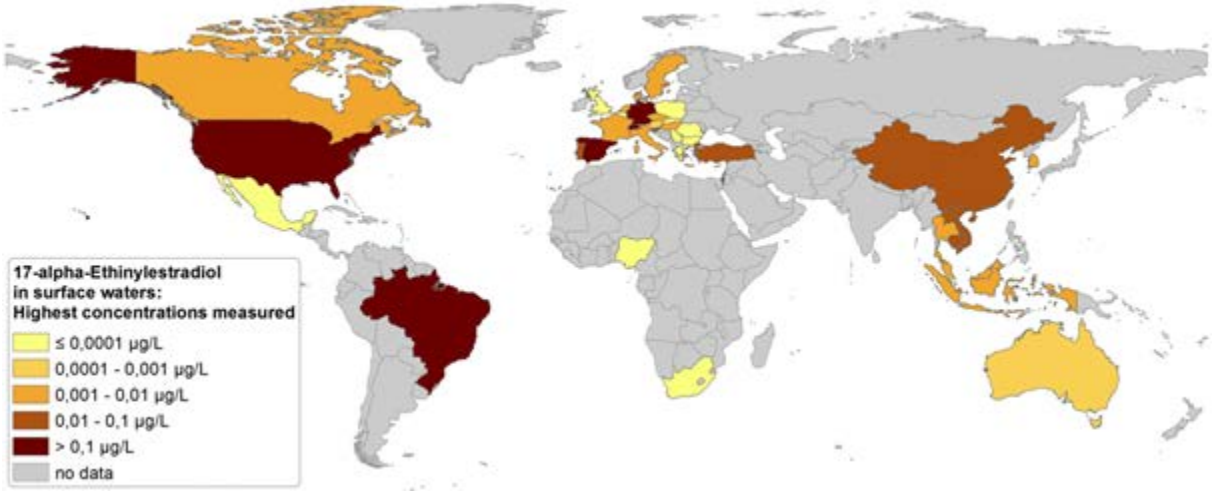
Case study: ethinylestradiol

A second pharmaceutical substance, which has been found in the environment of each UN region, is the estrogen ethinylestradiol, which is being used as a contraceptive pill by 8.9% of all women globally, who are married or in a union (UN 2013). Ethinylestradiol can cause ecotoxicological effects at population level at low concentrations of 0.01 ng/L (Caldwell et al. 2012; Kidd et al. 2007). Therefore, the global distribution of environmental occurrences has been further investigated. Figure 10 illustrates the highest ethinylestradiol concentrations measured in surface waters of each country. Most measurements have been available in Europe and North America but also South East Asian countries provide a multitude of data sets. More than half of the countries feature maximum concentrations of more than 0.001 µg/l. Globally, the highest concentration has been detected in Brazil with 5.9 µg/l. However, as ethinylestradiol is sold and used in very small doses, this value appears to be unrealistically high. This assumption is also supported by analyzing maximum concentrations within other countries, which are all one magnitude lower than the Brazilian value; for example the second highest maximum concentration has been 0.28 µg/l in Spain. Also, the Brazilian value has been pub-

lished by Machado (2010) as a thesis, which does not necessarily include a quality check, as for example a peer-review in a scientific journal. Nevertheless, this outlier value could theoretically be explained by, for example, an upstream located contraceptive pill production facility, which could divert untreated sewage directly into the river where the water sample was taken. Therefore, in the database, this entry was flagged as "questionable" but not deleted. Next to Brazil and Spain, high maximum ethinylestradiol concentrations above 0.1 µg/l have also been detected in the United States, Germany, and Switzerland. In Africa, very few water samples in only two countries have been tested for ethinylestradiol.

A comprehensive table, which lists the average and maximum concentrations of all 631 pharmaceuticals for each environmental matrix, including the total number of measurements, can be found in the external supplement of aus der Beek et al. (2016).

Figure 10: Numbers on maximum ethinylestradiol concentrations in surface waters per country



4.6 What are the dominant emission pathways?

To mitigate ther future entry of pharmaceuticals into the environment, it is necessary to analyze their emission pathways. Thus, whenever an emission source had been listed in the publication from which data had been transferred, it has also been added to the specific database entry. However, as a result, only 13% of the database entries include information about emission sources. This can be explained by the large number of samples taken from surface waters and waste water treatment plants (see Table 2), where most often it is unknown which kind of pollutants have been introduced to the water system at any location upstream the river or the sewage canal. These samples need to be considered to include integrative information about all upstream emissions, which cannot be separated into single emission pathways.

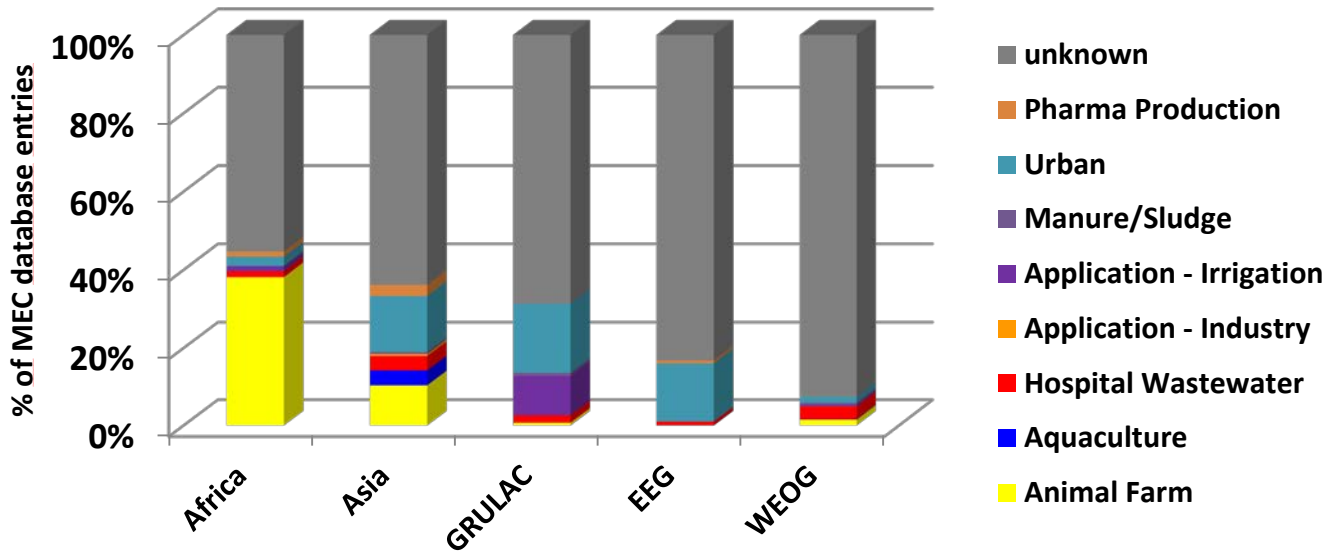
From the 13% known emission sources, urban wastewater is the dominant emission pathway (see Figure 11). As most pharmaceuticals are being used at home, and considering that 54 % of the global population lives in urban areas (WHO 2014), this pattern can be regarded reasonable. The second most often listed emission sources are hospitals. Here, a multitude of different pharmaceuticals, often at high concentrations (Orias & Perrodin 2013) can be found in the sewage outlet. Most hospitals do not include on-site sewage treatment and are connected to urban sewage systems. However, urban

wastewater treatment plants have not been designed to remove pharmaceuticals, which in addition cannot be considered a homogeneous group of chemicals, as their sorption coefficients, transformation kinetics and half-life largely vary between different pharmaceutical substances. Therefore, pharmaceuticals from hospital sewage can reach rivers and lakes in sometimes high concentrations, for example x-ray contrast agents, which are designed as stable chemical compounds (Weissbrodt et al. 2009). The third most often listed emission sources for pharmaceuticals are animal farms. Here, veterinary pharmaceuticals are used to treat or prevent diseases. Via urine and feces, any remaining pharmaceutical substances and transformation products reach soil, drainage canals, groundwater, and finally open water bodies, such as rivers and lakes. Some pharmaceuticals, as for example the analgesic diclofenac and the antibiotic sulfamethoxazole, are used for both veterinary and human application. Here, it is not possible to derive their origin from water samples. Further important emission sources, which can locally cause an increase of pharmaceutical concentrations in the environment, are pharmaceutical manufactures, aquaculture, and irrigation with waste water. Especially, pharmaceutical manufactures can cause high concentrations in the mg/l range in rivers adjacent to production facilities (Cardoso et al. 2014). Many pharmaceutical manufacturers are located in developing and emerging countries, where environmental legislation and environmental law enforcement are often not defined as high priority measures. Therefore, most high concentrations in the database are connected to pharmaceutical production in these countries. There are of course exceptions, for example, Dolar (2012) have reported a maximum concentration of 27.68 mg/l for the antibiotic trimethoprim in the sewage of a Croatian pharmaceutical production facility.

Most emission sources have been available for WEOG and Asia, whereas regional differences exist. For example, in Asia, more data on pharmaceutical concentrations from aquaculture, i.e. fish farms, and agriculture have been published, whereas more data on hospital sewage has been available for WEOG. Nevertheless, as most database entries have been available for WEOG (see Figure 5), a normalization of these patterns to the same main units has not been possible and any derived assumptions on regional differences need to be evaluated carefully. For example, Africa features about 1,000 MEC-database entries. Therefore, already few measurements can cause a high percentage within the emission sources, especially as for many entries the source is unknown. In contrast, for WEOG with about 96,000 entries more reliable conclusions concerning emission sources can be drawn. Also, this contrast shows that a direct comparison between UN regions only allows limited derivations.

Figure 11 also depicts the regional differences of emission sources. For example, in Africa, many samples have been measured close to animal farms, and in Asia, more aquaculture samples have been reported than in any other UN regional group. Please note that due to the different amount of MEC database entries for each UN region, a direct comparison of emission sources is not recommended and may lead to biased derivations.

Figure 11: Emission sources according to the MEC database



4.7 Are monitoring programs affected by biases?

Most monitoring data in the database rely on a limited number of grab samples at individual sampling sites, with limited long-term monitoring data. Therefore, consistent data sets describing potential seasonal or annual dynamics are scarce. Also, within each country, monitoring has often focused on a limited number of sampling sites; the criteria for their selection remain unclear in many publications. Therefore, it must be doubted that the reported MEC provide a representative picture of the prevailing concentrations, neither in terms of average nor maximum concentration. A possible explanation for the lack of robust sampling strategies can be attributed to the relatively high portion of studies published in analytical chemistry journals focusing on method development rather than representative sampling strategies (Hughes et al. 2012).

While reliable analytical methods have been established at laboratories worldwide, there is currently no internationally standardized analytical protocol for pharmaceuticals in different environmental matrices. Different limits of detection may result in biases that technologically advanced countries report more positive detections than other countries, in which the pharmaceuticals occurring at the same concentration range are below detection limits of the analytical method available.

Another bias may be caused by regional focuses on monitoring specific therapeutic groups. Regional patterns in the dominantly measured therapeutic group (Figure 4) could falsely be misinterpreted that, for example, estrogens are the largest pharmaceutical problem in the African environment, as they are being more often reported than other therapeutic groups. Indeed, estrogens seem to be more often measured than other groups because two South African scientific communities have focused on developing methods for the detection of estrogens. This pattern is further increased by the so called Matthew Effect (Daughton 2014), which states that those substances, which have already been detected by one research group, will be further investigated by other research groups.

In addition, it can be assumed that globally more than 3,000 different pharmaceutical substances exist for use in human and veterinary medicines (WHO 2014). This number does not include the nu-

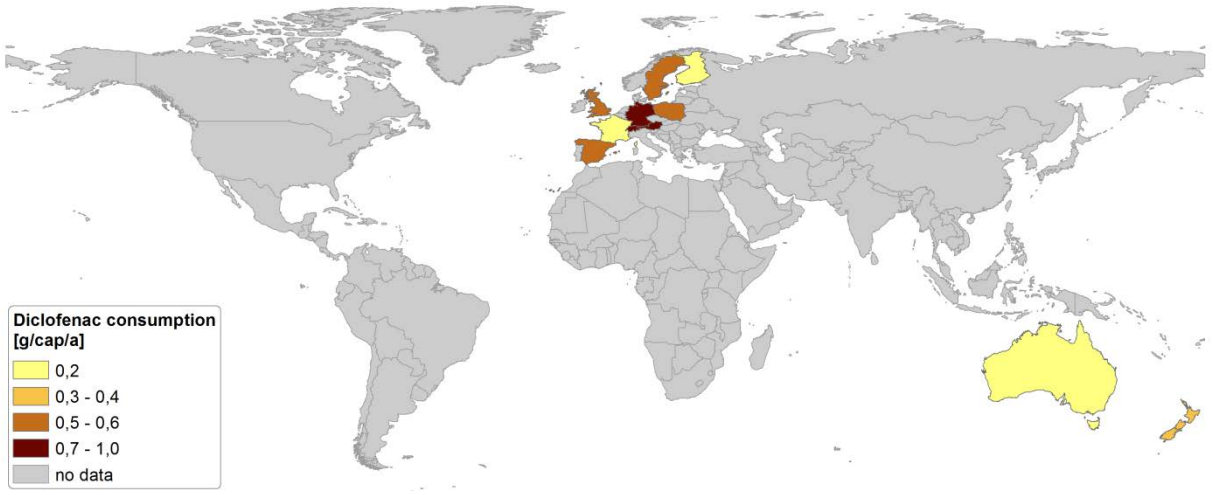
merous often unknown transformation products. This study has shown that, so far, analytical procedures have been developed for 713 substances and transformation products. More than 75% of all pharmaceutical substances cannot be, or have currently not been, analyzed in the environment. However, it needs to be mentioned that the most often used and top selling substances are included in the analytical methods already developed.

4.8 Do consumption data show regional differences in pharmaceuticals availability and use? Can consumption data help to substitute MEC data?

As urban wastewater can be considered the dominant emission pathway, global pharmaceutical consumption patterns have been further investigated. Similar to the MEC-database, a database with country-specific entries for each pharmaceutical substance, consumption amount, and year of consumption has been set up. Only those data points referring to metric units, such as kg/a, have been transferred to the consumption database. Some publications have used Defined Daily Doses (DDD) to provide information about the consumption of specific pharmaceutical substances. However, as additional information was missing, most often no metric conversion had been possible. Also, the Endnote© library, which includes all literature sources of the MEC-database (see Chapter 3.2), has been extended to incorporate all sources of the consumption database as well. In total, 69 publications have been identified, which provide consumption data for at least one pharmaceutical and country. From these publications about 4,500 database entries have been transferred to the database. However, in many publications only partial consumption/sales are reported as they are provided for specific sectors, such as outpatients, hospitals, prescriptions, veterinary, community, and pharmacies. Therefore, when analyzing the data it needs to be kept in mind that not all of the database entries refer to total national consumption values. The database provides consumption data for 257 different pharmaceuticals, while the database MEC is nearly three times as large. Also, consumption data is not equally distributed in space and time. In Africa, only 156 database entries are available for two countries (Kenya and Morocco), whereas 81 entries are available for Asia, unfortunately none for China, which is the largest provider of Asian MEC data. Within EEG, 186 data points can be found, for a total of eight countries. Interestingly, GRULAC offers a far better database with 619 entries for ten countries. WEOG has the largest share of the consumption database with nearly 3500 data points for 18 countries.

The temporal range of the consumption database includes all years between 1984 and 2012, whereas the majority of entries are listed for the last decade. The most often reported pharmaceutical substance is amoxicillin (142 entries), followed by trimethoprim (123), erythromycin (103), ciprofloxacin (92), vancomycin (91), clarithromycin (79), and azithromycin (76). This ranking also shows that the therapeutic medication groups within the consumption database do not follow a normal distribution, as each of the ten most often reported pharmaceutical substances belongs to the antibiotic group. Therefore, antibiotic consumption has been more often reported (more than 3,000 database entries) and analyzed than all the other therapeutic groups together. The largest values within the database have been reported for paracetamol for the United States (5,790 tons in 2002) and France (3,303 tons in 2005) as well as for chlortetracycline in South Korea (2,763 tons in 2005 for veterinary purposes). The smallest value has been reported for pirlimycin in the Netherlands (0.3 g in 2009 for veterinary purposes).

Figure 12 : Country survey on publicly available data on diclofenac consumption per capita



National diclofenac consumption data were only available for certain WEOG countries and Poland (Figure 12). When comparing with national weighted-average diclofenac concentrations measured in the environment (Figure 8), it becomes apparent that any analysis is limited to European countries, as only here data for both factors, environmental occurrence and consumption data, is available. Furthermore, except for diclofenac, only few other pharmaceutical substances feature an overlap of occurrences in the environment with consumption data for more than 10 countries. Thus, as long as no more consumption data will be made publically available, especially outside WEOG, it will be difficult to predict environmental concentrations of pharmaceuticals from consumption data on a national scale. Generally, the direct linkage of environmental occurrence and consumption of a pharmaceutical substance is complex, as a variety of factors, such as sorption, type of wastewater treatment, environmental conditions, half-life, and disposal schemes need to be considered. A better availability of consumption data would help to prioritize pharmaceuticals for monitoring and testing.

4.9 What are the conclusions on Global Occurrence of Pharmaceuticals in the Environment?

The literature review has demonstrated that pharmaceutical substances occur globally in the environment, in industrialized, developing, and emerging countries covering all five UN regional groups. More monitoring results in developing and emerging countries have become available in recent years including analyses conducted by ourselves (e.g. Shimizu et al. 2013; K'Oreje et al. 2012). We thus oppose the conclusion of others stating there would be little evidence for pharmaceutical pollution outside North America, Europe, and China. Part of the discrepancy in recent review articles is attributed to a global bias in publication behavior, missing relevant evidence from developing and emerging countries when restricting literature reviews to high-ranking English-language journals.

Nevertheless, the assessment of the database MEC has shown that there is order-of-magnitude more data available for WEOG countries than for other UN regional groups. More monitoring programs are thus needed globally to fully assess the occurrence and prevailing concentrations, especially to enhance coverage in developing and emerging countries. Compared to surface water samples, monitor-

ing of pharmaceutical in groundwater, tap/drinking water, and soil are underrepresented in these regions.

However, one main conclusion of the literature review is that the more often pharmaceuticals are being measured in a country, the more often they are being detected. The smaller spectrum of different pharmaceuticals detected in Africa and GRULAC is thus likely not caused by lower pollution levels but a result of the lack of environmental laboratories equipped and funded to monitor pharmaceuticals in environmental matrices. The required instrumental equipment, such as gas or liquid chromatography coupled to tandem mass spectrometer, is expensive both to acquire and maintain, and thus, nearly all water samples reported for Africa in the database (except for South Africa) have been analyzed in industrialized countries (K'Oreje et al. 2012). Therefore, international cooperation and knowledge transfer is a prerequisite to sharpen the picture on prevailing concentrations of pharmaceuticals in developing countries.

The underrepresentation of some Asian, African, and South American countries in the database MEC is troublesome for a number of reasons. Some of these countries belong to the most densely populated regions of the world, potentially exhibiting high pharmaceutical concentrations in draining streams due to high consumption and low dilution of discharged sewage. The pharmaceutical manufacturing sector has shifted to countries with lower production costs, potentially leading to increased emissions from manufacturing in these countries (Larsson 2014). In addition, key differences between the low-, middle- and high-income countries cover factors such as population and demographics, manufacture, prescriptions, treatment, disposal, and reuse of wastewater. The differences in populations (both human and animal), urbanization of mega cities, sewer connectivity, creeks with high sewage fractions, and other factors have revealed that the environmental compartments receiving the bulk of pharmaceutical substances differ markedly between low- and high-income countries. High sewer connectivity in developed countries allows capture and treatment of the waste stream (point-source). However, in many low- or middle-income countries, sewerage connectivity is generally low and in some areas waste is collected predominantly in septic systems. Consequently, the diffuse-source impact, such as on groundwater from leaking septic systems or on land due to disposal of raw sewage or septage, may be of greater concern (Kookana et al. 2014).

5 Regional Data Availability on Pharmaceuticals in the Environment

The database has been evaluated on the scale of UN regions to assess and compare regional data availability (see also Chapter 4.2 and4.4). Different factors influence the usage of pharmaceuticals as well as their entry into the environment. According to Kookona et al. (2014) the following factors, amongst others, are relevant: (I) population density; (II) income; (III) availability of pharmaceuticals; (IV) sanitary infrastructure; (V) agricultural methods; and (VI) healthcare systems and availability.

5.1 African Group

The African Group consists of 54 members, of which most are being categorized as develop-ing or emerging nations. The literature review includes 23 publications, which provide MEC data on the occurrence of pharmaceuticals in one of the studied matrices in Africa, most of which have been published about South Africa. In total, 1159 MEC database entries have been added for 59 different active pharmaceutical substances, sampled between 1998 and 2013. The vast majority of database

entries relates to South Africa (62 %), followed by Nigeria (20 %), Kenya (8 %), Cote d'Ivoire (8 %), Tunisia (1.3%), Zimbabwe (0.4 %), Tanzania (0.2 %), and Ghana (0.1 %). Most of the Nigerian data were analysed by IWW within the UBA funded project "Analysis of Environmental Samples from Nigeria with respect to relevant Pharmaceutical Agents". No data on pharmaceuticals in the environment has been found in the literature for the remaining 46 African countries. This also depends on the fact that very few African countries, such as South Africa, possess the laboratories necessary to detect active pharmaceutical substances at trace concentration levels. For example, the water samples collected in Kenya and Ghana have been analyzed in Belgium, Finland, and Japan.

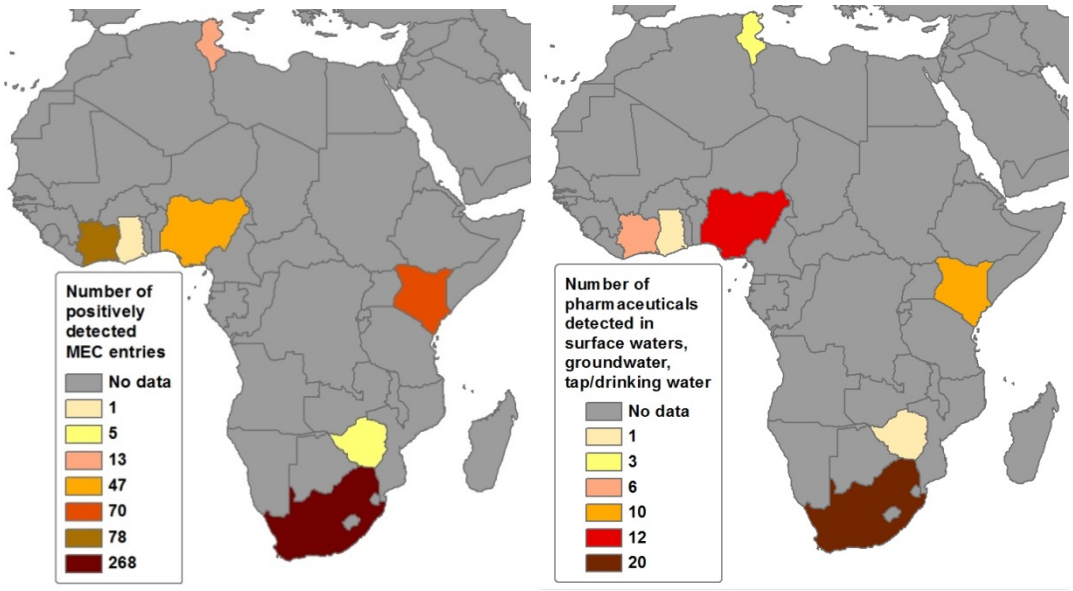
Estrone is the most frequently sampled active pharmaceutical substance, followed by 17-beta-estradiol, estriol, and 17-alpha ethinylestradiol. This short ranking already shows that the most common compound group is hormones with 57% of all analyzed samples, next to antibiotics (21 %) and analgesics (10 %). Also, five new estrogenic pharmaceutical substances, which were not included in the WEOG database, have been detected in Africa: methyltestosterone, nandrolone, trenbolone, and zilpaterol. The latter drug is used for hormonally induced growth in cattle production. Within the MEC database, 58 % of the samples have been collected from surface waters, 17 % from wells, and 15 % from wastewater. In total, 675 MECs (58 %) were below the specific technical detection level of the individual pharmaceuticals. For the positive detections, 50 % feature concentrations of less than 0.1 µg/L; 28 % fall into the intermediate range of 0.1 to 1 µg/L, and 22 % show high concentration levels of more than 1 µg/L. Furthermore, 13 of the collected samples feature extremely high values in the mg/L range. It needs to be mentioned that these MECs were observed in the wastewater of a pharmaceutical production site in Kenya. It remains unclear if this highly contaminated water undergoes further treatment or is released to the environment. Other high concentration levels have been found in a cattle feeding pond in South Africa (23.7 µg/L zilpaterol) and in the Nairobi River, Kenya (21 µg/L sulfamethoxazole).

National summary of the African MEC and literature database:

1. South Africa 713 MECs (15 publications)
2. Nigeria 231 MECs (2 publications)
3. Kenya 96 MECs (3 publications)
4. Cote d'Ivoire 96 MECs (1 publication)
5. Tunisia 15 MECs (1 publication)
6. Zimbabwe 5 MECs (1 publication)
7. Tanzania 2 MECs (1 publication)
8. Ghana 1 MEC (1 publication)

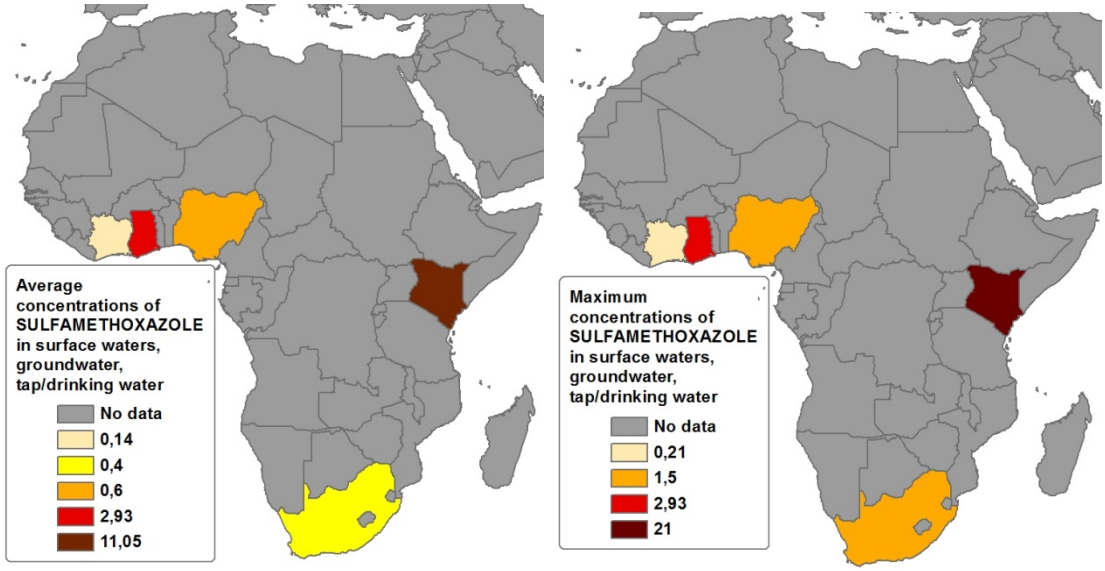
This relatively small number of reports is also shown as a map in Figure 13. Most data and thus also occurrences have been reported for South Africa. Here, several research groups have set up laboratory equipment to measure pharmaceutical substances in the environment.

Figure 13: Number of pharmaceutical occurrences (left) and number of pharmaceuticals found in surface, drinking, and groundwater (right) in the UN regional groupf of Africa



One of the most often measured pharmaceuticals in the UN regional group of Africa is the antibiotic sulfamethoxazole. Average and maximum concentrations in surface, drinking, and groundwater are depicted in Figure 14. In all countries, where sulfamethoxazole has been detected, the average concentrations are in the range of 0.1 to 11 µg/l. Maximum concentrations are in a similar range, which is caused by the small amount of data sets available. As the PNEC of sulfamethoxazole has been reported at 0.1 µg/l (Knacker et al. 2008), even average concentrations are in a range where risks for aquatic organisms are expected.

Figure 14: Average (left) and maximum concentrations (right) of the antibiotic sulfamethoxazole found in surface, drinking, and groundwater in the UN regional groupf of Africa



5.2 Asia-Pacific Group

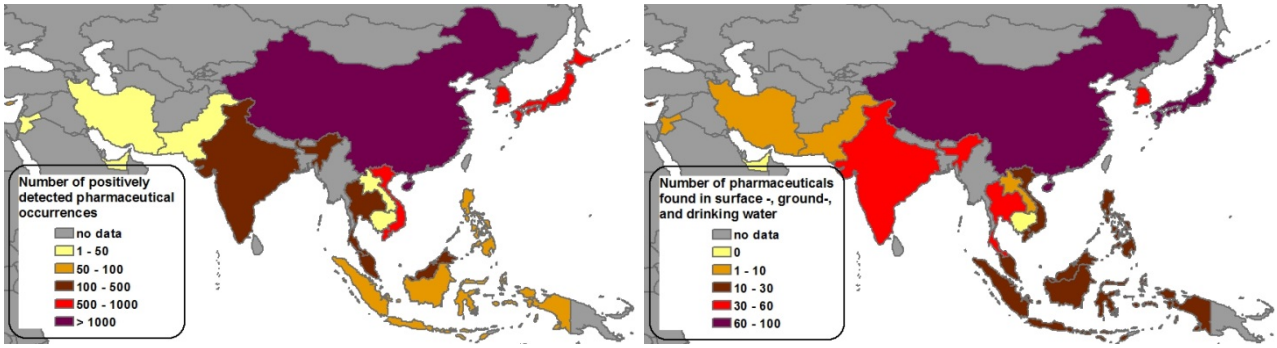
The Asian-Pacific group consists of 53 member countries. Our review has found MEC data for 16 countries in 145 publications with a total of 15,664 database entries. The literature review provided a large number of publications on MECs in China. We have evaluated 66 different publications featuring 8239 MEC data points in different regions of China. This includes also data measured by IWW at the Three Gorges Reservoir at the Yangtze River. The second most MEC entries for Asia are available for Vietnam (2144), followed by South Korea (1629), Japan (1286), and India (932). In India, the high concentrations of pharmaceuticals measured in the WWTP outflow of production facilities have received large media attention. Meanwhile, several publications are available providing data also on river, lake and well water close to pharmaceutical production sites, e.g. in the region of Patancheru, which shows high river water concentrations downstream of the production facility. This is relevant, since a large share of the globally sold pharmaceuticals is produced at least partly in Patancheru (e.g., 31% of all Swedish products; Larsson and Fick 2009). Therefore, maximum concentrations in Asia are high, with 37 entries in the mg/L range. The largest values have been found in South Korea (43.9 mg/L lincomycin) and Patancheru in India (31 mg/L ciprofloxacin), both near pharmaceutical production sites. MEC publications in Asia generally focus on antibiotics as 68 % of all reported values fall into this therapeutic group. 57 % of all MECs have been reported as positive detections, from which 49 % have been measured in sewage matrices and 35 % in surface waters. 52 % of all MECs are below 0.1 µg/L, 28 % are between 0.1 µg/L and 1 µg/L, and 20 % are higher than 1 µg/L.

National summary of the Asian MEC and literature database:

1. China 8,239 MECs (66 publications)
2. Vietnam 2,144 MECs (5 publications)
3. South Korea 1,629 MECs (17 publications)
4. Japan 1,286 MECs (34 publications)
5. India 932 MECs (8 publications)
6. Thailand 366 MECs (5 publications)
7. Philippines 238 MECs (1 publication)
8. Malaysia 217 MECs (5 publications)
9. Indonesia 173 MECs (2 publications)
10. Jordan 76 MECs (2 publications)
11. Singapore 67 MECs (5 publications)
12. Pakistan 30 MECs (5 publications)
13. United Arab Emirates 24 MECs (1 publication)
14. Iran 17 MECs (2 publications)
15. Cambodia 3 MECs (1 publication)
16. Laos 3 MECs (1 publication)

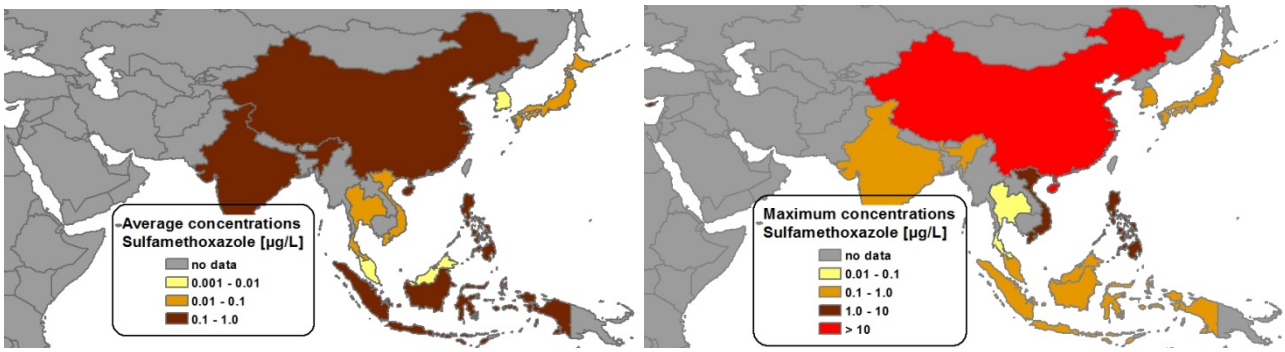
These numbers are also well depicted in Figure 15, which shows the number of occurrences of pharmaceuticals as a map for Asian and Pacific countries.

Figure 15: Number of pharmaceutical occurrences (left) and number of pharmaceuticals found in surface, drinking, and groundwater (right) in the UN regional groupf of Asia and the Pacific



One of the most often measured pharmaceuticals in the UN regional group of Asia and the Pacific is the antibiotic sulfamethoxazole. Average and maximum concentrations in surface, drinking, and groundwater are depicted in Figure 16. In most countries, where sulfamethoxazole has been detected, the average concentrations are in the range of 0.1 to 1 µg/l. Maximum concentrations are usually one to two orders of magnitude higher. Thus, even average concentrations are higher than the PNEC of 0.1 µg/l for sulfamethoxazole (Knacker et al. 2008).

Figure 16: Average (left) and maximum concentrations (right) of the antibiotic sulfamethoxazole found in surface, drinking, and groundwater in the UN regional group of Asia and the Pacific



5.3 Latin American and Caribbean Group (GRULAC)

The Latin American and Caribbean Group (GRULAC) consists of 33 member countries. The literature review includes 59 publications, which provide MEC data on the occurrence of pharmaceuticals in Latin America.

In total, 2247 MEC entries have been included in the database for 86 different active pharmaceutical substances, sampled between 1996 and 2012. The database entries relate to Brazil (55 %), Mexico (38.5 %), Costa Rica (2.5 %), Colombia (2.1 %), Puerto Rico (0.9 %), Venezuela (0.6 %), and Argentina (0.4 %). Just as in Africa, the most commonly analyzed substances fall within the estrogen group

(33 %), next to analgesics (23 %), and antibiotics (17 %). The most often detected pharmaceutical substance of all 1182 positive MEC entries are 17-beta-estradiol (11 %), diclofenac (8.5 %), naproxen (7.8 %), 17 alpha-ethinylestradiol (7.1 %), and estrone (6.7 %). Within the MEC database, 31 % of the samples refer to sewage and 29 % to surface waters. 1065 MECs are below the specific technical detection level of the individual pharmaceutical. About 60 % of the positively detected values feature concentrations below 0.1 µg/L, 15 % indicate intermediate concentrations of 0.1 to 1 µg/L, and another 15 % have high concentration levels of more than 1 µg/L. The highest MEC value of 589 µg/L is reported for dexamethasone in the Brazilian Ceara River, followed by 203 µg/L paracetamol in Mexican urban sewage, and 155 µg/L of ciprofloxacin in untreated sewage of the hospital of the University of Santa Maria in Brazil in the year 2003.

National summary of the GRULAC MEC and literature database:

1. Brazil 1234 MECs (44 publications)
2. Mexico 868 MECs (10 publications)
3. Costa Rica 56 MECs (1 publication)
4. Colombia 48 MECs (1 publication)
5. Puerto Rico 20 MECs (1 publication)
6. Venezuela 13 MECs (1 publication)
7. Argentina 8 MECs (1 publication)

5.4 Eastern European Group (EEG)

The Eastern Europe Group (EEG) consists of 23 members. Totally, 59 important publications have been identified. Here, especially the NORMAN database (Network Of Reference laboratories for Monitoring of emerging environmental pollutANts), which has been established in the EU-FP6 activity, proved to be an important data source. The literature analysis has resulted in MEC data for 13 countries. However, the data is unequally distributed among these countries. The majority of database entries can be found for Slovakia (27 %), followed by Czech Republic (16 %), Slovenia (13 %), Croatia (11 %), Poland (8.3 %), Hungary (6.6 %), Romania (4.7 %), Serbia (4.1 %), Lithuania (3.9 %), Bulgaria (2.1 %), Estonia (1 %), Russia (0.9 %), and Ukraine (0.7 %). Totally, 8,809 MEC records from 206 different active pharmaceutical substances have been included in the database. The most frequently analyzed compound is ibuprofen, next to diclofenac, pentoxifylline, naproxen, estrone, and carbamazepine. Concerning the compound groups, analgesic, antibiotic, and estrogen drugs dominate, which clearly is related to the high number of the specific active pharmaceutical substances mentioned above. Half of the samples have been taken from sewage matrices, and 47 % from surface waters. About 59 % of all samples are below the specific technical detection level of the individual pharmaceuticals. With respect to the remaining positive MEC database entries, about 62 % feature a concentration level of less than 0.1 µg/L. 25 % fall into the intermediate range of 0.1 to 1 µg/L, and 13 % have high concentration levels of more than 1 µg/L. The six highest concentrations have been found in Croatian sewage near a pharmaceutical production site: 28.5 mg/L febantel, 27.7 mg/L trimethoprim, 17.5 mg/L ciprofloxacin, 13.6 mg/L dexamethasone, and 9 mg/L sulfamethoxazole.

National summary of the EEG MEC and literature database:

1. Slovakia 2388 MECs (3 publications)
2. Czech Republic 1396 MECs (15 publications)
3. Slovenia 1174 MECs (12 publications)
4. Croatia 1004 MECs (16 publications)
5. Poland 732 MECs (11 publications)
6. Hungary 585 MECs (10 publications)
7. Romania 413 MECs (7 publications)
8. Serbia 364 MECs (4 publications)
9. Lithuania 342 MECs (2 publications)
10. Bulgaria 181 MECs (3 publications)
11. Estonia 85 MECs (3 publications)
12. Russia 81 MECs (4 publications)
13. Ukraine 64 MECs (1 publication)

5.5 Western European and Others Group (WEOG)

WEOG consists of 31 countries, while MEC data has been reported for 28 countries. As most analytical methods have been developed in this UN region, it is no surprise that most publications and MECs have been reported here. In total, 730 publications have been evaluated, from which 95,882 MEC database entries have been extracted. Most database entries can be found for the Netherlands, even though only 16 publications have been analyzed. However, NORMAN provided many single value data points, which explains the large number of Dutch MECs. Germany features the second most entries from 221 publications, followed by Spain, the United States, Belgium, Sweden, Switzerland, Canada, United Kingdom, and France. 646 different pharmaceutical substances have been analysed in the aquatic environment, of which 574 have been detected. The most common therapeutical groups are antibiotics (25 % of all MEC entries) and analgesics (18 %), while the most often positively detected pharmaceuticals are diclofenac, ibuprofen, and carbamazepine. In total, 45 % of all MEC entries feature positive detections, of which 60 % feature a concentration level of less than 0.1 µg/L. 28 % fall into the intermediate range of 0.1 to 1 µg/L, and 12 % have high concentration levels of more than 1 µg/L. The most analysed environmental matrices are surface waters (49 % of all MEC entries) and sewage (39 %). The highest concentrations have been found in untreated Spanish sewage with values of 299 mg/L for naproxen, 214 mg/L amitriptyline, and 188 mg/l for diclofenac.

National summary of the WEOG MEC and literature database:

1. Netherlands 17,547 MECs (16 publications)
2. Germany 16,343 MECs (221 publications)
3. Spain 13,092 MECs (83 publications)
4. USA 9,515 MECs (143 publications)

5. Belgium 5,059 MECs (13 publications)
6. Sweden 4,728 MECs (29 publications)
7. Switzerland 3,999 MECs (47 publications)
8. Canada 3,886 MECs (64 publications)
9. U. Kingdom 3,450 MECs (45 publications)
10. France 3,349 MECs (41 publications)
11. Portugal 2,964 MECs (18 publications)
12. Italy 2,774 MECs (33 publications)
13. Australia 2,508 MECs (25 publications)
14. Greece 1,548 MECs (21 publications)
15. Finland 1,373 MECs (16 publications)
16. Austria 1,041 MECs (17 publications)
17. Norway 733 MECs (15 publications)
18. Ireland 418 MECs (8 publications)
19. Denmark 408 MECs (14 publications)
20. Turkey 311 MECs (8 publications)
21. Luxembourg 283 MECs (5 publications)
22. Cyprus 220 MECs (2 publications)
23. New Zealand 190 MECs (2 publications)
24. Israel 172 MECs (12 publications)
25. Faroe Islands 69 MECs (1 publication)
26. Greenland 49 MECs (1 publication)
27. Iceland 46 MECs (1 publication)
28. Malta 27 MECs (1 publication)

6 Strategies of Action under SAICM

The analyses of the global MEC database have shown that pharmaceuticals occur globally in the environment with certain pharmaceuticals prevailing at concentrations above PNEC at certain locations, mainly in surface waters. While not yet addressed by an international agreement or arrangement, various stakeholders have proposed options for action and / or undertaken actions to reduce the emission of pharmaceutical substances into the environment, mitigate potential ecotoxicological effects, and/or reduce pharmaceutical occurrence in drinking water (e.g., START 2008, Kümmerer & Hempel 2010, WHO 2012, UBA 2012, Boxall et al. 2012, Holm et al. 2013, BIO-IS 2013, Vidaurre et al. 2010). However, ongoing activities need to be coordinated on an international level.

Actions may be country or region specific, due to differing conditions (e.g. environment, infrastructure, etc). Given the undisputable benefits to society of the application of pharmaceuticals in modern medicine, activities must not compromise effectiveness, availability or affordability of medical treatment, especially in countries in which access to health care remains limited. Potential options may best be directed towards preventing or minimizing the entry of pharmaceuticals into the environment or minimizing their persistence and effects on the environment.

The following chapter provides an overview of various strategies of action that have been proposed in the literature. The proposed cooperative actions are restricted to those that fall within the scope of SAICM.

The objective of cooperative actions in SAICM is to "support enabling capacity building and implementation activities in developing countries, least developed countries, small island developing states and countries with economies in transition." It should mobilize resources for enabling activities of national priorities with respect to the work areas set out in the strategic objectives of section IV of the SAICM Overarching Policy Strategy, in particular:

- Development or updating of national chemical profiles and the identification of capacity needs for sound chemicals management;
- Development and strengthening of national chemicals management institutions, plans, programmes and activities to implement the Strategic Approach, building upon work conducted to implement international chemicals-related agreements and initiatives;
- Undertaking analysis, interagency coordination, and public participation activities directed at enabling the implementation of the Strategic Approach by integrating – i.e. mainstreaming – the sound management of chemicals in national strategies, and thereby informing development assistance cooperation priorities.

Chapter 6 is thus directed to initiate a discussion among SAICM stakeholders which of the activities proposed in the literature might be effectively addressed under SAICM.

6.1 Work areas proposed in the literature

The work areas are structured according to the five categories of objectives of the overarching policy strategy under SAICM: (1) measures to support risk reduction, (2) strengthening knowledge and information, (3) governance: strengthening of institutions, law and policy, (4) enhancing capacity building and technical cooperation, and (5) addressing illegal international traffic.

The proposed work areas and selected activities are described in detail below. The various work areas suggested are closely inter-connected (UNEP 2006). Several suggested risk reduction measures will need to be supported by improvements in our knowledge and information on chemicals, governance arrangements, and general practices associated with the sound management of chemicals throughout their life-cycles. Capacity-building and technical assistance in support of the actions of developing countries and countries with economies in transition are essential to making substantive improvements in risk reduction (UNEP 2006). Thus, although each work area is listed under a single principal category in Table 4, it may contribute to several objectives.

6.1.1 Work areas addressing risk reduction (Objective A)

A. Prioritizing action

A work plan to prioritize appropriate action is a prerequisite to identified effective activities. It has been suggested in the proposal for the nomination of pharmaceuticals in the environment as emerging policy issue under SAICM that the Inter-Organization Programme for the Sound Management of Chemicals (IOMC) could be appropriate to develop such a work plan. IOMC is a cooperative partnership among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD, so that each of the nine Participating Organizations could contribute in accordance with their expertise and effective collaboration (WHO 2014). This suggestion has been adopted by ICCM4 and taken up into the resolution on emerging policy issues. In addition, national and local governments need to strengthen monitoring campaigns to identify effected watersheds, relevant concentrations, and potential effects to enable the evaluation of suitable management options for effected watersheds.

B. Cleaner production

Wastewater discharge from production facilities of both the innovative and generic pharmaceutical industry can release substantial amounts of active pharmaceutical substances into downstream aquatic environments (Larsson et al. 2014). Occurrence of pharmaceuticals in rivers have been associated with pharmaceutical production mainly in developing and emerging countries where a large share of global generic pharmaceutical production is hosted but environmental regulation and/or compliance may partly be weak (Larsson et al. 2007; Li et al. 2008; Fick et al. 2009), but relevant emissions exist also in industrialized countries (e.g., Prasse et al. 2010).

Potential activities are to encourage cleaner production and promote the transfer and implementation and adoption of pollution prevention policies and cleaner production technologies, in particular best available techniques and best environmental practices (BAT/BEP), the establishment and/or enforcement of adequate pollution prevention measures at pharmaceutical manufacturing facilities (e.g. wastewater treatment), and/or the extension of Good Manufacturing Practice (GMP) to incorporate environmental quality guidelines.

GMP is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. The guidelines provide minimum requirements that a pharmaceutical must meet to assure that patients are not placed at risk due to inadequate safety, quality or efficacy. WHO´s GMP is used by pharmaceutical regulators and the pharmaceutical industry on a voluntary basis in over one hundred countries worldwide, primarily in the developing world. The European Union's GMP (EU-

GMP) and enforces similar requirements to WHO GMP, as does the FDA's version in the US. Since the 1999 publication of GMPs for Active Pharmaceutical Ingredients by the International Conference on Harmonization (ICH), GMPs now apply in those countries and trade groupings that are signatories to ICH.

Currently, GMP does not cover risks that production of medicinal products may pose to the environment (BIO-IS 2013). In the "Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part II: Basic Requirements for Active Substances used as Starting Materials" it is explicitly stated that the guide as a whole does not cover aspects regarding the protection of the environment. Proposals to take environmental risks into account in GMP guidelines are currently raised by some EU-member states (BIO-IS 2013; Pruden et al. 2013). If GMPs with respect to impacts on the environment are introduced, it is recommended to orchestrate this on the global scale in order to avoid locational economic disadavantages. These disadvantages are not only economic in nature, but also have ethical/social implications, i.e. pollution problem exported to developing countries. It should define threshold concentrations for individual pharmaceuticals in the sewage of the production facilities, which need to be monitored and reported by independent sources (LÄKEMEDELSVERKERT 2011). An environmentally sound, global GMP could lead to a strong reduction of point source emissions into the environment.

C. Procurement in the health care sector

Current procurement policies and practices that promote and protect health while not adversely affecting the environment may be further strengthened. For example, the Joint UN Programme of Green Procurement in the Health Sector develops evidence-based standards on what constitutes "green" procurement in the health sector, supports UN procurement officers, suppliers, and health actors to be able to operationalize green procurement practices (WHO 2014). The activities also involve greenhouse gas accounting for pharmaceutical products and medical devices. WHO's pre-qualifications programme on Quality and Safety of medicines was set up in 2001 to provide quality assurance for UN procured medicines, which represents a significant quantity of medicines in developing countries. Inspection of manufacturing sites is an integral part of the prequalification scheme (WHO 2014). Support is also provided to build local and national medicines regulatory capacity. WHO is also testing the use of environmental safeguards as a means to identify and address environmental and occupational health risks associated with its project-based activities.

D. Prescription/purchase and usage patterns of human medicine

Although the use of medicinal products to meet needs for medication is not questionable, inappropriate and excessive consumption might be at the origin of unnecessary emissions. Promoting the rational use of pharmaceuticals and reducing inadequate prophylactic use of pharmaceuticals could reduce overconsumption, but it is difficult to assess the scale of this phenomenon in practice (BIO-IS 2014). Through consultations and prescriptions, health care professionals need to be sensitive to assess the needs for each patient. Possibly, reducing the amount of over-the-counter sales by promoting sales via prescription only could potentially contribute to the rational purchase and usage of pharmaceuticals. Nevertheless, overconsumption of pharmaceuticals is not an issue in all parts of the world alike.

When purchasing medicines at the pharmacy, drug store, or supermarket, unnecessary large package sizes should be avoided as they increase the probability of inadequate unused drug disposal (also see

chapter 6.1.1K). Appropriate package size could contribute to the minimization of the volume of unused/expired drugs. There are no exact and reliable data available on the share of unused but sold pharmaceuticals, but estimates range from 10 to 35 % (Kümmerer & Hempel 2010).

In cases in which different active substances can be used to treat an illness effectively, it was proposed to guide the prescription/purchase and usage pattern to the more environmentally benign substance. Transparent, international recognized labelling schemes have been suggested to guide the preferences of patients, health care professionals, and pharmacists to administer environmentally friendly pharmaceuticals in such cases in which choices are available. A voluntary environmental classification scheme has been established in Sweden by LIF, the association for the research based pharmaceutical Industry in Sweden. The model was developed in 2004-2005 by LIF, Stockholm County Council, the pharmacy monopoly chain Apoteket AB (today the Swedish Pharmacy Association represents the pharmacies), the Swedish Association of Local Authorities and Regions and the Swedish Medical Products Agency, in conjunction with the international pharmaceutical industry (Wennmalm and Gunnarsson 2010, LIF 2012, LIF 2014).

E. Veterinary medicine

Veterinary medicines are extensively used in farming and aquaculture for therapeutic and metaphylactic purposes. Some commonly used treatment practices, such as campaign treatment of all animals in the farm, need high quantities of veterinary pharmaceuticals, especially in intensive livestock and aquaculture systems where animals are being kept in large herds and are prone to infection. Here, the prophylactic application of veterinary pharmaceuticals, often applied as feed additive, could be reconsidered. Thames et al. (2012) have shown that low animal density and improved nutritional programs can substitute subtherapeutic antibiotics for calves. Two other examples from Scandinavian countries have also shown that national regulations, which could be supported in SAICM, can have promising effects on reducing the entry of pharmaceuticals into the environment: “Antibiotics were phased out as growth promoters in 1986 in Sweden, followed by Denmark in the late 1990s, and subsequently the European Union. [...] Overall, a dramatic decline in the total use of veterinary antibiotics was achieved in Denmark: from ≥ 200 metric tons in 1994 to around 70 metric tons in 1999 (Pruden et al. (2013)).”

Also, non-chemical alternatives (Hanczakowska and Szewczyk 2007) should be promoted, as well as modifying livestock and aquaculture systems. Here, improved manure management can be considered as an important factor. Storteboom et al. (2007) have shown that “watering, aeration, and turning of compost offered some advantage to accelerating antibiotic decay of [the antibiotics] chlortetracycline, monensin, and tylosin, but even simple storage of manure stockpiles resulted in significant antibiotic degradation.” For aquaculture systems “infectious disease outbreaks among aquaculture stock species are of fundamental concern because of both loss of stock and detriment to animal welfare. Aquaculture is increasing worldwide (Bostock et al. 2010), which is likely to increase the disease risk (Pruden et al. (2013).” In most European and North American countries, national regulations on pharmaceutical usage in aquaculture have been implemented. However, in many developing and emerging countries, these regulations are either missing or are not enforced (FAO/OIE/WHO 2006). SAICM could support the transfer of regulations and codes of practice from industrialized to other countries.

Also, changes towards sustainable lifestyles, for example with less meat consumption, can lessen the amount of veterinary pharmaceuticals entering the environment. Further details on options for action concerning veterinary medicine are provided by e.g. Pruden et al. (2013).

F. Environmental Risk Assessment (ERA) of Pharmaceuticals

This section mainly addresses the EU and North American situation, but may also reflect on the developing country perspective with regards to ERA. Both in Europe and North America, regulatory requirements have been established requiring ERA prior to the regulatory submission of a new drug (US FDA 1998, VICH 2000, VICH 2004, EMEA 2006). It is widely accepted that the EU regulations are currently the most demanding and data intensive, requiring environmental fate and effects tests to be undertaken.

Studies regarding environmental properties of pharmaceuticals that have been determined and submitted with ERAs to the competent authorities during authorisation procedure are considered proprietarily and have generally not been published or are difficult to find. For new products, the study results (endpoints) are now mostly published in the (European) Public Assessment Reports (EPAR/PAR) at the web site of EMA or the national agencies. The US FDA also publishes the endpoints of their assessments. Attempts towards more transparent environmental risk assessments were made by the Swedish Prescribing guide (LIF 2014) and by some companies. AstraZeneca, for example, made environmental data for their products available on their corporate responsibility webpages (AstraZeneca 2012). Further activities leading to an increase in transparency and availability of environmental data could contribute to a better understanding of the risk assessment of pharmaceuticals in the environment. The fate and effect data could help designing monitoring programs or evaluating concentrations measured in the environment.

While the ERA guidelines in Europe and North America have largely global relevance, they reflect EU and US pharmaceutical usage patterns, but are not directly applicable in other regions of the world. For example, the EMA guideline does not consider irrigation as a potential route to the terrestrial environment, whilst this is normal practice in water-stressed areas. Similarly, disease prevalence, cultural practices and connectivity of the population to wastewater treatment may differ regionally (e.g. unanticipated impact of diclofenac on vulture populations in India). It has thus been suggested to review the inherent assumptions made in ERA to reflect region-specific exposure scenarios in other parts of the world or establish a harmonized global ERA regulation that suits global exposure scenarios (Holm et al. 2013). In case of veterinary medicines, only experimental studies are harmonized in the VICH guideline. The exposure calculations are conducted separately for each region.

Many of the drugs used today in high quantities pre-date current ERA-regulatory requirements. For these drugs typically no ERA has been conducted. It has been estimated that of the more than 3.000 active pharmaceutical substances on the market today only about 10 % have sufficient data to calculate a PEC/PNEC ratio (Boxall et al. 2012). Therefore, it has been suggested that ERA should be conducted for relevant older drugs on the market, which could follow a priorisation list (Boxall et al. 2012).

If an environmental risk is identified in the ERA of a human pharmaceutical, the EC regulation states that ‘‘specific arrangements to limit it should be envisaged’’ (EC 2001b). However, no effective mitigation measures are yet specified. The only known example of a mitigation measure beyond risk refinement is for an EE2 patch for which special package inserts were required with instructions for proper disposal (Janssen cit. in Holm et al. 2013).

The European Directive on the authorization for veterinary medicines also provides the option for "specific provisions seeking to limit" the environmental impact (EC 2001a). The European medicines agency has therefore published a reflection paper on risk mitigation measures (EMA 2012).

G. Ecopharmacoviligance

Post-marketing surveillance for adverse side-effects in humans is performed under traditional pharmacovigilance programmes. The concept to extent these monitoring systems to post-marketing surveillance of environmental impacts is called "Ecopharmacoviligance" or Eco-pharmacology (Holm et al. 2013), which could range from documenting occurrence and concentration ranges of the pharmaceutical in the environment to documenting impacts on non-target organisms to updating or reviewed pre-marketing ERA as more and more data become available.

H. Green and sustainable pharmacy

Green pharmacy is the design of pharmaceutical products and processes that eliminate or reduce the use and generation of hazardous substances and the prevention/reduction of environmental/safety and health impacts at the source (Clark 2006 cited in Kümmerer & Hempel 2010). Innovation and development of environmentally sound pharmaceuticals (e.g., the design of pharmaceuticals that are better absorbed by the human and veterinary body and/or that are less persistent in the environment), whereas effectiveness and affordability must not be compromised was suggested as a long-term strategy. Combined finance strategies of international research funds and pharmaceutical industries could be used to advance the development of green and sustainable pharmacy (Kümmerer & Hempel 2010).

I. Improve sanitation and sewage treatment

Pharmaceuticals are incompletely removed by conventional sewage treatment processes currently in place (WHO 2012), but treatment does significantly reduce the pharmaceutical load in sewage for some of the better degradable pharmaceutical substances. Switzerland reported plans to upgrade about 100 out of over 700 municipal wastewater treatment plants with advanced treatment processes in the next 25 years, resulting in an enhanced treatment of more than 50 % of all wastewater being produced in Switzerland. The implementation concept targeted (1) the largest WWTPs in order to reduce high loads, (2) WWTPs at stretches of water with insufficient dilution, and (3) WWTPs at stretches of water which are of significance for drinking water production. The upgrade of the WWTPs will be financed by Swiss tax payers. Further explanations on options for financing WWTP upgrades in Germany can be found in Gawel et al. (2015).

In developing countries and countries with economies in transition, an improvement of the current wastewater infrastructure should be strongly promoted for sanitation and human health reasons and could - as a secondary effect - contribute to reduce pharmaceuticals entering the aquatic environment. Especially, densely populated areas, such as fast growing mega cities, are prone to produce high pharmaceutical sewage loads while sanitary capacities have not kept pace with population growth. The UN Water GEMI Initiative establishes an integrated monitoring system for water and sanitation, to fulfil the sustainable development goal (SDG) goal 6 on sustainable water and sanitation for all.

The following options are considered as most promising:

- Construction of municipal sewage treatment in urban areas;
- Promotion of sewage treatment at point sources, for example at hospitals (Thomas et al. 2007);
- Separate piping of municipal waste water and rain water to increase pharmaceutical concentration and removal efficiency in wastewater treatment;
- Maintenance and repair of broken sewage/piping to reduce leakage of sewage to groundwater.

J. Raw water for drinking water production

Pharmaceuticals have also been found in drinking water, largely at concentrations several orders of magnitude below the minimum therapeutic doses. The substantial margins of safety for individual substances suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking water (WHO 2012). However, at the local level, the production of pharmaceuticals has led to relatively high concentrations in well water that is used as drinking water (Fick et al. 2009). Systematic monitoring programmes are scarce, and there have been few comprehensive, systematic studies of the occurrence of pharmaceuticals in drinking water. This lack of data presents a key challenge to assessing the potential health risks of long-term, low-level exposure to pharmaceuticals in drinking water, especially for vulnerable sub-populations, including infants and the chronically ill.

In addition, if pharmaceuticals are repeatedly detected in drinking water – even at concentrations below what is considered harmful – the public may lose confidence in the overall quality of their drinking water. The precautionary principle calls for actions to minimize the occurrence of pharmaceuticals in drinking water.

K. Disposal of unused/expired pharmaceuticals

Sustainable collection and disposal schemes for unused pharmaceuticals should be established and promoted, if necessary. In addition, drug take-back schemes, e.g. at pharmacies, can avoid pharmaceuticals entering the environment via inadequate drug disposal or burning them in open fires at home. Public awareness needs to be raised about not flushing unused drugs down the drain. Best management practices for collection and disposal schemes should be implemented at hospitals, health care facilities, but also for households and farmers/veterinarians. They should also apply to donated pharmaceuticals, for example pharmaceuticals supplied in emergencies. As a second step, adequate facilities for management of pharmaceutical waste (e.g. incineration facilities) will have to be established.

In the area of environmental health, pharmaceuticals in the environment have been addressed to varying degrees in WHO reports and guidelines on health care waste management, including for example: in both editions of the WHO “Blue Book” on the safe management of health care wastes (2014); as well as in the WHO/Interagency “Guidelines on the safe disposal of pharmaceuticals in and after emergencies” (1999).

6.1.2 Work areas addressing knowledge and information (Objective B)

L. Global awareness

In many parts of the world, people are not aware that pharmaceutical consumption, disposal, and production have potentially adverse effects on the environment. Therefore, awareness raising via information campaigns, regional workshops, brochures, and online resources, including guidance on suitable disposal mechanisms and drug take-back-programmes are essential.

M. Support informed decision-making

Due to the expanding scientific knowledge on the fate of pharmaceuticals in the environment, it is important to provide up-to-date information and scientific advice to decision-makers and stakeholders. This holds especially true for developing countries and countries with economies in transition. Producing a document on the "state of the science" could be administered for example by the Inter-Organization Programme for the Sound Management of Chemicals (IOMC), who has also administered the state of the science of endocrine disrupting chemicals report (UNEP & WHO 2013).

National and local governments should strengthen monitoring campaigns to identify effected watersheds, relevant concentrations, and to enable a sound risk assessment and the evaluation of suitable management options for effected watersheds.

Furthermore, an international network of scientists, risk managers, and others stakeholders could facilitate information exchange, discussion forums, and mutual support in research and advice on translation of research results into actions. An online collaboration platform may be a helpful tool for such a network, such as the online consultation on EPPP conducted by UBA in June/July 2015.

Understanding the behaviour and fate of pharmaceuticals and the formation of transformation products in the environment should be further developed. Modelling techniques could be a promising tool in river catchments that enable the design of cost-effective strategies to reduce pharmaceutical concentrations in the environment (Ort et al. 2009, Plósz et al. 2012, Versteeg et al. 2005). Here, these modelling techniques can pinpoint hot spots and provide spatial and temporal information on pharmaceutical occurrences in the environment without expensive measuring campaigns.

N. Knowledge base

Many processes concerning environmental behaviour, fate, and effects of pharmaceuticals entering the environment are still unknown. In order to mitigate the occurrences and effects, it is important to establish and disseminate a common knowledge base and to know which substances pose a risk to the environment. Knowledge gaps concerning the issue of pharmaceuticals in the environment should be addressed, e. g. by conducting fate and effect tests for highly used pharmaceuticals according to OECD test guidelines. It would be helpful if endpoints of effect and fate tests generated for environmental risk assessments e. g. in Europe or the U.S. would be easily available. This could also aid in assessing the measured concentrations in other UN regions. Establishing effect values and information on the behaviour of pharmaceuticals in the environment and the formation of metabolites and transformation products is important for the risk assessment and management decisions.

Other knowledge gaps relate to the risks of long-term, low-level exposure of humans to pharmaceuticals in drinking water and the combined (additive, synergistic or antagonistic) effects of multiple pharmaceuticals and/or other pollutants concurrently present in drinking water (cocktail effect).

O. Consumption data availability

Available data on consumption or prescription of pharmaceutical is not available in most countries. Sales data is often confidential and it is particularly difficult to obtain data on medicinal products sold over the counter or via the internet or for veterinary medicines (except for antibiotics). It is recommended to establish national prescription/consumption/production databases. They should be publicly available to identify relevant pharmaceuticals used in high or rising quantities for designing efficient monitoring campaigns. Within the European Union, several countries, such as Sweden and Denmark, have already established national systems. In contrast, especially in developing and emerging countries these systems are missing.

6.1.3 Work areas addressing governance (Objective C)

P. Use synergies

Building synergies with other SAICM initiatives, such as on EDCs, and, for example, the joint UN initiative on sustainable procurement of health care products, may be an effective strategy for bundling ongoing efforts. Governmental institutions will also need to assess and fill gaps in existing policies and in legal and institutional frameworks. It would also be beneficial to learn from the experiences made in several countries and the results of the high number of research performed in some regions.

Q. Containment of Antimicrobial Resistance

An alarming public health threat is the spread of pathogenic organisms that are resistant to antimicrobials. The presence of antimicrobials in the gut of humans and treated animals leads to the development of resistant bacteria and genes that can be excreted in faeces and spread to wastewater, sludge, manure, or soil. However, resistance genes can also develop in the environment if antibiotic substances are present; these genes can then be transferred to pathogenic bacteria (Allen et al. 2013). There is also evidence of an exchange of resistance genes between environmental bacteria and clinical isolates (Forsberg et al. 2012). Thus, strategies to reduce the introduction of antibiotics into the environment can also help to contain antimicrobial resistance worldwide (WHO 2014, Wilton Park 2015).

A variety of organisations including the WHO, FAO, EMA, and national agencies are working on the threat of anti-microbial resistance and have well-established programmes implementing activities at national, regional and global levels.

Pruden et al. (2013) provide a comprehensive overview of options for action concerning containment of antimicrobial resistence. The main options can be summarized as follows: (a) optimizing antibiotic use, (b) maintaining good animal health, (c) using antibiotic alternatives, (d) manure management and treatment, (e) sanitation and sewage treatment, (f) wastewater reuse, (g) hospital and industrial wastewater management, (h) aquaculture management, and (i) policy synergies.

R. Industry participation

The participation of pharmaceutical companies to address the issue of pharmaceuticals in the environment has to be promoted. This would also reflect the SAICM multi stakeholder principle. Some pharmaceutical companies are already active in taking pro-active measures, often collaboratively with academics and governments, however, many issues still need to be addressed. Moreover, internalization of costs by the private sector is currently discussed under SAICM, in order to apply the polluter pays principle, as set out in Principle 16 of the *Rio Declaration on Environment and Development*.

S. Environmental quality standards

The implementation and enforcement of environmental quality standards of relevant pharmaceuticals in different environmental compartments as well as in drinking water has been advocated to ascertain regulatory effective protection of water resources according to the multi-barrier principle (Umweltbundesamt 2012).

6.1.4 Work areas addressing capacity building and technical cooperation (Objective D)

T. Capacity building and technical cooperation

Internationally supported capacity building will help to bridge the gap between developing countries, countries with economies in transition, and developed countries. Especially, the transfer of knowledge about occurrences and effects of pharmaceuticals in the environment and potential mitigation measures is important. For example, transferring data and knowledge between countries can help to identify potential hot spots of occurrences, specific pharmaceuticals of high concern, and provide options for action. This helps in targeting efforts for measuring campaigns and duplicate fate and effect testing could be avoided. It would also aid in saving resources with regard to development of analytical methods or management strategies.

U. Environmental monitoring strategies

A large amount of information is now available, notably concerning the monitoring of certain active substances especially in surface water but also in groundwater, which are used for the production of drinking water, but the available data are not centralised and not in a standardised format (BIO-IS 2013). Environmental concentrations are scarce or missing for some environmental compartments. In order to assess the state of pharmaceutical pollution within a watershed or country, a monitoring strategy needs to be developed, that can represent actual pharmaceutical concentrations, both in time and space. Additionally, potential pharmaceutical sources and uses need to be analysed beforehand to identify the most often occurring pharmaceuticals, taking into account regional differences in pharmaceutical consumption patterns.

The database has shown that data and measurements coverage in industrialized countries is considerably better than in developing countries and countries with economies in transition. Still, as pharmaceutical concentrations can vary strongly in space and time, it is important to set-up coordinated

long-term measuring campaigns, tailored to local conditions, e.g. types of pharmaceuticals used. In developing countries and countries with economies in transition, more measuring campaigns are necessary.

V. Standardized analytics

It is necessary to establish standardized analytical protocols in order to compare and interpret laboratory results of environmental samples. Currently, different methodologies with different detection limits are available. Some pharmaceuticals, e.g. hormones and parasiticides, have shown ecotoxicological effects at very low concentrations. To measure the concentrations at which effects occur, small limits of detection are necessary. Therefore, they can only be detected in labs with high analytical and technological standards.

6.1.5 Work areas addressing illegal traffic (Objective E)

W. Illicit and fake drugs

Production and distribution of substandard, spurious, or counterfeit pharmaceuticals may contribute to pharmaceutical pollution. WHO operates a Member State Mechanism on substandard, spurious, falsely-labelled, falsified or counterfeit medical products to withdraw such products from the world market (WHO 2014).

6.2 Potential Cooperative Action under SAICM

The issue of pharmaceuticals in the environment meets all criteria of an emerging policy issue under SAICM, since the issue (1) involves each life-cycle phase (production, application, and disposal of both human and veterinary pharmaceuticals); (2) is insufficiently addressed by any other global regulation; and (3) it has clearly emerged from the current level of scientific information that pharmaceuticals can have significant adverse effects on ecosystems at the concentrations prevailing in the environment.

The Ministry of Environment of Peru, the Ministry of Housing, Land Planning and Environment of Uruguay and the International Society of Doctors for the Environment (ISDE) submitted in 2014 a revised dossier for the nomination of EPPP as emerging policy issue under SAICM. In the nomination dossier, the following cooperative actions are listed:

- To establish an international project on EPPP;
- To build synergies with the Endocrine Disruptor Strategy;
- To facilitate information exchange and networking;
- To provide international support for capacity building;
- To create an international network of scientists;
- To improve coordination and consolidation of ongoing initiatives;
- To build synergies with other international projects.

At the second Open Ended Working Group (OEWG2) meeting of SAICM in December 2014 in Geneva, Switzerland it had been concluded that pharmaceuticals in the environment are relevant for considering within the SAICM framework. Hence, this topic has been allowed for consideration at the fourth session of the International Conference on Chemicals Management (ICCM4) in Geneva in 2015.

ICCM4 adopted EPPP as emerging policy issue. In an omnibus resolution on emerging policy issues, The Conference:

- agreed that international cooperation is crucial to build awareness and understanding and promote action on EPPPs as an EPI;
- decided to implement cooperative action on EPPPs with the overall objective of increasing awareness and understanding among policymakers and other stakeholders;
- invited governments and other stakeholders to generate and share information to fill identified knowledge gaps;
- invited relevant IOMC[4] participating organizations, within their respective mandate as part of their work programme, to lead and facilitate cooperative action to develop an EPPP work plan;
- requested all interested stakeholders and organizations to provide support on a voluntary basis, for such cooperative action; and
- invited relevant IOMC participating organizations and other SAICM stakeholders to report on cooperative action to ICCM5 or any other session as decided upon by the Conference.

SAICM will be an appropriate policy framework to address the issue of pharmaceuticals in the environment on a global level. The scope of SAICM excludes the health and environmental aspects of pharmaceuticals to the extent that they are regulated by a domestic authority of arrangement (SAICM OPS section II). Emissions into the environment from production, use and disposal are however generally not regulated.

In Table 4, we have evaluated the work areas and associated activities proposed above according to their suitability and effectiveness to be addressed under SAICM based on three potential options:

1. Inclusion into the Global Plan of Action under SAICM given the current time und budget constraints (current SAICM mandate ending in 2020).
2. Implementation within small projects.
3. Implementation within medium to large projects.

The analysis was not restricted to the cooperative actions proposed in the nomination dossier. The information if the action is included in the nomination dossier is included in Table 4. As the analysis of potential options for action was performed before ICCM4, the suggested options are also not restricted to the adopted resolution. Several of the larger projects with a medium to long-term time frame may not be applicable for the remaining time of the current SAICM process until 2020, but may have to addressed/completed by a follow-up process.

[4] IOMC: Inter-Organization Programme for the Sound Management of Chemicals

6.2.1 Inclusion into the Global Plan of Action under SAICM

The Global Plan of Action of SAICM (see text box) offers the ideal setting to include options for action in order to reduce the entry of pharmaceuticals into the environment. These options include the work areas for risk reduction addressed in Chapter 6.1.

Additional activities, which are not mentioned above, could also be included into a global plan of action to reduce the entry of pharmaceuticals into the environment without compromising effectiveness, availability, or affordability of medical treatment, especially in developing and emerging countries.

Global Plan of Action

The Global Plan of Action of SAICM provides work area and associated activities that may be undertaken voluntarily by stakeholders in order to pursue the commitments and objectives expressed in the Dubai Declaration on International Chemicals Management and the Overarching Policy Strategy, reaffirming the 2020 goal (see Chapter 1).

Within the Global Plan of Action, possible work areas and their associated activities, actors, targets and timeframes, indicators of progress and implementation aspects are grouped according to five categories of objectives contained in the Overarching Policy Strategy of the Strategic Approach, namely, risk reduction, knowledge and information, governance, capacity-building and technical assistance and illegal international traffic.

The Global Plan of Action also serves as guidance to all stakeholders at the global, regional, national and local levels, including when assessing the current status of their actions in support of the sound management of chemicals and identifying priorities to address gaps in such management.
(UNEP 2006)

6.2.2 Options for action recommended under SAICM

All options for action, which have been described in Table 4, have also been analyzed according to their suitability for inclusion into the Global Plan of Action under SAICM. With respect to the boundary conditions of the SAICM framework, e.g. time and financial constraints, the following seven options have been selected as most suitable:

<u>Risk Assessment and prioritizing action (Option A)</u>

This option can be considered a prerequesite for all potential options for action, as it includes gathering knowledge about the status quo of the current situation on pharmaceuticals in the environment. Based on the risk assessment of the current situation, potential options for action can be selected and ranked according to their suitability. Within SAICM, the selection and ranking of options for action does not only rely on mitigation potentials but also on financial and political applicability.

Global awareness raising (Option L)

SAICM would be an appropriate platform to inform society, politicians, medical professionals, farmers and other stakeholders on pathways of pharmaceuticals into and effects on the environment, their technical removal options, and mitigation measures. SAICM could orchestrate global and regional strategies and efforts to reach this goal. Awareness raising could for example be conducted by social media campaigns, brochures and flyers. Also, involving schools and teachers could have noticeable effects.

Disposal of unused/expired pharmaceuticals (Option K)

Within the SAICM Global Plan for action, several procedures and/or information campaigns can be introduced to reduce the inadequate disposal of unused/expired pharmaceuticals. The first step includes public awareness raising via information campaigns, e.g. that drains are an environmental unfriendly disposal pathway. This campaign could be initiated on the global scale, for example at SAICM regional meetings. Also, short- and / or long-term projects can be implemented in order to increase the impact at hot spot regions, i.e. mega cities. The second option for action focusses on Best Management Plans (BMP) at health care facilities and for veterinary purposes. SAICM could help develop environmentally friendly BMPs and introduce them globally. Further options include improvement of facilities for waste management and take back programmes, whereas the latter are more suitable for mid to long-term projects, as they need to consider local and national circumstances.

Support informed decision making (Option M)

As a first step, the current knowledge about pharmaceuticals in the environment should be summarized by the IOMC participating organizations or other relevant stakeholders. This includes compilation of monitoring, fate, and effect data for specific pharmaceuticals. SAICM can then share this base data, which is necessary to support informed decision making, by coordinating regional and global networks based on the already existing regional and global workshops and meetings. Furthermore, SAICM can promote establishing analytical methods and campaigns, especially in countries where no suitable laboratories are available, yet.

Capacity building and technical cooperation (Option S)

SAICM can be used to support capacity building, monitoring programmes, and case studies in developing countries and countries with economies in transition. SAICM can set up workshops, and/or on-site training on technological and informative topics, for example on national institutional strengthening, research cooperation or monitoring plans.

Environmental monitoring strategies (Option T)

SAICM could provide a guideline on how to develop environmental monitoring strategies, especially in countries where no regulatory frameworks on this topic are provided. As monitoring and analytics are time and budget consuming, it will be necessary for SAICM to conduct a priorization of pharmaceutical substances. For example, a SAICM working group can rank pharmaceuticals based on local consumption and their toxicity. Furthermore, SAICM can define indicator substances and protocols (e.g. caffeine), which provide short-cuts for cost-effective monitoring. As a second step, a relevant financial mechanism could support monitoring projects in regions where little/no data on the occurrence of pharmaceuticals exist, yet.

Standardize analytics (Option U)

SAICM can help standardizing protocols and analytical capabilities to measure pharmaceuticals in environmental matrices at relevant concentrations. Here, SAICM could set up international working groups, which define standardized analytical protocols. Thereafter, the regional and global SAICM network could be used to introduce these protocols to governments and other stakeholders.

Table 4: Catalogue of potential work areas, associate activities, main actors, timeframes, and suitability to be effectively addressed under SAICM and a potential post 2020-framework based on three potential implementation options *

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
WORK AREAS ADDRESSING RISK REDUCTION (OBJECTIVE 1)								
A. Risk assessment and prioritizing action	Develop a workplan to prioritize appropriate activities.	IOMC National governments Regional arrangements (e.g. EU)	short- to medium-term	++	++	+	yes	This work area can be considered a pre-requesite for all potential options for action.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
B. Cleaner production	Encourage cleaner production and promote the transfer, implementation and adoption of pollution prevention policies and cleaner production technologies, in particular best available techniques and best environmental practices (BAT/BEP).	IOMC National governments Regional arrangements Pharmaceutical companies Academia	short- to long-term	+	o	++	no	SAICM cannot coordinate cleaner production on the global scale. However, a medium demonstration project, which involves local stakeholders, could be supported.
	Establish and/or enforce adequate pollution prevention measures at pharmaceutical manufacturing facilities (e.g. wastewater treatment).	Pharmaceutical companies National/local governments	short- to long-term	+	o	++	no	SAICM can provide information on pollution prevention measures and could support a medium to large demonstration project. Regulation and enforcement is subject to national governments.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Extent Good Manufacturing Practice (GMP) to incorporate environmental quality guidelines.	WHO ICH Pharmaceutical companies	medium- to long-term	o	o	+	no	SAICM cannot develop GMP on the global scale.
C. Procurement in the health care sector	Strengthen green procurement in health care sector.	iIATT – SPHS[5], national health care providers, insurance companies	short- to medium-term	+	+	+	yes	SAICM offers a large potential of promoting environmentally friendly pharmaceuticals by providing information on green procurement.
D. Prescription/ purchase and usage patterns of human medicine	Provide information on environmentally benign pharmaceuticals (e.g., classification and labelling scheme) to guide procurement/prescription/purchase/usage behaviour.	Pharmaceutical companies Health care professionals Patients General public	medium- to long-term	+	+	+	no	SAICM can offer information on the environmental impact of pharmaceuticals and thus, provide the background for "green" labelling schemes.
	Offer suitable package sizes to minimize disposal of unused/expired medicine	Pharmaceutical companies	medium- to long-term	+	o	o	no	SAICM can encourage to provide suitable package sizes.

[5] UN Informal Interagency Task Team on Sustainable Procurement in the Health Sector

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Enhance rational / sound use of pharmaceuticals. Intake of pharmaceuticals only if necessary and after prescription by a medical doctor. Reduce prophylactic use of pharmaceuticals, if appropriate.	Patients Health care professionals	short- to medium-term	++	+	+	no	SAICM can support an information campaign on rational use of pharmaceuticals.
	Enhance prescription medicine, reduce over-the-counter drugs.	Regulatory authorities	long-term	o	o	+	no	SAICM cannot change the prescription scheme within countries but provide knowledge.
E. Veterinary medicine	Reduce over-subscription of veterinary pharmaceuticals in animal husbandry and aquaculture	Regulatory authorities Veterinarians Farmers, aquaculture operators Extension services	medium- to long-term	+	+	+	no	SAICM can support local authorities with information on environmental impacts of veterinary pharmaceuticals.
	Promote non-chemical alternatives (e.g., improvement of hygiene, less exchange of animals between flocks and farms)	Regulatory authorities Veterinarians, Farmers, Extension Services	medium- to long-term	+	o	++	no	SAICM can demonstrate in regional projects, how non-chemical alternatives can be applied to reduce pharmaceutical consumption.
F. Environmental Risk Assessment (ERA) of pharmaceuticals prior to launch of new drugs	Increase transparency and publish relevant data for environmental assessment	National authorization agencies, e.g. EU EMA, US FDA, IOMC Pharmaceutical companies	short- to medium-term	++	+	o	no	SAICM can be used as a platform to publish and discuss relevant data.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Establish and publish analytical methods suitable to measure substances in different environmental matrices at relevant concentrations	OECD Pharmaceutical companies Academia	short- to medium- term	+	++	+	no	SAICM can support local projects for establishing analytical methods for new pharmaceuticals.
	Review and if appropriate revise assumptions made in existing ERA regulation to reflect a global perspective with region-specific exposure pathways.	Regulatory authorities, e.g. EU EMA, US FDA, IOMC Pharmaceutical companies, Academia	short- to medium-term	++	+	+	no	SAICM can assess current ERA assumptions based on multiple global and regional exposure pathways.
	Assess pharmaceuticals pre-dating current ERA-regulatory requirements	Regulatory authorities, e.g. EU EMA, US FDA, IOMC, Pharmaceutical companies	medium- to long- term	+	o	o	no	SAICM can promote ERAs for existing pharmaceuticals and facilitate information exchange on the results.
	Establish a harmonized global ERA regulation	IOMC Pharmaceutical companies	long-term	+	o	o	no	SAICM can act as link between different main actors.
	Specify procedures if risks are identified (e.g. information, risk mitigation measures, rejection of approval)	IOMC Regulatory authorities Pharmaceutical companies OECD	medium- to long-term	+	o	o	no	SAICM can act as link between different main actors.
G. Ecopharmacoviligance	Establish adequate procedures to track environmental risks after launch of a drug via literature monitoring for emerging data on exposure and effects	Regulatory authorities Pharmaceutical companies OECD	medium- to long-term	+	o	o	no	SAICM can provide databases to inform about occurrences and potential effects.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Further research, testing or monitoring when a risk is identified after launch of a drug	Pharmaceutical companies, Regulatory authorities	medium- to long-term	+	o	o	no	SAICM can support authorities with information about specific pharmaceuticals and their related risks.
	Establish Environmental Risk Management Plans (ERMP) to assess and manage risks of a drug throughout its life cycle	Pharmaceutical companies	medium- to long-term	+	o	o	no	SAICM can support pharmaceutical companies to develop ERMPs to promote transparency.
H. Green and sustainable pharmacy	Promote innovation and development of environmentally sound pharmaceuticals without compromising effectiveness and affordability.	Pharmaceutical companies Academia	long-term	o	o	o	no	SAICM can promote regional demonstration projects where local companies develop environmentally friendly pharmaceuticals.
	Integrate environmental aspects into the development of new pharmaceuticals (e.g. benign by design)	Pharmaceutical companies Academia	long-term	o	o	o	no	SAICM can support background information for stakeholders.
I. Improve sanitation and sewage treatment	Promote municipal sewage treatment in urban areas	National governments WWTP operator	medium- to long-term	+	o	++	no	SAICM can promote regional demonstration projects, which improve sanitation infrastructure to lessen pharmaceutical concentrations in surface waters.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Promote sewage treatment at point sources (e.g., hospitals)	Hospitals	medium- to long-term	**o**	**o**	**++**	no	SAICM can promote regional demonstration projects, which improve on-site treatment.
	Separate piping of municipal waste water and rain water to increase pharmaceutical concentration and removal efficiency in wastewater treatment	WWTP operator	medium- to long-term	**o**	**o**	**++**	no	SAICM can promote regional demonstration projects, which improve sanitation infrastructure to lessen pharmaceutical concentrations in surface waters.
	Maintain and repair broken sewage/piping to reduce leakage of sewage to groundwater	WWTP operator	medium- to long-term	**o**	**o**	**++**	no	SAICM can promote regional demonstration projects, which improve sanitation infrastructure to lessen pharmaceutical concentrations in surface waters.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
J. Drinking water	Systematically monitor pharmaceutical substances in drinking water	Drinking water utilities	medium- to long-term	+	++	+	no	SAICM can support smaller projects to measure pharmaceutical substances in drinking water, especially in countries where no information is available and in areas with potentially high concentrations.
	Establish advanced treatment technology only if necessary due to multi-barrier approach	Drinking water utilities	long-term	o	o	+	no	SAICM can promote regional demonstration projects, which improve sanitation infrastructure to lessen pharmaceutical concentrations in drinking water.
K. Disposal of unused/ expired pharmaceuticals	Establish and promote Best Management Practices (BMP) for collection and disposal schemes at health care facilities	Hospitals	short- to medium-term	++	++	++	no	SAICM can develop BMPs for suitable disposal mechanisms in order to avoid pharmaceuticals entering the environment.
	Establish and promote Best Management Practices for collection and disposal schemes at farmers/veterinary doctors	Veterinarians Farmers Aquaculture operator Extension services	short- to medium-term	++	++	++	no	SAICM can develop BMPs for suitable disposal mechanisms in order to avoid pharmaceuticals entering the environment.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Establish and promote take-back programmes for households drugs	Pharmacists Patients Pharmaceutical companies	short- to medium-term	**o**	**++**	**++**	no	SAICM can develop a framework for the programmes, which is globally applicable.
	Raise public awareness, e.g. not flushing unused drugs down the toilet or sink	Pharmacists Health care professionals Pharmaceutical companies NGOs	short- to medium-term	**++**	**++**	**+**	no	SAICM can produce informative handouts and social media campaigns.
	Establish adequate facilities for management of pharmaceutical waste (e.g. incineration facilities)	National/local governments Regional arrangements	medium- to long-term	**+**	**+**	**++**	no	SAICM can promote regional demonstration projects, which improve the correct disposal of pharmaceuticals.
WORK AREAS ADDRESSING KNOWLEDGE AND INFORMATION (OBJECTIVE 2)								
L. Global Awareness	Raise global awareness on adverse effects of pharmaceuticals entering the environment to affect purchase, usage and disposal patterns	National governments, Internat. Organizations, e.g. IOMC, Health care professionals Pharmaceutical companies Veterinarians, farmers, extension services, NGOs, Academia	short- to medium-term	**++**	**++**	**+**	yes	SAICM can produce informative handouts and social media campaigns.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
M. Support informed decision-making	Provide up-to-date information and scientific advice to decision-makers and stakeholders for chemical risk management, with particular attention to needs of developing countries and countries with economies in transition.	IPCS Academia	short- to medium-term	++	++	+	yes	SAICM can compile data on fate, effects, and risks for specific pharmaceuticals.
	Conduct monitoring campaigns to identify effected watersheds, relevant concentrations, and potential effects.	National governments Regional arrangements Local authorities Water resource manager Drinking water utilities Academia	short- to medium-term	+	++	++	yes	SAICM can promote establishing analytical methods and campaigns, especially in countries where no suitable laboratories are available, yet.
	Produce a document on the "state of the science" on pharmaceuticals in the environment.	IPCS IOMC Academia Environment agencies	short- to medium-term	++	o	o	no	SAICM can summarize the current knowledge about pharmaceuticals in the environment.
	Create an international network of scientists, risk managers, and others to facilitate information exchange, discussion forums, and mutual support in research and advice on translation of research results into control actions.	Internat. organizations Pharmaceutical companies NGOs Academia	short- to medium-term	++	o	o	yes	SAICM can coordinate regional and global networks based on the already existing regional and global workshops and meetings.
N. Knowledge base	Establish and disseminate knowledge on the environmental behaviour, fate and effects of pharmaceuticals.	Regulatory agencies Pharmaceutical companies Academia	short- to medium-term	++	+	o	yes	SAICM can set up databases on environmental occurrences and related literature.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Develop and implement labelling schemes for environmentally friendly pharmaceuticals.	Pharmaceutical companies Regulatory authorities Academia	medium- to long-term	+	o	o	no	SAICM can offer information on the environmental impact of pharmaceuticals and thus, provide the background for "green" labelling schemes.
O. Consumption data availability	Establish national inventories of prescription/ consumption data to identify relevant pharmaceuticals used in high quantities.	Regulatory authorities Pharmaceutical companies	medium- to long-term	+	o	o	no	SAICM can support setting up a prescription/ consumption database.
WORK AREAS ADDRESSING GOVERNANCE (OBJECTIVE 3)								
P. Use synergies	Assess and fill gaps in existing policies, legal and institutional framework	National governments Internat. Organisations	short- to medium-term	+	+	+	no	SAICM can provide an overview of current policies and legislations.
	Establish synergies with other policy frameworks, i.e. water management, health system	National governments Internat. Organisations	short- to medium-term	++	+	++	yes	SAICM can establish links to other institutions/frameworks and set up working groups.
	Lessons learnt from implementing cooperative actions on Endocrine Disrupting Chemicals (EDCs)	Internat. Organisations National governments	short- to medium-term	++	+	+	yes	SAICM can inform about implementing actions on EDCs and transfer lessons learnt to pharmaceuticals.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
	Support strategies for containment of antimicrobial resistance pursued in other arrangements	WHO FAO	short- to medium-term	++	+	++	no	SAICM can link containment strategies of main actors with environmental occurrences.
Q. Industry participation	Promote industry participation and responsibility	National governments Pharmaceutical companies	short- to medium-term	++	+	o	no	SAICM can set up working groups between industries and authorities.
R. Environmental quality standard	Derive limits/thresholds for APIs in different environmental compartments and drinking water	Regulatory authorities Academia	short- to medium-term	+	+	o	no	SAICM could support the derivation of threshold values with knowledge, but is not able to derive legal threshold concentrations for pharmaceuticals.
	Include and enforce standards in environmental legislation	National governments	medium- to long-term	+	o	o	no	SAICM can promote EQS to be included but not enforce legislations.
	Establish and enforce legislation for the management of unused/expired drugs	National governments	short- to medium-term	++	+	+	no	SAICM can inform about drug management but not enforce legislations.

Work Area	Associated Activities	Main Actors	Time Frame	SAICM Global Plan of Action	Suitable Option for Small Projects	Suitable Option for Medium to Large Projects	Proposed in SAICM Nomination Dossier?	Comment
WORK AREAS ADDRESSING CAPACITY BUILDING AND TECHNICAL COOPERATION (OBJECTIVE 4)								
S. Capacity building and technical assistance	Support capacity building, monitoring programmes, and case studies in developing countries and countries with economies in transition	Internat. Organisations NGOs Academia	short- to medium-term	++	++	++	yes	SAICM can set up workshops, and/or on-site training on technological and informative topics.
T. Environmental monitoring strategies	Prioritization of pharmaceuticals for monitoring	Academia Agencies	short- to medium-term	++	++	+	no	SAICM can rank pharmaceuticals based on local consumption and toxicity of pharmaceuticals.
	Develop indicator substances and protocols (e.g. caffeine) for cost-effective monitoring	Academia	short- to medium-term	++	++	+	no	SAICM can provide a database on indicators.
U. Standardize analytics	Establish standardized protocols and analytical capabilities to measure pharmaceuticals in environmental matrices at relevant concentrations	ISO, ICH Academia	short- to medium-term	++	++	++	no	SAICM can set up international working groups, which define standardized analytical protocols.
WORK AREAS ADDRESSING ILLEGAL TRAFFIC (OBJECTIVE 5)								
V. Illicit and fake drugs	Withdraw substandard/spurious/falsely-labelled/ falsified/counterfeit medical products from the market	Internat. Organisations National governments Regional Arrangements Pharmaceutical companies	short- to medium-term	o	o	o	no	SAICM can provide informative material on illicit drugs.

* Suitability to be addressed under SAICM is rated according to three categories (++ very good, + good, **o** fair) and whether the option is proposed in the nomination dossier as endorsed at OEWG2. Within the "Time Frame", short– to medium-term is defined as up to five years, whereas medium- to long-term is defined as more than five years. This table only reflects and assesses potential options for action under SAICM and cannot be transfered to other studies.

Based on a literature review, a catalogue of potential work areas and associated activities was compiled in Table 4. Multiple stakeholders could contribute in addressing the occurrence and effects of pharmaceuticals in the environment:

- Intergovernmental organizations
- National governments, regional arrangements
- Regulatory agencies and authorities
- Pharmaceutical companies, both innovative and generic
- Health care professionals, i.e. medical doctors, hospitals, and pharmacists
- Health insurance institutions
- Patients
- Veterinarians, farmers, and aquaculture operators
- Municipal sewage treatment plant operators
- Drinking water utilities
- Development cooperation
- NGOs
- Academia

7 Conclusions

This study has reviewed data on pharmaceutical concentrations from more than 1,000 publications, which have then been transferred into a global database with more than 123,000 entries. Key finding are:

- Pharmaceuticals occur globally in the environment (not just in industrialized countries):
    - Pharmaceuticals are detected in 71 countries covering all 5 UN regional groups
    - 631 out of 713 pharmaceuticals measured are positively detected in the environment
    - While there is order-of-magnitude more data available in WEOG countries, measured environmental concentrations become increasingly available in emerging and developing countries, revealing the global scale of the occurrence of pharmaceuticals in the environment.
- In a number of countries, certain pharmaceuticals prevail at concentrations above PNEC in surface waters, thus adverse ecotoxicological risks must be suspected at these locations.
- There is only partial overlap of the pharmaceuticals detected globally: different pharmaceutical groups have been in focus of monitoring/research in different UN regions, e.g. antibiotics in Asia and estrogens in Africa.
- Urban wastewater discharge is the dominant emission pathway, while discharge from manufacturing, hospitals, animal husbandry, and aquaculture are important locally.
- Publicly available data on national pharmaceutical consumption is currently not sufficient for regional analysis of relevant pharmaceuticals.

Given the undisputed benefits pharmaceuticals confer in modern medicine, potential strategies of action must be directed to prevent, reduce, and manage pharmaceuticals entering the environment without compromising effectiveness, availability or affordability of medical treatment, especially in countries, in which access to health care is still limited. The proposed nomination as an emerging policy issue under SAICM (Strategic Approach on International Chemicals Management) could initiate a multi-sectoral multi-stakeholder approach needed to globally address pharmaceutical occurrence in the environment in a life-cycle approach.

In conclusion, the following work areas have been considered most suitable for inclusion into the SAICM global plan of action:

- Risk Assessment and prioritizing action
- Global awareness raising
- Disposal of unused/expired pharmaceuticals
- Support informed decision making
- Capacity building and technical assessment
- Environmental monitoring strategies
- Standardize analytics

8 Outlook

Despite investing considerable efforts in compiling a global database, the literature review and database compilation may not be complete but miss relevant publications. Moreover, the database has to be continually improved and updated to incorporate the latest monitoring results. The development of a web interface in which additional data can be suggested in the required format for incorporation into the database is highly recommended. However, compliance and quality insurance must be ensured by a responsible project team.

Furthermore, it is also recommended to enhance the database by conducting analyses on a river-basin scale approach, in addition to national assessments. It is also suggested to couple the MEC database with modelling approaches on regional pharmaceutical consumption patterns and emission pathways into the environment, which urgently requires enhanced knowledge on pharmaceutical prescription, usage, and disposal volumes.

Over the next years, the updated MEC database could serve as a global reference tool for regulatory authorities, the general public, NGOs, and the private sector for information about the regional occurrence of pharmaceuticals in the environment.

9 References

Aguayo, S., A. D. L. Torre, M. Carballo, R. Cabrera and J. Méndez (2010): A review of the most relevant residues of pharmaceuticals products of human use in effluents and sludges from waste water treatment plants. Toxicology Letters 196, DOI: 10.1016/j.toxlet.2010.03.248.

Allen H., Donato J., Wang H., Cloud-Hansen K., Davies J., Handelsman J. (2010): Call of the wild: antibiotic resistance genes in natural environments. Nat. Rev. Microbiol. 8, 251-259.

AstraZeneca (2012): Environmental risk assessment data. Available from http://www.astrazeneca.com/Responsibility/The-environment/Pharmaceuticals-in-the-environment/era-data-2012

aus der Beek, T., 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(4), 823-835.

Bergmann, A., Fohrmann, R., Weber, F.-A. (2011): Zusammenstellung von Monitoringdaten zu Umweltkonzentrationen von Arzneimitteln. UBA Texte 66, Umweltbundesamt Dessau, Deutschland, 108pp. http://www.umweltbundesamt.de/sites/default/files/medien/461/publikationen/4188.pdf

Besse, J.-P., J.-F. Latour and J. Garric (2012): Anticancer drugs in surface waters What can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs? Environment International 39 (1): 73-86.

BIO-IS (2013): Study on the environmental risks of medicinal products. Final Report on behalf of the Executive Agency for Health and Consumers. BIO Intelligence Service, Paris, 12. December 2013.

Bostock J., McAndrew B., Richards R., Jauncey K., Telfer T., Lorenzen K., (2010): Aquaculture: global status and trends. Philos Trans R Soc Lond B Biol Sci 365(1554): 2897–2912.

Boxall A.B.A., Rudd M.A., Brooks B.W., Caldwell D.J., Choi K., Hickmann S., et al. (2012): Pharmaceuticals and personal care products in the environment: what are the big questions? Environ. Health Perspect. 120(9):1221–9.

Brodin T., Fick J., Johnsson M., Klaminder J. (2013): Dilute Concentrations of a Psychiatric Drug Alter Behaviour of Fish from Natural Populations. Science 339, 418-815.

Bruchet, A., C. Hochereau, C. Picard, V. Decottignies, J. M. Rodrigues and M. L. Janex-Habibi (2005): Analysis of drugs and personal care products in French source and drinking waters: the analytical challenge and examples of application. Water Science and Technology 52 (8): 53-61.

Bu, Q., B. Wang, J. Huang, S. Deng and G. Yu (2013): Pharmaceuticals and personal care products in the aquatic environment in China: A review. Journal of Hazardous Materials 262: 189–211.

Buchberger, W. W. (2011): Current approaches to trace analysis of pharmaceuticals and personal care products in the environment. Journal of Chromatography A 1218 (4): 603-618.

Caldwell D.J., Mastrocco F., Anderson P.D., Länge R., Sumpter J.P. (2012): Predicted-no-effect concentrations for the steroid estrogens estrone, 17beta-estradiol, estriol, and 17alpha-ethinylestradiol. Environ. Toxicol. Chem. 31(6), 1396-1406.

Calisto, V. and V. I. Esteves (2009): Psychiatric pharmaceuticals in the environment. Chemosphere 77 (10): 1257-1274.

Cardoso, O., J.-M. Porcher and W. Sanchez (2014): Factory-discharged pharmaceuticals could be a relevant source of aquatic environment contamination: Review of evidence and need for knowledge. Chemosphere 115: 20-30.

Daghrir, R. and P. Drogui (2013): Tetracycline antibiotics in the environment: a review. Environmental Chemistry Letters 11 (3): 209-227.

Daughton, C. G. (2014): The Matthew Effect and widely prescribed pharmaceuticals lacking environmental monitoring: Case study of an exposure-assessment vulnerability. Science of The Total Environment 466–467 (0): 315-325.

de Jager, C., A. Swemmer, N. H. Aneck-Hahn, C. van Zijl, S. van Wyk, M. S. Bornman, I. Barnhoorn, M. Jonker, J. H. J. van Vuren and A. E. C. Burger (2011): Endocrine Disrupting Chemical (EDC) Activity and Health Effects of Identified Veterinary Growth Stimulants in Surface and Groundwater. Water Research Commission South Africa. 195 pp.

Dolar, D., T. I. Zokic, K. Kosutic, D. Asperger and D. M. Pavlovic (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 19 (4): 1033-1042.

Ebert I., Bachmann J., Kühnen U., Küster A., Kussatz C., Maletzki D., Schlüter C. (2011): Toxicity of the fluoroquinolone antibiotics enrofloxacin and ciprofloxacin to photoautotrophic aquatic organisms. Environ. Toxicol. Chem. 30, 2786-2792.

EC (2001a): Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82/dir_2001_82_en.pdf

EC (2001b): Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Off. J. Eur. Commun. 2004:311, 67. http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

EC (2013): Diclofenac EQS dossier. 26 pp. Available at https://circabc.europa.eu/sd/a/d88900c0-68ef-4d34-8bb1-baa9af220afd/Diclofenac%20EQS%20dossier%202011.pdf (last accessed on Jan 26th, 2015).

EMA (2012): Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products. Committee for Medicinal Products for Veterinary Use (CVMP). EMA/CVMP/ERAWP/409328/2010. 11 pp., London, UK.

EMEA (2006): Guideline on the environmental risk assessment of medicinal products for human use. Committee for medicinal products for human use (CHMP). Doc. Ref. EMEA/CHMP/SWP/4447/00 corr 2, 12 pp. London, UK.

Falås, P., H. R. Andersen, A. Ledin and J. la Cour Jansen (2012): Occurrence and reduction of pharmaceuticals in the water phase at Swedish wastewater treatment plants. Water Sci. Tech. 66 (4): 783-791.

FAO/OIE/WHO (Food and Agriculture Organization of the United Nations/World Organization for Animal Health/ World Health Organization). (2006): Antimicrobial Use in Aquaculture and Antimicrobial Resistance. Available: http:// www.who.int/topics/foodborne_diseases/aquaculture_ rep_13_16june2006%20.pdf [accessed 18 April 2013].

Fatta-Kassinos, D., M. I. Vasquez and K. Kümmerer (2011): Transformation products of pharmaceuticals in surface waters and wastewater formed during photolysis and advanced oxidation processes – Degradation, elucidation of byproducts and assessment of their biological potency. Chemosphere 85 (5): 693-709.

Fent, K. Weston; A.A., Caminada, D. (2006): Ecotoxicology of human pharmaceuticals. Aquat. Toxicol. 76(2):122-59.

Fick J., Soderstrom H., Lindberg R.H., Phan C., Tysklind M., Larsson D.G.J (2009): Contamination of surface, ground, and drinking water from pharmaceutical production. Environ. Toxicol. Chem. 28(12), 2522-2527.

Forsberg K., Reyes A., Wang B., Selleck E., Sommer M., Dantas G. (2012): The shared antibiotic resistome of soil bacteria and human pathogens. Science 337, 1107-11110.

Foster H.R., Burton G.A., Basu N., Werner E.E. (2010): Chronic exposure to fluoxetine (Prozac) causes developmental delays in Rana pipiens larvae. Environ. Toxicol. Chem. 29, 2845-2850.

Gawel E., Köck W., Schindler H., Holländer R., Lautenschläger S. (2015): Mikroverunreinigungen und Abwasserabgabe. UBA Texte 26. Umweltbundesamt Dessau. 132 pp.

González, S., R. López-Roldán and J.-L. Cortina (2012): Presence and biological effects of emerging contaminants in Llobregat River basin: A review. Environmental Pollution 161 (0): 83-92.

Green, R. E., M. A. Taggart, D. Das, D. J. Pain, C. Sashi Kumar, A. A. Cunningham and R. Cuthbert (2006): Collapse of Asian vulture populations: risk of mortality from residues of the veterinary drug diclofenac in carcasses of treated cattle. Journal of Applied Ecology 43 (5): 949-956.

Günthert, F.W. and S. Rödel (2013). „ Bewertung vorhandener Technologien für die Elimination anthropogener Spurenstoffe auf kommunalen Kläranlagen.“ Bericht der Universität der Bundeswehr München, Siedlungswasserwirtschaft und Abfalltechnik; 176 pp.

Hamscher, G., H. T. Pawelzick, S. Sczesny, H. Nau and J. Hartung (2003): Antibiotics in Dust Originating from a Pig-Fattening Farm: A New Source of Health Hazard for Farmers? Environmental Health Perspectives 111 (13): 1590 - 1594.

Hanczakowska E,, Szewczyk A.(2007): Application of herbs and herbal preparations in pig feeding. Ann Anim Sci 7:3–11.

Harris, C.A., Hamilton, P.B., Runnalls, T.J., Vinciotti, V., Henshaw, A., Hodgson, D., Coe, T.S., Jobling, S., Tyler, C.R. and Sumpter, J.P. (2011): The consequences of feminization in breeding groups of wild fish. Environmental Health Perspectives 119 (3) : 306- 311.

Holm G., Snape J.R., Murray-Smith R., Talbot J., Taylor D:, Sörme P. (2013): Implementing Ecopharmacovigilance in Practice: Challenges and Potential Opportunities. Drug Saf. 36, 533–546.

Hughes, S. R., P. Kay and L. E. Brown (2012): Global Synthesis and Critical Evaluation of Pharmaceutical Data Sets Collected from River Systems. Environmental Science & Technology 47 (2): 661-677.

Joss A., Keller E., Alder A.C., Göbel A., McArdell C.S., Ternes T.A., Siegrist H. (2005): Removal of pharmaceuticals and fragrances in biological wastewater treatment. Water Research 39 (14),3139–315.

JRC – Joint Research Center (2012): FATE SEES -Results of a Pan - European Snapshot of randomly taken sewage sludge sample. Presentation available (accessed on Dec 11th, 2014) at http://ec.europa.eu/environment/waste/sludge/pdf/FATE_SEES_pres.pdf.

Kemper, N. (2008): Veterinary antibiotics in the aquatic and terrestrial environment. Ecological Indicators 8 (1): 1-13.

Kidd K.A., Mills K.H., Palace V.P., Evans R.E., Lazorchak J.M., Flick R.W. (2007): Collapse of a fish population after exposure to synthetic estrogen. P. Natl. Acad. Sci. USA 104, 8897-8901.

Klecka, G., C. Persoon and R. Currie (2010): Chemicals of Emerging Concern in the Great Lakes Basin: An Analysis of Environmental Exposures. Reviews of Environmental Contamination and Toxicology Volume 207. David M. Whitacre, Springer New York. 207: 1-93.

Knacker T., Liebig M., Moltmann J.F. (2008): Comparison of Prospective and Retrospective Environmental Risk Assessments of Human Pharmaceuticals. In: Pharmaceuticals in the Environment. Kümmerer (Editor), 385-391.

Kookana R.S., Mike Williams, Alistair B. A. Boxall, D. G. Joakim Larsson, Sally Gaw, Kyungho Choi, Hiroshi Yamamoto, Shashidhar Thatikonda, Yong-Guan Zhu, Pedro Carriquiriborde (2014): Potential ecological footprints of active pharmaceutical ingredients: an examination of risk factors in low-, middle- and high-income countries. Phil. Trans. R. Soc. B: 2014 369 20130586; DOI: 10.1098/rstb.2013.0586.

K'Oreje, K. O., K. Demeestere, P. De Wispelaere, L. Vergeynst, J. Dewulf and H. Van Langenhove (2012): From multi-residue screening to target analysis of pharmaceuticals in water: Development of a new approach based on magnetic sector mass spectrometry and application in the Nairobi River basin, Kenya. The Science of the Total Environment 437: 153-164.

Kümmerer K., Hempel M. (2010): Green and Sustainable Pharmacy. Springer-Verlag, Berlin.

Küster A., Adler N. (2014): Pharmaceuticals in the environment: scientific evidence of risks and its regulation. Philosophical Transactions of the Royal Society B 369 20130587; DOI: 10.1098/rstb.2013.0587.

LÄKEMEDELSVERKERT (2011): Platform to enable the initiation of a revision of EU legislation on Good Manufacturing Practice, GMP, in order for legislation also to comprehend environmental considerations - Report from the Medical Products Agency. 49pp. Uppsala, Sweden-

Lapworth, D. J., N. Baran, M. E. Stuart and R. S. Ward (2012): Emerging organic contaminants in groundwater: A review of sources, fate and occurrence. Environmental Pollution 163 (0): 287-303.

Larsson D.G.J., de Pedro C., Paxeus N. (2007): Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J. Hazardous Materials. 148, 751-755.

Larsson, D. G. J. and Fick, J. (2009): Transparency throughout the production chain--a way to reduce pollution from the manufacturing of pharmaceuticals? Reg. Toxicol. Pharmacol. 53(3): 161-3.

Larsson D.G.J. (2014): Pollution from drug manufacturing: review and perspectives. Phil. Trans. R. Soc. B 369: 20130571. http://dx.doi.org/10.1098/rstb.2013.0571

Li, W. C. (2014): Occurrence, sources, and fate of pharmaceuticals in aquatic environment and soil. Environmental pollution (Barking, Essex: 1987) 187: 193-201.

Li D., Yang M., Hu J.Y., Zhang Y., Chang H., Jin F. (2008): Determination of penicillin G and its degradation products in a penicillin production wastewater treatment plant and the receiving river. Water Research 42(1-2), 307-317.

Liebig M., Fernandez A.A., Blübaum-Gronau E., Boxall A., Brinke M., Carbonell G., Egeler P., Fenner K., Fernandez C., Fink G., Garric J., Halling-Sørensen B., Knacker T., Krogh K.A., Küster A., Löffler D., Ángel M., Cots P., Pope L., Prasse C., Römbke J., Rönnefahrt I., Schneider M.K., Schweitzer N., Tarazona J.V., Ternes T.A., Traunspurger W., Wehrhan A., Duisy K. (2010): Environmental risk assessment of ivermectin: A case study. Integr. Environ. Assess. Manag. 6, 567-587.

LIF (2012) Environmental classification of pharmaceuticals. Guidance of pharmaceutical companies. http://www.ivl.se/download/18.7b47b48513b0e45ae7818ff/1357715170180/Environmental+classification+of+pharmaceuticals+att+wwwfassse+120816.pdf

LIF (2014): Swedish prescribing guide. Available from http://www.fass.se/LIF/home/index.jsp

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.

Michelini L.A., Reichel R.B., Werner W.C., Ghisi R.A., Thiele-Bruhn S. (2012): Sulfadiazine uptake and effects on salix fragilis and zea mays plants. Water Air Soil Poll. 223, 5243-5257.

Miège, C., J. M. Choubert, L. Ribeiro, M. Eusèbe and M. Coquery (2009): Fate of pharmaceuticals and personal care products in wastewater treatment plants – Conception of a database and first results. Environmental Pollution 157 (5): 1721-1726.

Oaks J.L., Gilbert M., Virani M.Z.. Watson R.T., Meteyer C.U., Rideout B.A., Shivaprasad H.L., Ahmed S, Chaudry M.J.I., Arshad M., Mahmood S., Ali A., Khan A.A. (2004): Diclofenac residues as the cause of population decline of vultures in Pakistan. Nature 427, 630–633.

Orias, F. and Y. Perrodin (2013): Characterisation of the ecotoxicity of hospital effluents: A review. Science of The Total Environment 454–455 (0): 250-276.

Ort C., Hollender J., Schaerer M., Siegrist H.R. (2009): Model-Based Evaluation of Reduction Strategies for Micropollutants from Wastewater Treatment Plants in Complex River Networks. Environ. Sci. Technol. 43(9), 3214-3220.

Petrovic, M., M. D. Hernando, M. S. Diaz-Cruz and D. Barcelo (2005): Liquid chromatography-tandem mass spectrometry for the analysis of pharmaceutical residues in environmental samples: a review. Journal of Chromatography A 1067 (1-2): 1-14.

Plósz B.G., Benedetti L., Daigger G.T., Langford K.H., Larsen H.F., Monteith H., Ort C., Seth R., Steyer J.-P., Vanrolleghem P.A. (2012): Modelling micro-pollutant fate in wastewater collection and treatment systems: status and challenges. Water Sci. Technol. 67(1), 1-15.

Prasse C., Schlüsener M.P., Schulz R., Ternes T.A. (2010): Antiviral Drugs in Wastewater and Surface Waters: A New Pharmaceutical Class of Environmental Relevance? Environ. Sci. Technol. 44, 1728-1735.

Pruden A., Larsson D.G.J., Amézquita A., Collignon P., Brandt K.K., Graham D.W., Lazorchak J.M., Suzuki S., Silley P., Snape J.R.,. Topp E. Zhang T., Zhu Y-G. (2013): Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Environ. Health Perspect. 121, 878–885. http://dx.doi.org/10.1289/ehp.1206446

Sadezky, A., D. Löffler and T. Ternes (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.

SAICM (2013): Table of projects funded by the Quick Start Programme (QSP) trust fund of the Strategic Approach to International Chemicals Management (SAICM) http://www.saicm.org/images/saicm_documents/qsp/QSP%20trust%20fund%20approved%20%20Projects%2001.02.2013.pdf

SAICM (2015): Nomination for new emerging policy issue: environmentally persistent pharmaceutical pollutants - Note by the Secretariat. 6 pp., Geneva, Switzerland.

Shimizu, A., H. Takada, T. Koike, A. Takeshita, M. Saha, Rinawati, N. Nakada, A. Murata, T. Suzuki, S. Suzuki, N. H. Chiem, B. C. Tuyen, P. H. Viet, M. A. Siringan, C. Kwan, M. P. Zakaria and A. Reungsang (2013): Ubiquitous occurrence of sulfonamides in tropical Asian waters. Science of The Total Environment 452–453 (0): 108-115.

START (2008): Humanarzneimittelwirkstoffe: Handlungsmöglichkeiten zur Verringerung von Gewässerbelastungen. Eine Handreichung für die Praxis. Ergebnisse zum Forschungsprojekt start. Institut für sozial-ökologische Forschung (ISOE) GmbH, Frankfurt am Main. www.start-project.de/downloads/start.pdf

Storteboom H., Arabi M., Davis J.G., Crimi B., Pruden A. (2010): Tracking antibiotic resistance genes in the South Platte River basin using molecular signatures of urban, agricultural, and pristine sources. Environ Sci Technol 44:7397–7404.

Thames C.H., Pruden A., James R.E., Ray P.P., Knowlton K.F.(2012): Excretion of antibiotic resistance genes by dairy calves fed milk replacers with varying doses of antibiotics. Front Microbiol 3:139.

Ternes, T., Janex-Habibi, M.-L., Knacker, T., Kreuzinger, N., Siegrist, H (2004): Assessment of Technologies for the Removal of Pharmaceuticals and Personal Care Products in Sewage and Drinking Water Facilities to Improve the Indirect Potable Water Reuse. Project summary available at http://ec.europa.eu/research/endocrine/pdf/poseidon_final_report_summary_en.pdf (accessed on Dec 11th, 2014).

Thomas K.V., Dye C., Schlabach M., Langford K.H. (2007): Source to sink tracking of select-ed human pharmaceuticals from two Oslo city hospitals and a wastewater treatment works. Journal of Environmental Monitoring, 9, 1410-1418.

Triebskorn R., Casper H., Scheil V., Schwaiger J. (2007): Ultrastructural effects of pharmaceuticals (carbamacepine, clofibric acid, metoprolol, diclofenac) in rainbow trout (Oncorhynchus mykiss) and common carp (Cyprinus carpio). Anal. Bioanal. Chem. 387, 1405-1416.

Triebskorn R., Schwarz S., Köhler H.-R., Berg K., Jungmann D., Frey M., Oehlmann J., Oetken M. (2014): From theory to reality – Evaluation of suitable organisms and test systems for the biomitoring of pharmaceuticals. Part I: Literature review. UBA-Texte 64/2014. http://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/texte_64_2014_from_theory_to_reality_biomonitoring_pharmaceuticals.pdf

Umweltbundesamt (2012): Maßnahmen zur Minderung des Eintrags von Humanarzneimitteln und ihrer Rückstände in das Rohwasser zur Trinkwasseraufbereitung. Empfehlung des Umweltbundesamtes vom 30.08.2011 nach Anhörung der Trinkwasserkommission des Bundesministeriums für Gesundheit. Bundesgesundheitsblatt 55: 143-149. http://www.umweltbundesamt.de/sites/default/files/medien/377/dokumente/massnahmen_humanarzneimittel.pdf

UN – United Nations (2013): World contraceptive patterns 2013. UN New York, ST/ESA/SER.A/326 - Sales No. 13.XIII.12, Available (accessed on Dec 11th, 2014) at http://www.un.org/en/development/desa/population/publications/pdf/family/worldContraceptivePatternsWallChart2013.pdf.

UNEP & WHO (2013): State of the science of endocrine disrupting chemicals 2012. An assessment of the state of the science of endocrine disruptors prepared by a group of experts for the United Nations Environment Programme and World Health Organization. Åke Bergman, Jerrold J. Heindel, Susan Jobling, Karen A. Kidd and R. Thomas Zoeller (Eds). http://www.who.int/ceh/publications/endocrine/en/

UNEP (2006): Strategic approach to international chemical management. SAICM texts and resolutions of the International Conference on Chemical Management. United Nations Environment Programme. Geneva. http://www.saicm.org/images/saicm_documents/saicm%20texts/SAICM_publication_ENG.pdf

US FDA (1998): Guidance for industry: environmental assessment of human drug and bio-logics application. U.S. Food and Drug Administration, Silver Spring.

Van Boeckel T.P., Gandra S., Ashok A., Caudron Q., Grenfell B.T., Levin S.A., Laxminarayan R. (2014): Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014. http://dx.doi.org/10.1016/S1473-3099(14)70780-7.

Versteeg D.J., Alder A.C., Cunningham V.L., Kolpin D.W., Murray-Smith R., Ternes T., (2005): Environmental Exposure Modeling and Monitoring of Human Pharmaceutical Concentrations in the Environment. In: "Human Pharmaceuticals: Assesssing the impacts on aquatic ecosystems", Ed: R.T. Williams.

VICH (2000): Environmental impact assessment for veterinary medicinal products – Phase I. VICH GL6 (Ecotoxicity Phase I). 9 pp., Bruxelles, Belgium.

VICH (2004): Environmental impact assessment for veterinary medicinal products – Phase II. VICH GL38 (Ecotoxicity Phase II). 38 pp., Bruxelles, Belgium.

Vidaurre R., Touraud E., Roig B., Kampa E. (2010): Recommendations on communication and education. In: Pharmaceuticals in the Environment: Current knowledge and need assessment to reduce presence and impact. Ed: B. Roig. IWA Publishing, London.

Weissbrodt D., Kovalova L., Ort C., Pazhepurackel V., Moser R., Hollender J., Siegrist H., McArdell C.S. (2009): Mass flows of X-ray contrast media and cytostatics in hospital wastewater. Environmental Science and Technology 43(13):4810-4817.

Wennmalm A., Gunnarsson B. (2010): Experiences with the Swedish Environmental Classification Scheme. In. Kümmerer K., Hempel M. (Eds.) Green and Sustainable Pharmacy, Springer Verlag, Berlin, Heidelberg.

WHO (1999): Guidelines for Safe Disposal of Unwanted Pharmaceuticals in and after Emergencies. WHO/EDM/PAR/99.2. 36 pp. http://apps.who.int/medicinedocs/en/d/Jwhozip51e/

WHO (2012): Pharmaceuticals in drinking-water.
http://apps.who.int/iris/bitstream/10665/44630/1/9789241502085_eng.pdf?ua=1

WHO (2014): Safe management of wastes from health-care activities – edited by Y. Chartier et al. – 2nd ed. 329 pp. ISBN 978 92 4 154856 4

WHO (2014): Comments on the SAICM emerging policy issues proposal "Environmentally Persistent Pharmaceutical Pollutants", 11 July 2014,
http://www.saicm.org/images/saicm_documents/OEWG2/CommentsEPPP/who%20comments%20on%20eppp.pdf

WHO (2014): Antimicrobial Resistance. Global Report on Surveillance.

WHO (2014): Substandard/spurious/falsely-labelled/falsified/counterfeit medical products. Report by the Director-General.

WHO (2014). Collaborating Centre for Drug Statistics Methodology, ATC classification index with DDDs. Oslo 2014.

Wilton Park (2015): Antimicrobial resistance in humans and animals in low and middle income countries - How can knowledge and action be strengthened at national level? Report WP 1399.Wilton Park, UK.

Zrnic, M., M. Gros, S. Babic, M. Kaštelan-Macan, D. Barcelo and M. Petrovic (2014): Analysis of anthelmintics in surface water by ultra high performance liquid chromatography coupled to quadrupole linear ion trap tandem mass spectrometry. Chemosphere 99 (0): 224-232.