Options for a strategic approach to pharmaceuticals in the environment

Task 1 Report
Revised version

September 2016
## Document information

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<tr>
<td><strong>PROJECT TEAM</strong></td>
<td>Deloitte, INERIS, Klaus Kümmerer, LSE, Milieu Ltd</td>
</tr>
<tr>
<td><strong>AUTHORS</strong></td>
<td>Ms Sarah Lockwood, Deloitte</td>
</tr>
<tr>
<td></td>
<td>Ms Nada Saïdi, Deloitte</td>
</tr>
<tr>
<td></td>
<td>Ms Valerie Ann Morgan, Deloitte</td>
</tr>
<tr>
<td><strong>REVIEWERS</strong></td>
<td>Ms Katherine Salès, Deloitte</td>
</tr>
<tr>
<td></td>
<td>Ms Florence Didier-Noaro, Deloitte</td>
</tr>
<tr>
<td></td>
<td>Mr Sébastien Soleille, Deloitte</td>
</tr>
<tr>
<td></td>
<td>Mr Klaus Kümmerer</td>
</tr>
<tr>
<td></td>
<td>Mr Tony Zamparutti, Milieu Ltd.</td>
</tr>
<tr>
<td></td>
<td>Ms Yoline Kuipers, Milieu Ltd.</td>
</tr>
<tr>
<td></td>
<td>Ms Sandrine Andres, INERIS</td>
</tr>
<tr>
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<th>Description</th>
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<tr>
<td>ABR</td>
<td>Antibiotic Resistant Bacteria</td>
</tr>
<tr>
<td>AMR</td>
<td>Anti-Microbial Resistance</td>
</tr>
<tr>
<td>AOP</td>
<td>Adverse Outcome Pathway</td>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical (Classification System)</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human use</td>
</tr>
<tr>
<td>CMR</td>
<td>Carcinogenic, Mutagenic and Reprotoxic</td>
</tr>
<tr>
<td>CVMP</td>
<td>Committee for Medicinal Products for Veterinary use</td>
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<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
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<tr>
<td>DDE</td>
<td>Dichlorodiphenyldichloroethylene</td>
</tr>
<tr>
<td>DID</td>
<td>DDD per 1,000 inhabitants per day</td>
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<tr>
<td>E2</td>
<td>17 beta-estradiol</td>
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<tr>
<td>EE2</td>
<td>17 alpha-ethinylestradiol</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EC₅₀</td>
<td>Half maximal Effective Concentration</td>
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<tr>
<td>ECDC</td>
<td>European Centre for Disease Prevention and Control</td>
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<tr>
<td>EDC</td>
<td>Endocrine-disrupting chemical</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EPAR</td>
<td>European Public Assessment Report</td>
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<td>EPR</td>
<td>Extended Producer Responsibility</td>
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<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>FDW</td>
<td>Finished Drinking Water</td>
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<tr>
<td>IED</td>
<td>Industrial Emissions Directive (2010/75/EU)</td>
</tr>
<tr>
<td>IMI</td>
<td>Innovative Medicines Initiative</td>
</tr>
<tr>
<td>LC₅₀</td>
<td>Half maximal Lethal Concentration</td>
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</tbody>
</table>
LC/MS  Liquid Chromatography / Mass Spectrometry
LOAEL  Lowest-observed-adverse-effect level
MA  Market Authorisation
MEC  Measured Environmental Concentration
MoA  Mode of Action
MUMS  Minor Use Minor Species
MRL  Maximum Residue Limit
MS  Member State
NOAEL  No-observed-adverse-effect level
NSAID  Nonsteroidal Anti-inflammatory Drug
OTC  Over The Counter
PAR  Public Assessment Report (national)
PBT  Persistence, Bioaccumulation and Toxicity
PCU  Population Correction Unit
PEC  Predicted Environmental Concentration
PNEC  Predicted No Effect Concentration
QSAR  Quantitative structure–activity relationship
R&D  Research & Development
REACH  Regulation on the Registration, Evaluation, Authorisation and Restriction of Chemicals (1907/2006)
RMM  Risk Mitigation Measure
UF  Uncertainty Factor
VICH  Veterinary International Conference on Harmonization
WHO  World Health Organization
WWE  Waste Water effluents
WWI  Waste Water Influents
WWTP  Waste Water Treatment Plant
1. Introduction

This introductory chapter presents the background to and the objectives of the study on Options for a strategic approach to pharmaceuticals in the environment, of which this report constitutes the first deliverable.

1.1. Background to the study

Health care as practised in the European Union (EU) heavily relies on the consumption of pharmaceuticals, as reflected by the continuous growth of the European market for medicines for human and veterinary use. The EU is even considered the second biggest consumer in the world after the United States of America. While the benefits of a responsible use of these substances for human health and veterinary care are recognised, there is, however, increasing concern over the potential adverse effects of these substances on the environment and on human health via the environment.

It is now widely acknowledged that pharmaceuticals and their residues – including Active Pharmaceutical Ingredients (API), metabolites and transformation products – are emitted into the environment at different stages of their life cycle, from their production to their use to their disposal. A large body of literature \(^1\) reports the presence of pharmaceuticals in environmental compartments (e.g. surface and ground water, soils, biota) in different parts of the world, including the EU Member States. They are generally detected at low concentrations (e.g. in the range of sub ng/L to µg/L in the aquatic environment).

The level and frequency of exposure of biota (e.g. plants, animals, bacteria) and humans to these substances and their residues is a key component of the risk they pose to human health and the environment, along with their inherent hazard level. Actual exposure can be particularly complex to determine, because of the multiplicity of sources of emissions and contamination pathways (diffuse contamination, point source pollution from sewage networks or landfill leachates) as well as transformation and transfer processes in different environmental compartments. Another challenge lies in assessing the potential effects on the environment and human health of chronic exposure to low doses of mixtures of pharmaceuticals.

In the EU, the issue of pharmaceuticals in the environment is to some extent addressed in the chemicals (including pharmaceuticals), industrial emissions, water, waste and food legislation. Most do not include specific provisions for pharmaceuticals, but can be applicable to the issue.

The present study is part of the effort to develop the EU strategic approach for pharmaceuticals mentioned in Directive 2013/39/EU,\(^2\) which is likely to take the form of a Commission Communication. This approach must allow coordinating and balancing efforts across Member States and categories of stakeholders towards:

- better knowledge of the issue (e.g. through fostering research and adequate monitoring and reporting activities);
- more sustainable production, consumption and disposal patterns; and
- cost-efficient measures to mitigate associated risks.

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\(^1\) See for instance the review in Pharmaceuticals in the Environment (2015), Editor(s) R E Hester, R M Harrison, ISBN 978-1-78262-189-8

It must also ensure that the clear and undisputable benefits of the sustainable use of pharmaceuticals for human and animal life and the competitiveness of EU healthcare systems are maintained.

In order to achieve these objectives, many possible options have been identified at the different stages of the life-cycle of pharmaceuticals, notably by the 2014 BIO study (BIOIS, 2014). The Commission organised a workshop in September 2014 aimed at prioritising those options according to various stakeholders’ inputs. Those and other options will be further considered under later tasks in this study.

1.2. Objectives of the study and of this report

The general objective of the study is to assist the Commission with the development of a strategic approach to pharmaceuticals in the environment, by identifying uncertainties, helping to fill knowledge gaps and providing details and documentation regarding options that could address the issue. The options will be given a preliminary assessment with regard to their feasibility (including political feasibility, i.e. acceptability and support of the different categories of stakeholders), efficiency, effectiveness and coherence with other policy developments. This approach is proposed by analogy with the Commission’s usual approach to impact assessment, although it is not intended that the strategic approach requires impact assessment. The strategic approach is expected to be followed by proposals for measures, as appropriate, and any legislative proposals would then be subject to impact assessment.

The specific objectives of the study are threefold:

1. Providing the Commission with an update of:
   a. the main issues and uncertainties regarding pharmaceuticals in the environment relevant to the EU;
   b. the options to be considered for further assessment, based on the outcomes of the 2014 workshop and on further research;

2. Perform a preliminary assessment of all identified options by evaluating their feasibility, efficiency, effectiveness and coherence with other policy developments; and

3. Conduct a public consultation on the most promising options, in order to evaluate the level of support of different stakeholders and to gather their experience and opinions about them.

1.3. Objectives of this report

This Task 1 deliverable covers the objective 1a.

During the period 2000–2015, the numbers of articles published on the issue of pharmaceuticals in the environment (in journals and books) had increased yearly — from a rate of 200 per year to a rate of 1800 per year. Daughton et al. (2016) recently published a bibliometric analysis of the literature available on Pharmaceuticals in the environment and we invite the interested reader to explore this document (Daughton et al., 2016).

The present report does not aim to provide an exhaustive review of the literature. It rather aims at highlighting main findings regarding the scale of the problem and remaining uncertainties relevant to the EU, based on a selection of EU or international publications mostly published since 2013.

Recent findings tend to increase the body of evidence supporting the ubiquity of pharmaceuticals in the environment, at concentrations which may pose risks to the environment, and possibly to human health via the environment. However, uncertainties regarding the scale of the problem remain high, due to the large number of pharmaceuticals and the challenges of assessing risks linked to multi-compound exposure at low doses, potentially over long periods of time. The update of options,
their rationale and preliminary assessment will be included in Task 2 deliverable.
This report is organised in 7 sections:

1. Chapter 1 provides the background and the objectives of the study. It also specifies the scope of work covered by the present report;

2. Chapter 2 highlights latest trends and projections with regards to human and veterinary consumption of pharmaceuticals (2.3) and provides key figures about the pharmaceutical industry (2.1) and marketing authorisations (1.1);

3. Chapter 3 highlights main pathways of contamination of the environment by pharmaceuticals, at the different stages of the life-cycle, from their manufacturing (3.1), to their use (3.2), to their disposal (3.3);

4. Chapter 4 describes the occurrence (4.1) and environmental concentrations (4.2) of pharmaceuticals in different environmental compartments, through a selection of recent examples;

5. Chapter 5 highlights how environmental risks are assessed (5.1) and based on which information (5.2), which risks are currently suspected (5.3) and which impacts are actually observed (1.1). Lastly, it focuses on the risks posed by endocrine disruptors, which are of increasing concern in the EU (5.5);

6. Chapter 6 highlights the latest state of knowledge about the risks and potential impacts on human health of environmental exposure to pharmaceuticals and their residues, through a selection of recent research findings (6.1). A focus is made on the phenomenon of anti-microbial resistance (AMR), which is subject to increasing concerns for human and animal health globally (6.3);

7. The last chapter highlights main conclusions on the knowledge, scale of the issue, and research needs with regards to human and veterinary pharmaceuticals in the environment.
2. Setting the scene: the production and consumption of pharmaceuticals in the EU

_In brief_

- The present chapter highlights latest trends and projections with regards to human and veterinary consumption of pharmaceuticals and provides key figures about production and marketing authorisations.

- On a global scale, the EU takes the second place for pharmaceuticals sales, with about 25% of the world pharmaceutical sales for human consumption vs. 31% for veterinary consumption. The overall market is estimated at €225 billion, with nearly 10% of this value dedicated to research and development of new products, and creates nearly 900,000 jobs in the EU.

- About 3,000 active pharmaceutical substances are currently authorised on the EU market as a whole, with a wide variability across Member States. The number of new pharmaceuticals reaching consumers per year has nearly doubled in the last decade (between 2005 and 2014), both for human and veterinary products. Stimulated by EU legislation, increasing trends can be observed in applications for orphan medicines for human consumption as well as veterinary medicines for minor species and rare diseases in major species.

- There is an increasing trend in the consumption of human and veterinary pharmaceuticals in the EU.

- For human pharmaceuticals, this trend has been driven in particular by the use of antimicrobials (in particular carbapenems and polymixins), although their overall use has been recently slowing down, as well as by the use of pharmaceuticals related to ageing and chronic diseases (antihypertensives, cholesterol lowering drugs, antidiabetics, and antidepressants) which has at least doubled in the last decade and is expected to increase further. For veterinary pharmaceuticals, the highest sales today concern parasiticides, vaccines and antimicrobials. Although animal production has been historically using an important amount of antibiotics (about 8,000 tonnes of antimicrobial APIs were used in the EU/EEA countries in 2013), the expert group on European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) shows the sales of antibiotics in the EU for use in animals fell by approximately 8% between 2011 and 2013. Whereas trends in antimicrobial consumption are slowing down in the EU, this is not the case globally as a 67% increase is expected on a global scale from 2010 to 2030 in the agricultural sector alone.

- The reporting of production, authorisation and consumption data of pharmaceuticals remain scattered, little harmonised and updated at the EU level.

This chapter provides an overview of key figures and trends with regards to the sales, marketing authorisations and consumption of both human and veterinary pharmaceuticals. Please note, however, that comparisons between both these sectors in terms of market value, number of products authorised and volumes of consumption must be considered with care given the different targets, types of pharmaceutical applications and number of APIs (much larger for human consumption).
2.1. The EU pharmaceutical industry in figures

On a global scale, the EU takes the second place for pharmaceutical sales, behind the United States of America, with 25% of the world pharmaceutical sales for human purposes vs. 31% for veterinary purposes (Eurostat, 2013; IFAH_website, 2016).

There is a significant difference in market size (in value) between human and veterinary pharmaceuticals in the EU: 97% of the value generated relates to pharmaceuticals for human consumption while 3% relates to veterinary medicines (both food producing and companion animals) (IFAH, 2015).

The EU market has grown substantially over the last 15 years to reach an estimated €220 billion for human pharmaceuticals (x4.5 since 2010) and €5 billion for veterinary pharmaceuticals in 2014. About 10% of this value is spent every year on Research & Development (R&D), both for human and veterinary pharmaceuticals (Eurostat, 2013; IFAH_website, 2016). The EU has maintained a consistent trade surplus for pharmaceuticals since before 2003, reaching €55 billion euros in 2013, with the largest trading partners being the United States of America and Switzerland. One fifth of the value added generated in the EU-28 pharmaceuticals manufacturing sector in 2013 was contributed by Germany alone (20%), followed by Ireland and France (13% each), the UK (11%) and Italy (7%) (Eurostat, 2013).

According to the latest data available on Eurostat, there were approximately 4,200 enterprises in the pharmaceutical manufacturing sector in the EU-28 (including veterinary products), of which half are concentrated in Germany, the UK, Italy, France, and Spain alone. Large enterprises dominate the pharmaceutical industry in Europe, employing 78% of the pharmaceutical manufacturing sector’s workforce, generating 87% of the total value added produced in 2013 (IFAH-Europe, 2016; EFPIA, 2015a; EFPIA, 2015b).

Key figures about the EU pharmaceutical market are summarised in Table 1.

Table 1: Key figures about the EU pharmaceutical market

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Veterinary</th>
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<tr>
<td>EU share of global market</td>
<td>25% (2nd after the United States of America)</td>
<td>31%</td>
</tr>
<tr>
<td>EU expenditure on R&amp;D</td>
<td>€27.5 billion/yr (2014)</td>
<td>€500 million/yr (2014)</td>
</tr>
<tr>
<td>Number of companies</td>
<td>~4,200 (mostly large companies, employing 250 persons or more)</td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>815,000 jobs full time jobs (incl. R&amp;D)</td>
<td>50,000 full time jobs</td>
</tr>
<tr>
<td>EU trade surplus</td>
<td>€55 billion euros (2013)</td>
<td></td>
</tr>
</tbody>
</table>

Sources: (IFAH-Europe, 2016; EFPIA, 2015a; EFPIA, 2015b; Eurostat, 2013)

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3 Value added is a method of evaluating the contribution to overall Gross Domestic Product. It is calculated by taking the difference of the industry’s gross output (sales, etc) and the cost of intermediate inputs.
2.2. Trends in marketing authorisations

Before reaching the consumers, any pharmaceutical must go through specific procedures for marketing authorisation and market access. A pharmaceutical can be placed on the EU market only after a marketing authorisation has been granted in accordance with the pharmaceutical legislation: (i) either by the competent authority\(^4\) of a Member State for its own territory (national authorisation) or (ii) by the European Commission for the entire EU (EU-wide authorisation). As a result of these procedures, new pharmaceutical products are authorised to be produced at industrial scale and placed on the market. The number of new pharmaceuticals reaching consumers per year has nearly doubled in the last decade, both for human and veterinary products. Below is a graphical representation of the trend of the total number of positive opinions for EU-wide marketing authorisations since 2005 up to the latest available data (year 2014) in the EU via the centralised procedure (Figure 1).

**Figure 1 Number of positive opinions for marketing authorisation in the EU 2005 – 2014, via the centralised procedure**

![Graph showing trend of positive opinions for marketing authorisation](source: EMA Annual Reports, years 2005 - 2014)

In 2014, the EMA recommended 82 pharmaceuticals for human use for marketing authorisation, with 81 approved by the Commission in 2015 (EMA, 2015b; EMA, 2014). Half of those approved in 2014 contained a new active substance. We see that increasingly, orphan medicines are being developed and approved. Orphan medicines are intended for the diagnosis, prevention or treatment of life threatening or chronically debilitating conditions that affect not more than five in 10,000 people in the EU. As it is not often profitable for companies to develop pharmaceuticals for rare diseases, EU legislation provides incentives for developers to develop such medicines. As such, an increasing trend can be observed in applications for approval, as well as an increase in overall authorisations of such pharmaceuticals (EMA, 2015b).

In 2014, 20 new veterinary pharmaceuticals were recommended for marketing authorisation - 9 for food producing species and 11 for companion animals – confirming the increase observed in previous years, in part due to the Minor Use Minor Species (MUMS) incentive policy that stimulates the development of veterinary medicines for minor species and rare diseases in major species (EMA, 2015b).

A few thousand APIs are currently authorised on the EU market as a whole. Of 4,000 APIs available in the world (KNAPPE, 2008), 3,000 are currently authorised on the EU market (Touraud et al., 2011). However, according to the variety of pharmaceutical

\(^4\) For a full list of the national competent authorities that authorise pharmaceuticals (for humans and animals) for each country, see the EMA’s list:

- **Human Consumption:**

- **Veterinary:**
Options for a strategic approach to pharmaceuticals in the environment

authorisation procedures at national level, the available estimations show that the number of APIs varies in different Member States (MS). For example, only 850 APIs are authorised in the Netherlands (Derksen et al., 2004) while 2,000 APIs are authorised in the UK (Ashton et al., 2004), 3,080 in Germany5 and 2,800 in France (ANSM, 2014). Several pharmaceutical products contain the same active ingredient. For example, in Germany, there are about 50,000 authorised drugs, with 2,700 of these drugs accounting for about 90% of total consumption, which contain 900 different active substances (Kummerer, 2004).

2.3. Trends in pharmaceuticals consumption

- Human consumption

Overall, there is an increasing trend in the consumption of pharmaceuticals in the EU6, in particular driven by the use of antimicrobials (see Box 1), as well as pharmaceutical drugs related to ageing and chronic diseases (antihypertensives, cholesterol lowering drugs, antidiabetics, and antidepressants) (see Table 3) (ECDC, 2015; OECD Library, 2016)7.

For further insights on available information on pharmaceutical consumption, an inventory of drug consumption in several Member States has recently been published in the context of the research project “PROTECT”, based on the review of previous drug inventories, national drug consumption databases and interviews (PROTECT Consortium, 2013).

Box 1: Trends in anti-microbial consumption in the EU

According to the European Centre for Disease Prevention and Control (ECDC), antimicrobial consumption (expressed in defined daily doses (DDD) per 1,000 inhabitants and per day) significantly increased from 2010 to 2014, in particular in households (see table below). This EU average hides large inter-country variations, both in trends and actual consumption. Antimicrobial consumption in Europe ranged from 10 DDD8 in the Netherlands to 32 DDD in Greece in 2014 (See Table 2 below).

Table 2: EU Consumption of anti-microbials (in DDD per 1,000 inhabitants and per day)

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>Average annual change</th>
<th>MS with highest consumption</th>
<th>MS with lowest consumption</th>
<th>MS with significant increases</th>
<th>MS with significant decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Households</td>
<td>20.1</td>
<td>20.8</td>
<td>21.2</td>
<td>21.8</td>
<td>21.6</td>
<td>0.39</td>
<td>Greece, Romania, France, Cyprus, Belgium</td>
<td>Netherlands, Estonia, Latvia, Sweden, Slovenia</td>
<td>UK (0.61)</td>
<td>Sweden (-0.36)</td>
</tr>
</tbody>
</table>

5 From http://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/amzulassungen-gentec.html, 154/0.05 = 3080

6 http://www.oecd-ilibrary.org/sites/9789264183896-en/03/11/index.html?itemId=/content/chapter/9789264183896-38-en&_csp_=45f4df11dc99cd20191aa39969f74f

7 Note that the latest medicinal use data for Europe is limited to 2008 in Eurostat. Currently, the database is being updated, with an expected publication in December 2016, therefore statistics from the Organisation for Economic Co-operation and Development (OECD) and the European Centre for Disease Prevention and Control (ECDC) statistics were used to illustrate the latest consumption trends.

8 Sales or prescription data presented in DDDs per 1,000 inhabitants per day may provide a rough estimate of the proportion of the study population treated daily with a particular drug or group of drugs. As an example, the figure 10 DDDs per 1,000 inhabitants per day indicates that 1% of the population on average might receive a certain drug or group of drugs daily (WHO, 2016).
Since recently, significant increases can be observed in the EU as well as globally for two ‘last resort’ antibiotic classes: carbapenems and polymixins. Carbapenems are a class of beta-lactams chiefly employed against Gram negative infections, which are the most difficult infections to treat. Carbapenem use has increased rapidly in Europe, albeit with regional variations: measured in DDD per 1,000 inhabitants per day (DID), the range was from 0.0136 DID in Bulgaria to 0.381 DID in the UK (in 2013) (Center for Disease Dynamics, 2015).

Figure 2: Consumption of Antibacterials for Systemic Use (ATC group J01) in the primary care sector in Europe for years 2005, 2010, and 2014

Source: Antimicrobial consumption database, ESAC-NET European Centre for Disease Prevention and Control, 2014
Figure 3: Geographical Heat Mapping of Consumption of Antibacterials for Systemic Use (ATC group J01) in the community (primary care sector) in Europe, 2014

Source: Antimicrobial consumption database, ESAC-NET European Centre for Disease Prevention and Control, 2014

Table 3: Consumption data of other most represented types of pharmaceuticals (in DDD per 1,000 inhabitants and per day in the EU)

<table>
<thead>
<tr>
<th>Type</th>
<th>Trends in EU-18 consumption between 2000 and 2012</th>
<th>Top 5 -MS with highest consumption (2013)</th>
<th>MS with lowest consumption</th>
</tr>
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<tbody>
<tr>
<td><strong>Antihypertensive</strong></td>
<td>x ~2, i.e. from &lt; 200 DDD in 2,000 to 357DDD per 1,000 people per day in 2012 (with Estonia (x ~3) &amp; Luxembourg (x ~4))</td>
<td>Germany, Hungary, Czech Republic, Finland, Slovenia, Luxembourg</td>
<td>Austria, Luxembourg, Portugal, France, Spain</td>
</tr>
<tr>
<td><strong>Cholesterol-lowering</strong></td>
<td>&gt; x 3, i.e. from 29 DDDs per 1,000 people per day in 2000 to nearly 100 DDDs in 2012</td>
<td>Slovakia, the UK, Belgium, Denmark (at least 30% higher than the EU average)</td>
<td>Estonia, Austria, Germany, Italy, Sweden</td>
</tr>
<tr>
<td><strong>Antidiabetics</strong></td>
<td>x ~2, i.e. from ~30 DDD per 1,000 people per day in 2000 to 66 DDD in 2012</td>
<td>Finland (86 DDD per 1,000 people per day), Germany (83) and the UK (82)</td>
<td>Austria, Denmark, Sweden, Estonia, Slovakia</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td>x ~2, i.e. + 20 % on average in Europe per year since 2000, from &lt; 30 DDD in 2000 to 56 DDD in 2012</td>
<td>Portugal, Denmark, Sweden</td>
<td>Estonia, Hungary, Slovakia, Italy, Netherlands</td>
</tr>
</tbody>
</table>

Sources: OECD Library, 2016; ECDC, 2015; Lower, O'Reilly, Mojtabai, & Evans-Lacko, 2015

Consumption patterns depend, amongst other factors, on the prevalence of illness, which may differ from a country to another. For example, in Europe, the prevalence of raised
blood cholesterol for both sexes aged 25 and older ranges from 39% of the population in Bosnia and Herzegovina, to 69% in Iceland (nonetheless it is to be noted that on average Europe has the highest levels of cholesterol of all continents based on latest World Health Organization data from 2008) (WHO, 2008). Whereas high cholesterol levels plague Western European countries, high blood pressure is more prevalent in Eastern European countries. In general, Western European countries have a lower prevalence of raised blood pressure for males aged 18 and over, ranging from less than 20% of the population in the UK suffering from high blood pressure, while in some Eastern European countries over 35% of the said population has high blood pressure, such as in Estonia, Latvia and Lithuania (WHO, 2014).

- Veterinary consumption of pharmaceuticals

Pharmaceuticals are used for livestock (food-producing animals, estimated at >700,000 in the EU, incl. cattle, pigs, sheep and poultry9, to add to the ~1.25 million tonnes of aquaculture goods that were produced in aquaculture farms in the EU in 201110 or for pets (which represented nearly 195 million in the EU in 201211). They can be used in different amounts depending on species: in Germany for instance, 98 % of the veterinary antibiotics are used for treating pigs and poultry, while the remaining 2 % are spread among other species (GACE, 2007). In the EU, their use is only authorised for prevention of disease and treatment of disease (therapeutic, prophylactic or metaphylactic use), as the use for growth promotion was banned in 2006. At the time, studies showed that this ban could temporarily lead to short-term increase in total therapeutic antibiotic consumption, but no lasting negative effects were detected on mortality rate, average daily weight gain, or animal production (e.g. (Aarestrup, Jensen, Emborg, Jacobsen, & Wegener, 2010)).

The highest sales concern parasiticides, vaccines and antimicrobials12 (see Box 2, with a focus on antimicrobials).

A recent publication from EMA highlights that substances that have been categorised as Persistent, Bioaccumulative and Toxic substances (PBTs) or potential PBTs are used mainly in veterinary medicinal products (VMPs) for the treatment of (a wide range of) parasites (both internal and external) in all major food-producing animal species. EMA also expects that they are used extensively throughout Europe (EMA, 2016).

### Box 2: Anti-microbial consumption in livestock

Animal production uses a large amount of antibiotics, although their use varies greatly by country. Globally, estimates of total annual global antibiotic consumption in food animals vary considerably, due to poor surveillance and data collection in many countries, ranging from 63,000 tonnes (Van Boeckel, et al., 2015) to 240,000 tonnes (Grace, 2015) (based on active ingredients). Van Boeckel et al. (2015) estimate that global consumption of antibiotics in food animals will increase by 67 % on a global scale from 2010 to 2030, mainly driven by Brazil, Russia, India, China, and South Africa. Yet, the latest report published in October 2015 by the EMA on veterinary antimicrobials shows that in the EU/EEA (based on data from 26 countries), the sales of antibiotics for use in animals amounted to about 8,050 tonnes in 2013, and fell by approximately 8% between 2011 and 2013 (EMA, 2015).

This report also shows that the usage of antibiotics, expressed in milligrams sold per Population Correction Unit (PCU13) in 1,000 tonnes, varies considerably country by country. For instance, Cyprus uses 100 times more antimicrobials (in mg per PCU) than Norway (EMA, Sales of veterinary antimicrobial agents in 26 EU / EEA Countries in 2013, 2015).

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9 [http://www.ifaeurope.org/food-producing-animals/about-food-producing-animals.html](http://www.ifaeurope.org/food-producing-animals/about-food-producing-animals.html)
12 Countries included in this estimate: AT, BE, CH, CZ, DE, DK, ES, FR, UK, GR, HU, IE, IT, NL, PL, PT, SK
13 Estimated weight at treatment of livestock and of slaughter animals in the corresponding year
Figure 4: Country sales of veterinary antimicrobial agents for food producing animals PCU (1,000 tonnes) mg/PC


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3. Pharmaceutical emissions throughout their life cycle

**In brief**

- The present chapter highlights main pathways of contamination of the environment by pharmaceuticals.
- Contamination of the environment by pharmaceuticals can occur all along the life cycle of pharmaceuticals, from their manufacturing to their disposal (see Figure 5), in their original form (APIs) or as metabolites or other transformation products.
- There are three main known pathways by which APIs can reach the environment:
  - a first pathway is through wastewater discharged from API manufacturing sites: the contribution of manufacturing facilities to emissions of medicinal products and/or their residues has been considered negligible until now. However, pollution downstream from manufacturing plants has been observed in the EU and has been recently subject to increasing attention;
  - a second pathway, considered the most important in terms of volumes, results from normal consumer and animal use and excretion: between 30 and 90% of the orally administered dose of pharmaceuticals are generally excreted as active substances in the urine and faeces of humans or animals despite metabolism;
  - a third pathway results from the improper disposal of unused or expired medicines by consumers. Although the treatment of wastewater can partly eliminate or remove pharmaceuticals, some traces are still detectable in effluents as well as in the receiving surface and groundwater.
- As a result of the second pathway, the environment may be contaminated through the application in the field of manure, sludge or reclaimed wastewater containing pharmaceuticals. In the EU, sludge, manure and wastewater have been found to contain a number of contaminants, including a variety of pharmaceuticals, and therefore are likely to contaminate the soils, while it has been shown that plants have the capacity to accumulate pharmaceuticals from the media in which they are growing.
- Emissions into the environment from incineration are *a priori* considered negligible because of the environmental legislation regulating the treatment of incinerator smoke, while long-term studies on leachates from landfills are still lacking to properly assess the importance of this pathway. Significant amount of work has been made in the EU about the efficiency of wastewater treatment plants (WWTPs) in removal and degradation of medicinal products, both through monitoring and modelling, although the actual costs-benefits of additional treatment steps remain to be assessed.
- There is still a need to improve monitoring strategies to characterise the emissions of pharmaceuticals from different facilities (households, hospitals, health care centres, WWTPs, incineration facilities, manufacturing sites, etc.) and centralise the information in a standardised format. In particular, the picture of pharmaceutical pollution from manufacturing is still highly fragmented, and emissions regarding WWTPs and use of potentially contaminated manure/sludge need to be better characterised.
Contamination of the environment by pharmaceuticals can occur all along the life cycle of pharmaceuticals, from their manufacturing to their disposal (see Figure 5), in their original form (APIs) or as metabolites or other transformation products.

- A transformation product is any new compound created from an API, biotically or abiotically. Biodegradation is a type of transformation allowing the API to be broken-down until – optimally – complete mineralisation;
- A metabolite is a transformation product obtained biotically, either by human/animal metabolism (and then excreted in the environment) or by microbial degradation in the environment.

Transformation products which are not metabolites also include for instance compounds obtained through photoreaction in the environment and compounds obtained through UV or chlorination treatment in WWTPs.

**Figure 5: Pharmaceuticals life-cycle steps and pathways of emissions (Deloitte)**

### 3.1. Manufacturing

Until recently, effluent from pharmaceutical production facilities had largely been neglected as a source of pharmaceutical contamination of the environment (Deegan et al., 2011). The contribution of manufacturing facilities to emissions of pharmaceuticals and/or their residues was generally considered negligible, even though pollution downstream of manufacturing plants has been sporadically observed while monitoring specific sites, e.g. the Rhine (Sacher et al., 2008) or the Lake Leman (Bernard et al., 2007).

However, a review conducted by Larsson showed that recent studies have identified direct emission from drug manufacturing as a source of potentially high discharge, notably when compared to emissions from consumption (Larsson, 2014). Because production (both of the API itself and its formulation into drug products for patient use) is concentrated in specific locations and not distributed across large areas, point-source pollution can arise, potentially leading to locally high concentrations. The picture of pharmaceutical pollution from manufacturing is still highly fragmented and the extent of discharge from pharmaceutical plants remains unknown (Larsson, 2014), but this step of the life-cycle of pharmaceuticals is now subject to increased interest. For instance Swedish county councils have started to request monitoring of emissions during manufacturing when producing pharmaceuticals and the scientific community calls for
better considering this issue in environmental risk assessments (e.g. (Caldwell D. J., 2016)).

### 3.2. Consumption

The consumption phase is considered to be the biggest contributor to the emissions of pharmaceuticals into the environment, in particular through excretions (BIO IS, 2014). There, pharmaceuticals can reach the environment as the original API or as metabolites after transformation by human or animal metabolism.

Pharmaceuticals can also reach the environment directly depending on the mode of administration (when the pharmaceutical cannot be administered directly to the animal but must be diluted into the aquatic medium as can be the case for some medicines used in aquaculture).

Figure 6 presents a schematic diagram of the known contamination pathways related to the use phase for both human and veterinary medicinal products. Emissions related to the wastewater treatments and the use of manure and sludge are described in section 3.3.

![Figure 6: Emission pathways related to the use-phase of medicinal products](image)

#### 3.2.1. Sources of emissions from human consumption

The main pathway of emissions from the use phase remains consumer excretion into sewer and in turn discharges from wastewater treatment systems, which result in continuous introduction of pharmaceuticals in the environment. Previous research shows that, despite metabolism, between 30 and 90% of the orally administered dose of pharmaceuticals are generally excreted as active substances in the urine and faeces (Halling-Sørensen et al., 1998; Rang et al., 1999; Alcock et al., 1999; Holtz et al., 2006). For instance, while pharmaceuticals such as atenolol, sotalol and valsartan are excreted mainly unchanged (>96%), others such as metoprolol, propranolol, diltiazem and verapamil undergo extensive metabolism with just a small percentage of the dose being excreted unchanged (up to 10%) (Brunton et al., 2012). By compiling 42 studies from 1998 to 2015, Godoy et al. highlighted (through the example of hypertensives) that even pharmaceuticals extensively metabolised can be frequently detected in their parental forms at toxicologically relevant concentrations in aquatic environments (see Chapter 4), in part as a result of their high consumption and continuous introduction into those compartments (Godoy et al., 2015).
These emissions mostly come from municipal wastewater systems following the consumption of medicines in households (Götz et al., 2010; Kümmerer, 2010; Michael et al., 2013). A small proportion of these emissions comes from hospitals and health care facilities, which differentiate itself from domestic ones by the nature of administrated molecules (Kümmerer, 2001). Several studies show that API emitted from hospitals can generally be found in low proportions in the urban wastewater (below 25%) (Kümmerer, 2010; Ort et al., 2010; Le Corre et al., 2012; Helwig et al., 2013). However, Santos et al. (2013) showed that this fraction can reach 74% according to the compound type and the hospital beds/inhabitants ratio of the watershed (Santos et al., 2013).

### 3.2.2. Sources of emissions from animal consumption

As with humans, substantial amounts of active substances can be excreted via urines and faeces of animals. Pharmaceuticals may reach soil, ground water (by leaching) and surface water (via direct excretions in water for pasture animals, via surface run-off or transfer from ground water). The contribution of excretions from farming animals in pasture to the environmental load of medicinal products has been investigated (e.g. Fernandez et al., 2009; 2014 study from UBA\(^{14}\)). In comparison, there is still no study quantifying the environmental emissions of medicinal products administered to pets.

Besides excretions, surface water can also be contaminated by run-off from treated animals (for example, in the case of bath treatments for sheep\(^{15}\)). Feed surplus is also a possible source of emissions, on occasions when medicated feed is used, notably in the case of aquaculture (see Box 3).

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In aquaculture, the route of administration of authorised treatments in fish is either via immersion bath or medicated feed. The treatments can thus be directly discharged into the aquatic environment.

<table>
<thead>
<tr>
<th>Administration route</th>
<th>Treatment location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hatcheries</td>
</tr>
<tr>
<td></td>
<td>At sea</td>
</tr>
<tr>
<td>In-feed</td>
<td>Disposal of manure from hatcheries as fertiliser on land</td>
</tr>
<tr>
<td></td>
<td>Waste water discharge</td>
</tr>
<tr>
<td></td>
<td>Food loss/wastage</td>
</tr>
<tr>
<td></td>
<td>Excretion from treated fish</td>
</tr>
<tr>
<td>Immersion bath</td>
<td>Waste water discharge</td>
</tr>
<tr>
<td></td>
<td>Discharge following well boat treatment</td>
</tr>
<tr>
<td></td>
<td>Discharge following treatment in a sea pen</td>
</tr>
</tbody>
</table>

Furthermore a recent study suggests that 70 to 80 % of antibiotics given to fish are excreted back into water (O'Neil, 2015), further contributing to the contamination of the environment. Use of antibiotics has been flagged as a particular concern in open aquaculture where they enter the surrounding marine environment via fish faeces and can persist for long periods in sediment. In 2013, the results of a survey on the occurrence of pharmaceuticals products in the sediments of Scottish marine fish farms showed that concentrations were often below the limit of detection. Yet, the results also highlighted some hotspots, with measured concentrations reaching 2.2 µg of teflubenzuron and 22 µg of emamectin per kg of dry weight sediment (SEPA et al., 2013). Significant emissions of pharmaceuticals were also detected in salmon and shrimps farming in Norway in the 2000’s (Grave et al., 1999). However, O'Neil indicates that the total quantity of antibiotics used in this country (main aquaculture producing country in the EEA) has decreased by 99% while the total volume of fish produced has increased 20 fold during the period 1987 – 2013, thanks to changes in treatment and production strategies (e.g. new vaccines which are used to control several major bacterial diseases; change in falling practices).

### 3.3. Waste management

Waste management reduces pharmaceutical emissions, but they can still enter the environment.

#### 3.3.1. Solid waste

Landfills accepting pharmaceutical solid waste and sewage sludge can produce leachates containing pharmaceuticals at concentrations reaching 1g/L (Table 4) – similar to or even higher than those found in wastewater treatment plant influents (Ramakrishnan et al., 2015).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Use</th>
<th>Concentration (µg/L)</th>
<th>References</th>
</tr>
</thead>
</table>

16 ibid
18 WHO guidelines specify that cytotoxic and narcotic drugs should never be landfilled
19 Adapted from (Eggen et al, 2010)
### Table 1: Summary of pharmaceutical compounds detected in wastewater

<table>
<thead>
<tr>
<th>Compound</th>
<th>Category</th>
<th>Detection Range (mg/L)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>NSAID</td>
<td>69.9–166.624</td>
<td>(Eggen et al., 2010)</td>
</tr>
<tr>
<td>Propyphenazone</td>
<td>Analgesic-rarely used today</td>
<td>&lt;100</td>
<td>(Slack et al., 2005)</td>
</tr>
<tr>
<td>Phenazone</td>
<td>Analgesic-rarely used today</td>
<td>&lt;10–1.250</td>
<td>(Slack et al., 2005)</td>
</tr>
<tr>
<td>Clofibric acid</td>
<td>Drug intermediate</td>
<td>2.9</td>
<td>(Slack et al., 2005)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Pain reliever, fever reducer</td>
<td>&lt;2–96.9</td>
<td>(Heberer et al., 1998)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>NSAID</td>
<td>520</td>
<td>(Daughton et al., 1999)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Anticonvulsant</td>
<td>1,000–6,300</td>
<td>(Kosjek et al., 2009)</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Lipid regulator</td>
<td>190–340</td>
<td>(Heberer et al., 2002)</td>
</tr>
</tbody>
</table>

However, long-term studies of changes in microbial structure and function in environments downgradient of landfills, which could provide insight into the potential concerns associated with continuous exposure to landfill leachate, are still lacking (Ramakrishnan et al., 2015).

Incineration of pharmaceutical waste is a preferred method of disposal than landfill regarding large quantities of pharmaceutical waste, according the WHO guidelines. Emissions into the environment from incineration are considered negligible because of the environmental legislation regulating the treatment of incinerator smoke (BIO IS, 2014).

3.3.2. **Effluents of wastewater treatment**

Important focus has been placed in the last few years on the occurrence of emerging contaminants and pharmaceuticals in particular in WWTPs effluents (Ternes et al., 2015; Evgenidou et al., 2015; Petrie et al., 2015).

Treatment of wastewater can partly eliminate or remove pharmaceuticals, but some traces are still detectable in effluents (Pereira et al., 2015; UK Water Industry Research, 2014) as well as in the receiving surface and groundwater (see Chapter 4).

Pereira et al. (2015) showed through a recent monitoring campaign in Portugal that lipid regulators, anti-inflammatories, and antibiotics were frequently found in influents (184.1, 1339.4, and 330.7 mg/day/1000 inhab., respectively) and effluents (22.3, 15.0, and 68.6 mg/day/1000 inhab., respectively) of WWTPs. A 2014 report by UK Water Industry Research found that in most of 160 sewage treatment works studied, several common drugs were present in the final effluent in concentrations high enough to potentially affect ecosystems. The drugs included the anti-inflammatories ibuprofen and diclofenac, the antibiotics erythromycin and oxytetracycline, and the female sex hormone 17b-estradiol (UK Water Industry Research, 2014). Such contamination of wastewater effluents has been observed earlier elsewhere in the world such as in the USA (e.g. (Karthikeyan, 2006)), Canada (e.g. (Al-Ansari, 2010)) and Japan (e.g. (Nakata, 2005)).

The residues remaining after wastewater treatment depend on the composition of the pharmaceutical, wastewater treatment process, and initial concentrations in the influent. For example, ibuprofen, which is present in significant amounts in wastewater influents, is

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20 [http://www.who.int/water_sanitation_health/medicalwaste/113to129.pdf](http://www.who.int/water_sanitation_health/medicalwaste/113to129.pdf)
yet reduced by 60 to 96% (Bendz et al., 2005). In comparison, carbamazepine removal rates are much lower (Joss et al., 2005).

Some pharmaceuticals have high removal rates but are in fact transformed into other compounds of concern, which might be of concern. For instance, metformin has high removal rates but bacterial treatment leads to the formation of guanylurea which can be recovered at rates up to 91% and 85% (in the WWTP effluent and receiving water, respectively) of the metformin content in the influent (Oosterhuis et al., 2013). The specific case of metformin has been increasingly discussed also because of its high volumes (it is the most commonly prescribed antidiabetic) and the fact that it is not metabolised by humans (100% excretion rate21). For instance, Trautwein et al. measured metformin and guanylurea in Southern German sewage treatment plant, which revealed very high average concentrations in influent (Met = 111,800 ng/L, Gua = 1300 ng/L) and effluent samples (Met = 4,800 ng/L, Gua = 44,000 ng/L) (Trautwein et al., 2014).

These last few years, the highly variable efficiency of wastewater treatments at removing pharmaceuticals has led to much research on treatment techniques and factors influencing their efficiency. It appears that advanced treatment is necessary to tackle the issue of pharmaceuticals. For instance, an ozone/granular activated carbon combination used for drinking water treatment proved to be effective in removing most antibiotics (except danofloxacin and enrofloxacin which have an ionisable character and insufficient ozonation kinetic constant) in experiments conducted by Guillon et al. (Guillon et al., 2015). Nevertheless, some techniques still need optimisation: it was for instance reported that photocatalytic treatment could result in an increased toxicity of effluents (Santiago-Morales et al., 2013; Romero et al., 2011).

### 3.3.3. Contamination of soil due to contact with waste

Amending soil with sludge or manure provides essential nutrients in agriculture, while irrigation with (reclaimed) wastewater allows for agriculture in regions where water resources are limited (EC, 2014)22. However, sludge, manure and wastewater have been found to contain a number of contaminants, including a variety of pharmaceuticals (Prosser et al., 2015).

The potential uptake of pharmaceuticals by plants growing in amended soil or irrigated with reclaimed wastewater has been explored in the last few years. The body of studies collected during a 2015 review shows that plants have indeed the capacity to accumulate pharmaceuticals from the media in which they are growing (Prosser et al., 2015). For instance, Boxall et al. observed that the veterinary pharmaceuticals florfenicol, levamisole, and trimethoprim in spiked soil can accumulate in lettuce, and enrofloxacin, florfenicol, and trimethoprim in carrots (Boxall et al., 2006)23. Wu et al. investigated whether 20 pharmaceuticals could accumulate in four plants species (lettuce, spinach, cucumber, and pepper) grown in a spiked nutrient solution. All were detected in the roots of the plants and 13 were detected in the leaves of the plants (Wu et al., 2013).

The authors of the aforementioned review found that there were considerably fewer studies examining uptake due to amendment with manure than due to sludge amendment or reclaimed wastewater irrigation (Prosser et al., 2015). The authors therefore highlight the need for more emphasis on investigating the accumulation of pharmaceuticals into plants grown in manure-amended soil.

Concentrations of antibiotics in manure may be similar or greater to those observed in sludge. In Europe agricultural soil is more frequently amended with manure than with activated sludge (9 million tons of N nutrient comes from manure, while a maximum of

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21 Metformin passes through the body unchanged. Guanylurea is formed in the aquatic compartment, after excretion, by the action of bacteria.

22 Amending soil means adding elements to improve its capacity to support plant life

23 The authors used soil which had measurable residues likely to occur in soils for at least 5 months following application of manure containing these compounds
200,000 tonnes come from sludge\textsuperscript{24}. In both cases (manure and sludge), research shows that digestion and composting reduced the levels of antimicrobials they contain (Box 4).

**Box 4: Impact of digestion and composting on antimicrobial levels in manure and sludge**

(Youngquist et al., 2016)

A recent review studied the fate of antibiotics, antibiotic-resistant bacteria (ARB), and antibiotic resistance genes (ARG) during anaerobic digestion and composting of manure and sludge. Research on 16 antibiotics in 11 different studies using both bench-scale and farm-scale composting systems demonstrates that composting significantly reduces levels of extractable antibiotics in livestock manure in nearly all cases. Calculated half-lives ranged from 0.9 to 16 days for most antibiotics. There is more limited evidence that levels of ARB are also reduced by composting. Studies of the fate of ARGs show mixed evidence for removal during both anaerobic digestion and during thermophilic composting.

Additional research would be of value to determine optimum anaerobic digestion and composting conditions for removal of ARB and to increase understanding of the fate of ARGs during anaerobic digestion and composting.

Irrigation with reclaimed wastewater may lead to even greater exposure of pharmaceuticals to crop plants than manure or sludge amendments, particularly for pharmaceuticals that have relatively high solubility in water. Irrigation can occur over the entire life cycle of the plant, which means exposure when the plant is growing at an exponential rate and has the greatest capacity to accumulate pharmaceuticals from the soil. In contrast, exposure of plants to pharmaceuticals via manure or sludge decreases over time\textsuperscript{25} (Prosser et al., 2015).

In the EU, the fate of emerging contaminants after irrigation with reclaimed wastewater has come under scrutiny in the context of the Commission’s work on the development of minimum quality requirements at EU level for water reuse. The Impact Assessment preceding the proposal for EU standards (EC, 2014), as well as recent EU guidance documents (Common Implementation Strategy (GIS)), highlight a lack of comprehensive understanding of emerging contaminants behaviour, fate and biological potency after their discharge in the environment, although literature to date and practical feedback from reuse schemes\textsuperscript{26} would suggest that water reuse in irrigation represent a \textit{de minimis} risk to human health. In this context, a recent JRC draft technical report stresses the need for a selection of indicators of occurrence for emerging contaminant, in particular pharmaceuticals (JRC, 2016). Nevertheless, the reuse applications eliciting the highest focus in this report is rather aquifer recharge\textsuperscript{27} than irrigation (the document proposes regular monitoring in reclaimed water before its use for potable or non-potable aquifer recharge, with an implementation of a watch-list for groundwater).

An example of the most recent development (use of black water) on the issue of pharmaceuticals in soils is presented in Box 5.

\textsuperscript{24}EUROSTAT data, code “Gross nutrient balance on agricultural land”

\textsuperscript{25}Mostly by transfer to another compartment

\textsuperscript{26}Cyprus, which has a long experience of reusing water for irrigation and groundwater recharge, and where almost all the (appropriately treated) effluents are now being reused, reports no cases of human diseases caused by treated wastewater

\textsuperscript{27}For potable and non-potable use
As an alternative to sludge or manure amendment, the use of black water (unseparated toilet waste) has been investigated in the recent years, notably in Sweden and Germany (Winker et al., 2010). Research has shown that black water could be a major resource for nutrients and be less contaminated by pharmaceuticals than manure: for instance, Winker et al. found 5 g/ha of oestrogens when fertilising with cattle slurry (according to N recommendation to winter wheat) and 1 g/ha when fertilising with human urine.

Nevertheless, more research is needed regarding potential health risks arising from the use of black water, in particular regarding the uptake of pharmaceuticals to crops.

For instance, black water contains 10 times more nitrogen than grey water (Jonsson et al., 2015).
4. Occurrence of pharmaceuticals in the environment

_In brief_

- The present chapter describes the occurrence and environmental concentrations of pharmaceuticals in different environmental compartments, through a selection of recent examples.

- Several pharmaceuticals of various categories (antibiotics, antineoplastics, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, antidiabetics, etc.) have been detected in the environment (surface water, groundwater, soil, air and biota), in their original form, as metabolites or other transformation products. The APIs detected in the environment include medicinal products put on the market several decades ago and no longer on the market as well as new medicines.

- APIs are present in the environment at concentrations ranging ng/l–μg/l, concentrations which vary both geographically and seasonally due to local practices and environmental factors. The highest concentrations are found in rivers and lakes that receive (treated) wastewater (see section 3.3).

- Few studies have focused so far on the occurrence of transformation products, including metabolites, but they show that their concentrations may be on the same order or even higher than those of the parent compound, and may often be more persistent. The identification of transformation products and the determination of transformation pathways have recently received increasing attention and are expected to benefit from rapid developments.

- The presence of pharmaceuticals in fresh surface water remains the most documented so far. Yet, increasing attention has been given recently to the presence of pharmaceuticals in drinking water, through the implementation of monitoring initiatives at national level. In comparison, and despite some interesting work published recently, evidence regarding the occurrence of pharmaceuticals in groundwater remains relatively scarce. The occurrence of pharmaceuticals in seawater, still little tackled a few years ago, is now receiving increasing attention.

- In comparison to the aquatic compartments, much less data are available in the public domain on pharmaceuticals in manure and soil. The presence of pharmaceutical in biota is also an issue which has not been well described yet, although recent studies show that pharmaceuticals can accumulate in aquatic organisms and especially fish.

- Nonetheless, emissions to all environmental compartments (e.g. soil, surface water) are of concern since the substances can move between compartments, for example from water to sediments, or from soils to water bodies. These transfers from a compartment to another are still little monitored, as few studies investigate the presence of a specific pharmaceutical (or class of pharmaceuticals) across various compartments.
4.1. Occurrence and concentrations of pharmaceuticals in the environment

Occurrence

Many individual studies have reported in the last decades the presence of pharmaceuticals in the environment (APIs, metabolites and/or their transformation products) from a variety of pharmaceutical classes – antibiotics, antineoplastics, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, antidiabetics, etc. They have been detected in different regions of the world including in the EU (see previous reviews and compilations such as mentioned in BIO IS (2014): WHO, 2011; Touraud et al., 2011; Bergmann et al., 2011; Loos et al., 2010; Kümerer, 2009; Fick et al., 2009; Kümerer, 2008; KNAPPE Project, 2008; GACE, 2007; Debska et al., 2004; Daughton CG, Ternes TA., 1999; Halling-Sørensen et al., 1998; or more recently Prasanna et al., 2015 and IWW, 2014).

Recently, a 2014 global review of pharmaceuticals in the environment, commissioned by Germany’s environment ministry (IWW, 2014), found that of the 713 pharmaceuticals tested for, 631 were detected in one or another environmental compartment. They were found all over the world — in 71 countries across all continents.

Figure 7: Global occurrence of pharmaceuticals in water

Note: Differences between countries in the figure above can be due to actual differences in the number of pharmaceuticals occurring in water or to a detection bias. Detection bias acknowledges the fact that in some countries, more pharmaceuticals are investigated than in others; therefore, more pharmaceuticals are likely to be detected in some countries than others (“we only find what we are looking for”).

Once in the environment, pharmaceuticals can remain in their initial compartment or transfer into another one, for example from water to sediments, or from soils to water bodies. This transfer depends on various factors (e.g. nature of the molecule, polarity, absorption behaviour, pH, content of organic substance, water saturation and aerobic properties), including the extent of degradation and characteristics of the receiving environment. Some pharmaceuticals are easily distributed over many aquatic compartments, especially if they are not degraded naturally: for instance, Trautwein et al. showed that metformin and its transformation product guanylurea, which are little degradable, could be detected in drinking, surface, and seawater (Trautwein et al., 2014). Other compounds likely to be distributed across many compartments are pharmaceuticals adsorbing to sewage sludge or manure and reaching groundwater by being released slowly during rainfall events.

The presence of pharmaceuticals in biota is an issue which has not been well described yet, but is subject to increasing attention, in particular in the aquatic compartments. The trophic transfer of pharmaceuticals remains largely unexplored, despite increasing evidence of the potential bioaccumulation of those compounds (Puckowski et al., 2016) (see Table 5).

The persistence of compounds plays a role in their presence in environmental compartments. For instance, Godoy et al. (2015) identified the high degree of persistence
of metoprolol and propranolol as one of the factors leading to their being the most frequently reported antihypertensives, and present at the highest concentrations – the half-lives of metoprolol and propranolol in the aquatic environment at 25°C can be assumed to be >1 year (Maszkowska et al., 2014; Godoy et al., 2015). This intrinsic persistence must be distinguished from another phenomenon called pseudo-persistence, which results from an equilibrium between the introduction and elimination of a specific compound in the environment. Both are important to consider as they will impact on exposure patterns (Kümmerer, 2010).

Concentrations

Although concentrations of compounds may not predict their risk – e.g., lower concentrations do not necessarily mean lower risk – they are essential for estimating exposure and for conducting risk assessment. The detected concentrations usually range from sub-ng/L level to µg/L level, with the highest concentrations found in rivers and lakes that receive (treated) wastewater29. The detected aquatic concentrations on a global scale are comparable with those found in Europe (IWW, 2014), although they can significantly vary from a location to another and across environmental compartments.

Most data available so far on the presence of pharmaceuticals in the environment concern the aquatic compartment. In comparison, much less data are available on pharmaceuticals in manure and soil.

Table 5 below sums up the level of knowledge on the presence of pharmaceuticals in the EU environment, as well as key recent findings. The studies reporting these findings either screen the presence of various classes of pharmaceuticals in the environment (Guillon et al., 2015; Houtman et al., 2014; Osorio et al., 2016) or target specific APIs or pharmaceutical classes in the environment (Trautwein et al., 2014; Godoy et al., 2015).

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29 In the EU, direct discharges are in certain cases allowed (see Council Directive 91/271/EEC concerning urban waste-water treatment).
Table 5: Synthesis table of available information per environmental compartment

<table>
<thead>
<tr>
<th>Env. compartment</th>
<th>Level of knowledge (+ to +++ for low to relatively good knowledge)</th>
<th>Examples of detected substances</th>
<th>Concentration range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aquatic – surface water (fresh water)</td>
<td>+++ The presence of pharmaceuticals in fresh surface water remains the most documented so far. E.g. (Hugues et al., 2013)</td>
<td>Latest results show that various veterinary antibiotics can be found in raw surface water of the French Seine-Normandie Basin (Guillon et al., 2015), and pharmaceuticals are ubiquitous in surface water and sediments of Iberian rivers (Osorio et al., 2016).</td>
<td>Veterinary antibiotics detected by Guillon et al. in raw surface water of the French Seine-Normandie Basin were present at concentrations reaching 100 ng/L at the highest and otherwise at around 10-50 ng/L (Guillon et al., 2015).</td>
</tr>
<tr>
<td>Aquatic – ground water</td>
<td>+ Despite some interesting work published recently (López-Serna et al., 2013) which complements previous reviews (e.g. Loos, 2010; Jurado, 2012; Stuart et al. 2012), evidence regarding the occurrence of pharmaceuticals in groundwater remains relatively scarce.</td>
<td>The most notable recent study on the subject is the work of López-Serna et al., which studied the occurrence of 95 pharmaceuticals and transformation products in urban groundwater underlying the metropolis of Barcelona, Spain. 31 samples were collected under different districts, and at different depths. Aquifers with different geologic features and source of recharge were included, i.e., natural bank filtration, infiltration from wastewater and water supply pipes, rainfall recharge, etc. Antibiotics were the most frequently found compounds (López-Serna et al., 2013). Hannappel et al. also studied the input of veterinary drugs in 48 shallow groundwater aquifers in Germany. They reported that single substances of the group of sulfonamides were detected in seven groundwater measurement points at very low concentration, and in very high concentrations at two other points.</td>
<td>López-Serna et al. reported concentrations in groundwater as high as or even higher than in the local river itself – for instance, concentrations of antibiotics reached 1000 ng/L for groundwater recharged with rivers containing effluents from WWTPs (López-Serna et al., 2013)</td>
</tr>
</tbody>
</table>
### Env. compartment | Level of knowledge (+ to +++ for low to relatively good knowledge) | Examples of detected substances | Concentration range
--- | --- | --- | ---
**Aquatic – marine and coastal areas** | + | The occurrence of pharmaceuticals in seawater, still little tackled a few years ago, is now receiving increasing attention (e.g. McEneff et al. 2014; Alygizakis et al. 2016; Álvarez-Muñoz et al. 2015). Some research focuses on marine areas, such as a survey campaign in Greece (Alygizakis et al., 2016), which detected amoxicillin and salicylic acid in the sea. Also others include seawater as a studied compartment: for instance, Trautwein et al. detected metformin and its transformation product guanylurea for the first time in North Sea water (Trautwein et al., 2014). McEneff et al. detected five targeted pharmaceuticals in marine surface water exposed to wastewater sewage discharges (McEneff et al., 2014). The Greek marine survey campaign detected amoxicillin and salicylic acid at concentrations in the range of 5.2–78.2 ng/L and 4–53.3 ng/L, respectively (Alygizakis et al., 2016); while Trautwein et al. measured in the North Sea average concentrations of metformin and guanylurea of 13 ng/L and 11 ng/L respectively (Trautwein et al., 2014). McEneff et al. detected the targeted pharmaceuticals in the high ng·L⁻¹ in marine surface water exposed to wastewater sewage discharges. |
**Aquatic – drinking water** | ++ | Increasing attention has been given to the presence of pharmaceuticals in drinking water, through the implementation of monitoring initiatives at national level. Previous relevant publications included e.g. Vulliet et al., 2009; Fick, 2009; Montpelat, 2008; WHO, 2011; Ségura, 2009; Touraud, 2011. One of the most frequently found pharmaceuticals in drinking water, according to recent research conducted in Spain (Boleda et al., 2014), Italy (Carmona et al., 2014) and the Czech Republic (Kozisek et al., 2013), is ibuprofen\(^\text{30}\). Diclofenac, carbamazepine and azithromycin were also among detected pharmaceuticals. Typically 10 ng/L and less; however higher concentrations have also been found depending on local hydrological conditions and treatment methods (Boleda et al., 2014) (Carmona et al., 2014) (Kozisek et al., 2013) |
Soil | + | There are still few new results on soil contamination. There are more A study (Kumara, 2005) showed that antibiotics in manure could be taken up by plants when they are fertilised with Oxytetracycline was found as a dominant compound in the solid animal manures samples, and its highest |

---

\(^{30}\) Those three studies each covered wide areas: finished drinking waters (FDWs) covering 12 million inhabitants for Boleda et al., public water systems supplying 5.3 million people (50.5% of the Czech population) for Kozisek et al. and the whole Turia basin for Carmona et al.
<table>
<thead>
<tr>
<th>Env. compartment</th>
<th>Level of knowledge (+ to +++ for low to relatively good knowledge)</th>
<th>Examples of detected substances</th>
<th>Concentration range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>technical difficulties to detect medicinal products in soils and sediments than in aqueous media (GACE, 2007; Ho, 2013).</td>
<td>animal raw manures containing antibiotics. The three crops (corn, onion, cabbage) absorbed Chlortetracycline (2-17 ng/g fresh weight), but not Tylosin. Cessna et al. even show that less than 7% of the amount of tetracyclines, sulfonamides and macrolides initially present in manure could remain after composting period (Cessna, 2001). Tetracyclines, fluoroquinolones, sulfonamides, and macrolides (17 substances in total) were detected in manure (Zhang H., 2015)</td>
<td>concentration reached 416.8 mg/kg in a chicken manure sample (Zhang H., 2015). Another study collected 50 chickens and 30 cow manure samples and measured tetracycline concentrations between 0.05 mg/kg and 5.36 mg/kg; and oxytetracycline concentrations ranged between 0.047 and 13.77 mg/kg (Alavi, 2015). Craballo et al. found concentrations of 3 tetracyclines in pig and chicken manure between &gt;0.01 and 1.38 mg/kg (Carballo, 2016).</td>
</tr>
<tr>
<td>Biota</td>
<td>+</td>
<td>The presence of pharmaceuticals in biota is an issue which has not been well described yet, although it is now receiving increasing attention, in particular in the aquatic environment. The trophic transfer of pharmaceuticals remains largely unexplored, despite increasing evidence of the potential bioaccumulation of those compounds (Puckowski et al., 2016).</td>
<td>Recent studies show that pharmaceuticals residues can accumulate in aquatic organisms and especially fish: Grabicova et al. found that pharmaceuticals present at low levels in water were found in benthic organisms at relatively high concentrations23 (Grabicova et al., 2015), while the uptake and accumulation of parent compounds and their metabolites at measurable quantities was demonstrated in marine mussels (Boillot, 2015; McEneff et al., 2014) and crucian carp (Liu et al., 2014)24. Another recent study showed that the anti-inflammatory drug diclofenac and the lipid regulator gemfibrozil can be found in (at least) one macroinvertebrate taxon (Ruhí et. al, 2016).</td>
</tr>
</tbody>
</table>

23 up to 85 ng/g for azithromycin
24 Parent compounds were carbamazepine for Boillot and erythromycin for Liu
<table>
<thead>
<tr>
<th>Env. compartment</th>
<th>Level of knowledge (+ to +++ for low to relatively good knowledge)</th>
<th>Examples of detected substances</th>
<th>Concentration range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>-</td>
<td>Nearly no data in air are available (concentrations considered negligible) (BIO IS, 2013)</td>
<td>-</td>
</tr>
</tbody>
</table>
4.2. Occurrence and concentrations of transformation products

There are a few studies which have focused on the occurrence of metabolites excreted by humans or animals. Studies from Gracia-Lor et al., Martinez et al. and Rosal et al. show that for some substances, metabolite concentrations may be on the same order or even higher than those of the parent compound (Gracia-Lor et al., 2014; Martinez et al., 2007; Rosal et al., 2010). In particular, the work of Gracia-Lor et al., conducted in surface water and wastewater effluents in the Spanish Mediterranean area, shows that a wide range of metabolites can be detected: out of 14 relevant metabolites investigated, only 3 metabolites were never found and 6 out of 14 metabolites were present in 50 % of the surface samples analysed. Research work such as Gracia-Lor et al.’s also shows that the occurrence of excretion metabolites depends on excretion rates and types of removal in WWTPs.

Previous studies have shown that, once in the environment, a number of pharmaceuticals (including APIs, metabolites after consumption or transformation products from WWTPs) can be further degraded in soils and water (BIO IS, 2014). For instance, once added to soil, antibiotics interact with the soil solid phase and are prone to microbial transformation (see Figure 8).

![Figure 8: Fate of antibiotics in soil and its compartments (Jechalke, 2014)](image)

The identification of transformation products and the determination of transformation pathways has therefore received increasing attention. Although it is still a challenge, it is expected to benefit from rapid developments of Liquid Chromatography/Mass Spectrometry (LC/MS) techniques. The review conducted by Haddad et al. on the scientific evidence of the transformation products of 15 APIs from the groups of antibiotics and antineoplastics, describes selected aspects of transformation products in the environment and their formation within effluent and water treatment (Haddad, 2015). They identified literature evidences for up to 294 transformation products from these 15 parent products. The transformation products that were found most frequently came from the two antibiotics, ciprofloxacin and trimethoprim. In general, structures of transformation products were more often reported for antibiotics (275 transformation products) than for

33 For instance, the use of a novel analysis method allowed Jakimska et al. to identify transformation products of ketoprofen, ibuprofen, and furosemide in surface water, some of them for the first time (Jakimska et al., 2014).
anticancer drugs (19 transformation products). He concluded that a slight change in treatment conditions and processes results in the formation of different transformation products, which complicates the efficiency of treatment processes. Hübner et al. (2015) also recently investigated the persistence of transformation products from ozonation of trace organic compounds through a critical literature review (Hübner et al., 2015).

A recent review conducted in 2014 on biodegradation and transformation in water/sediment systems stressed that pharmaceuticals do not commonly achieve complete mineralisation and that transformation products are generally observed. In 45 % of the studies investigated, indications were found that transformation products were more persistent than the parent compounds (Berkner et al., 2014). Latest publications confirm this observation. Indeed, Trautwein et al. measured the concentration of the anti-diabetes drug Metformin (Met) and its transformation product Guanylurea (Gua) in various aquatic environment. Sewage treatment plant revealed very high concentrations in influent (111,800 ng/L for Met and 1300 ng/L for Gua) and effluent samples (4800 ng/L for Met and 44,000 ng/L for Gua), with higher concentration for the transformation product. The drug and its transformation product were also detected in a lake (102 ng/L for Met and 16 ng/L for Gua), a river (349-472 ng/L for Met and 9-137 ng/L for Gua), and in seawater (13 ng/L for Met and 11 ng/L for Gua) (Trautwein et al., 2014). The study from López-Serna et al., investigating the occurrence of 72 pharmaceuticals and 23 transformation products in groundwater, showed that transformation products were found at lower concentrations than the corresponding parent compounds, with some exceptions, such as 4-hydroxy-propanolol and enalaprilat (López-Serna et al., 2013).

### 4.3. Factors influencing the types and concentrations of pharmaceuticals in the environment

High concentrations of pharmaceuticals are commonly found where (and when) discharges of pharmaceuticals are likely to be the highest: in densely populated areas (in particular in high seasons), downstream of sewage treatment plants and/or downstream of farming areas. However, this is not always true. For water for instance, large population means high water flow and thus high dilution, so that highly populated zones may contain lower concentrations of pharmaceuticals than rural areas (this of course depends on other factors such as the area or demographics). Furthermore, the scale and flow of the river can be decisive on the final concentrations in the environment. For instance, in a large river such as the River Seine, there will be dilution effects that may impede the monitoring of pharmaceuticals. By contrast, in a small river (e.g. flow rate lower than 0.5 m³/s), the impact of a single horse-riding stable can be observed, such as in the study of Guillon et al. (2015) which measured significant concentration levels of quinolones between 50 and 75 ng/L (Guillon et al., 2015). It is therefore difficult to reach direct conclusions on emissions based on the level of urbanisation.

Concentrations of pharmaceuticals also change with time and the introduction of new pharmaceuticals and other market dynamics (patent life time, old pharmaceuticals potentially removed from market, etc.). There is no general conclusion as to whether concentrations are higher currently than in the past: although some pharmaceuticals may be prescribed at lower doses than before, and thus be present at lower concentrations in the environment; some new pharmaceuticals are designed to be active at lower thresholds, and thus may have a higher hazard to non-target organisms.

Emission pathways have been described in chapter 3. Further details on the possible causes leading to the introduction of pharmaceuticals into the environment will be discussed in a following report (Task 2 of this study).
5. Risk to ecosystems

In brief

- The present chapter highlights how environmental risks are assessed (5.1) and based on which information (5.2), which risks are currently suspected (5.3) and which impacts are actually observed (5.4). Lastly, it focuses on the risks posed by endocrine disruptors, which are of increasing concern in the EU (5.5).

- Although the scientific assessment of ecotoxicological effects of pharmaceuticals on non-target organisms is yet to be fully developed, it is becoming increasingly clear that some pharmaceuticals, in particular anti-parasiticides, anti-mycotics, antibiotics and (xeno)oestrogens, pose environmental risks in specific exposure scenarios.

- The information regarding the environmental risk is not sufficient for the majority of pharmaceuticals currently on the EU market, either because of the limited knowledge on environmental occurrence or because of the insufficient publically available data on the ecotoxicology of many pharmaceuticals. There are still several challenges to overcome when assessing the environmental risks posed by pharmaceuticals:
  - Chronic exposure to pharmaceuticals at low doses is still scarcely described in scientific publications, which makes it difficult to determine Predicted No Effect Concentrations (PNECs) without much extrapolation;
  - The risks posed by compounds which are known to be active at very low concentrations, such as antineoplastic pharmaceuticals, are currently not so well taken into account through the risk ratio Predicted Environmental Concentration (PEC)/PNEC;
  - With increasing evidence of the presence of pharmaceutical transformation products – including metabolites – in the environment, the ecotoxicity of those compounds is beginning to be investigated, but this toxicity highly depends on the degradation stage considered and must be studied on a case-by-case basis. Environmental Risk Assessments (ERAs) conducted for the authorisation of pharmaceuticals in the EU do not consider metabolites or other transformation products in the preliminary exposure assessment; and
  - There is still a need for further investigation of the ecotoxicology of pharmaceutical mixtures in environmentally realistic settings, while there is still no consistent, cross-sector approach to the risk assessment of mixtures in the EU.

- Recent studies show that the environmental exposure to pharmaceuticals and their residues can lead to toxic effects for non-target organisms such as flora and fauna. Numerous studies report the adverse effects of pharmaceuticals at concentrations encountered in the environment (e.g. effect of endocrine-disrupting chemical (EDC) such as contraceptive ethinylestradiol on fish in the EU, effect of veterinary non-steroidal anti-inflammatory drug diclofenac on vultures populations in India due to unanticipated route of exposure). The endocrine-disrupting effect of some pharmaceuticals which are released to the environment is subject to increasing concern, although little is known about their relative contribution compared to other EDCs.

5.1. Environmental risk assessments (ERA)

The widespread occurrence of medicinal products in the environment (see Chapter 4) obviously begs the question whether realistic concentrations might pose a risk for exposed biota (non-target plants and animals). The ERA is a procedure that aims to
evaluate this probability of an adverse effect of a chemical substance on the environment, considering three main factors:

- the exposure of the environment to the substance (described through PEC or MEC parameters);
- the intrinsic toxicity of the substance (described through T or PNEC parameters); and
- the fate of the substance in the environment.

Table 6 below shows the parameters used in an ERA in the EU to characterise exposure, toxicity and fate, and Box 6 exposes the few basic ERA principles that are common to human and veterinary pharmaceuticals.

This short background is necessary to understand the importance of exposure and (eco)toxicity parameters in the assessment of environmental risks and the consequences of the current state-of-knowledge and uncertainties in this respect. The information regarding the environmental risk is indeed not sufficient for the majority of pharmaceuticals currently on the European market, either because of the limited knowledge on environmental occurrence (section 5.2.1) or because of the insufficient publically available data on the ecotoxicology of many pharmaceuticals (section 5.2.2).

Table 6: Factors considered in an ERA and associated parameters

<table>
<thead>
<tr>
<th>Factor influencing risk</th>
<th>Parameters</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure</strong></td>
<td>Predicted Environmental Concentration (PEC)</td>
<td>Estimation of the concentration of the pharmaceutical in the different environmental compartments. See Annex 1 for further details on estimation methods.</td>
</tr>
<tr>
<td></td>
<td>Measured Environmental Concentration (MEC)</td>
<td>Concentrations determined from monitoring studies. In the specific case of ERAs for the authorisation of new pharmaceuticals, MECs cannot be used (the pharmaceutical has not been put in the market yet and therefore is not effectively present in the environment).</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>‘T’ parameter of the PBT assessment</td>
<td>Acute and chronic toxicity studies are necessary to assess the ‘T’ parameter of the PBT assessment(^\text{34}).</td>
</tr>
<tr>
<td></td>
<td>Predicted No Effect Concentration (PNEC)</td>
<td>PNEC is the concentration at which no effects on environmental organisms are expected to occur. It is derived from chronic (preferred) or acute ecotoxicity indicators. More information on the derivation is available in section 5.2.2.</td>
</tr>
</tbody>
</table>

\(^{34}\) Acute toxicity refers to short-term and high-dose toxicity, while chronic toxicity deals with long-term toxicity. This ecotoxicity is generally tested in laboratories but can also be observed directly in the environment.
### Factor influencing risk

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octanol/water partition coefficient ($K_{ow}$)</td>
<td>Substances with large $K_{ow}$ values (i.e. very lipophilic substances) are of great concern since they can be adsorbed in soils and living organisms.</td>
</tr>
<tr>
<td>Soil adsorption coefficient $K_{oc}$</td>
<td>$K_{oc}$ is a measure of the tendency of a chemical to bind to soils. Substances with low $K_{oc}$ are likely to leach into groundwater.</td>
</tr>
<tr>
<td></td>
<td>Both those parameters are used in PBT assessment and as decision points in the ERA in specific cases.</td>
</tr>
</tbody>
</table>

**Box 6: Basic ERA principles.**

*These principles are valid for the assessment of human and veterinary pharmaceuticals, although the specifics are different for both types of pharmaceuticals*

The basic principle of ERAs is the comparison of the PEC or MEC of a substance with its PNEC. If the PEC or MEC of a substance is higher than or equal to the PNEC, i.e. the risk characterisation ratio is $\geq 1$, and thus an unacceptable risk for the environment is indicated. In such a case, either a refined ERA with improved data is conducted or appropriate risk management measures have to be implemented.

The ERA procedure in the EU is a tiered assessment. In Phase I, only exposure is considered and no further investigation is required for compounds whose PECs are below a pre-determined threshold. For human pharmaceuticals, PBT criteria are also taken into account. This first step is focused on compartments into which the vast majority of a substance is released: surface water for human pharmaceuticals; soil and groundwater for veterinary pharmaceuticals.

Phase II is mainly based on the ratio PEC/PNEC and involves two tiers (A and B) for refinement of the assessment. Thus, in the EU, the outcome of the ERA procedure for authorisation of pharmaceuticals is largely dependent on the ratio PEC/PNEC. It may also be influenced by the PBT properties of the compound. The risk approach based on the ratio PEC/PNEC is relevant for a number of substances but not all, because of the high uncertainties linked to the determination of ecotoxicity thresholds for some of them (see section 5.2.2).

### 5.2. State of knowledge on environmental concentrations and ecotoxicity used in the ERA

#### 5.2.1. State of knowledge on environmental concentrations used in the ERA

The ERA procedure included in authorisation dossiers in the EU relies only on PECs to evaluate the exposure of environmental compartments to the assessed pharmaceutical. PECs, by essence, have to be estimated by model calculations. The level of refinement in the estimation of PECs, as well as the environmental compartments they cover, depend on the nature of the pharmaceutical (human or veterinary) and the phase of the assessment (see Annex 1 for methodological details).

As the determination of PECs is based on models (see Annex 1 for the different modelling methods), it relies heavily on hypotheses and is linked to the appropriate use of the substance following medical or veterinary specifications. PECs may fail to mirror the
complexity of the real environment, by under- or overestimating a number of factors likely to influence environmental concentrations: e.g. potential degradation, misusage of pharmaceuticals, failure of WWTPs, unexpected contamination pathways, or uncertainties related to combined concentrations with a mixture of other chemicals. PECs also fail to consider local conditions, as they are annual average (nation- or EU wide) values based on a standard dilution factor (Kümmerer, 2016, pers. comm.).

Already in 2006, Liebig et al. compared MECs and PECs for a selection of human pharmaceuticals and showed that PECs, although in most cases close to the corresponding MECs, may underestimate actual environmental concentrations (Liebig et al., 2006). Unexpected high lipophilicity and overestimation of sorption to sewage sludge were the main factors explaining the discrepancies. More recently, a study by Verlicchi et al. (2014) revealed more important discrepancies between measured and predicted concentrations of 11 antibiotics and the antiepileptic carbamazepine in wastewater and surface water. The results show that the concentrations were accurately predicted for ciprofloxacin in wastewaters, and for azithromycin, trimethoprim and carbamazepine in surface water. For all the other compounds and sampling points, the difference between the measured and the predicted concentrations was very high. There also, key factors for discrepancies included predicted rates of removal and excretion (Verlicchi et al., 2014).

Several very recent studies have focused on the predictions of emissions of pharmaceuticals by data on their consumption. Box 7 shows a selection of recent findings.

**Box 7: Predicting emissions with consumption data**

Several recent studies have shown that emissions of pharmaceuticals can be predicted, to a certain extent, by data on their consumption. The development of such methodologies may, in the near future, complement (sometimes limited) monitoring data for a better knowledge of the emissions and occurrence of pharmaceuticals in the environment (Acuna et al., 2015) (ter Laak et al., 2014). For instance, ter Laak et al. showed that regional differences in pharmaceutical loads and concentrations in different catchments can be related to differences in sales patterns (and absence of sewage treatment). Osorio et al. showed significant positive correlations between mean pharmaceuticals concentrations in surface water and both population density and livestock units (Osorio et al., 2016).

Those predicting models could also address the lack of data regarding emissions from hospitals. Herrman et al. showed that the consumption-based approach is a useful method to predict the contributions of health institutions (psychiatric hospitals and nursing homes) to wastewater (Herrman et al., 2015).

For highly consumed products, MECs would be the alternative for the assessment of exposure in ERAs; however, these are still lacking for most pharmaceuticals. Although several monitoring programmes measure selected pharmaceuticals on the local, national, and international levels, general coordination is lacking (Brown et al., 2014). Despite several monitoring campaigns, the knowledge on environmental occurrence remains limited for many pharmaceuticals, making a sound and transparent ERA almost impossible in many cases.

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35 According to Brown et al. PEC has two main shortcomings for risk assessments:
- It either overestimates the environmental concentration, as potential degradation is not included; or
- It underestimates the environmental impact, as the PEC is calculated for individual products only, neglecting the fact that nearly all active ingredients are used by more than 1 pharmaceutical product. This is especially true for high-consumption products such as ibuprofen, diclofenac, and carbamazepine.
36 A catchment is the area covering an entire river system, from the sources of small tributaries to the estuary, including its groundwater.
37 Obviously not ERAs conducted for the authorisation of new pharmaceuticals. However, a posteriori ERAs, for instance conducted in the case of a renewal with a significant change in exposure, would be concerned.
For the ERAs conducted for authorisation of new pharmaceuticals, where MECs cannot be used, further development of calculation models appears to be necessary (Liebig et al., 2006).

### 5.2.2. State of knowledge about ecotoxicity data for the ERA

Ecotoxicity is measured through specific indicators: acute ecotoxicity is generally measured by EC₅₀ ³⁸ or LC₅₀ ³⁹ and chronic ecotoxicity by NOEC ⁴⁰ or LOEC ⁴¹. PNECs are directly derived from these indicators using so-called assessment factors, which take into account uncertainties linked to extrapolation (see Annex 1 for examples of assessment factors for the aquatic compartment).

The accuracy of PNECs is very much dependent on the state-of-knowledge about chronic ecotoxicity (long-term studies). Nevertheless, short-term studies are still the main source of data for PNECs as they often are the only toxicity data available ⁴³.

Ecotoxicity data is also used for testing the T criterion in PBT assessments. The T criterion is tested for substances which were already proven to be P and B, as long-term exposure can be anticipated for persistent and bioaccumulative substances. Therefore, chronic ecotoxicity data should in principle be used for the assessment of the T criterion. However, as mentioned for PNECs, most available data will be from acute tests and the Technical Guidance Document on Risk Assessment for New Notified and Existing Chemical Substances (TGD) provides elements for concluding using acute data.

- **Acute toxicity of active substances**

As mentioned in the guidelines for ERA (see previous paragraphs) and frequently reminded in recent publications ⁴⁴, the acute toxicity of active pharmaceutical substances to aquatic organisms is the type of toxicity which is the most described although knowledge is not yet extensive (BIO IS, 2014). This is true in particular for antimicrobials (below).

Very little is actually known about the effects of antibiotic use on the marine environment surrounding aquaculture sites (Pittenger et al., 2007). However, studies conducted to date indicate it may carry ecological risks. For example, (Ferreira et al., 2007) found that high concentrations of oxytetracycline and florfenicol, both active against *furunculosis* in salmon, inhibit growth of the wild alga *Tetraselmis chuii*, an important food source for other marine organisms. Such studies are largely limited to short-term laboratory studies and the concerns they raise highlight the need to further investigate the effects of ‘real-world’ chronic, low-level exposure to antibiotics on wild species.

It is acknowledged that ERAs often heavily rely on acute toxicity data ⁴³, when chronic data is not available. A recent study evaluating the relationship between PNECs derived from acute and chronic tests showed that for most compounds, PNECs derived from acute data were lower than PNECs derived from chronic data, with the exception of steroid oestrogens. These analyses suggest that the use of acute data in ERAs may be acceptable if chronic data are unavailable, unless specific mode of action concerns suggest otherwise ⁴⁵ (Caldwell, 2016).

Latest research regarding acute toxicity focuses on mixture assessment (see last subsection).

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³⁸ Half maximal Effective Concentration  
³⁹ Half maximal Lethal Concentration  
⁴⁰ No-observed effect concentration  
⁴¹ Lowest-observed effect concentration  
⁴³ These parameters are obtained by laboratory tests  
⁴⁵ E.g. some cytotoxic compounds used in anti-cancer treatment – see paragraph on non-threshold effects
Chronic exposure to pharmaceuticals at low doses

According to information collected from an EU pharmaceutical industry leader, only about 500–600 of the roughly 3,000 APIs in use in the EU have a full ERA with data on the chronic effects (Owens, 2015).

Chronic exposure to pharmaceuticals at low doses is still scarcely described in scientific publications, which makes it difficult to determine PNECs without much extrapolation. Yet it may be the most likely scenario, as presented in chapter 1, which highlights the widespread presence of EU pharmaceuticals at low concentrations in the environment (generally lower than 100 ng/L in water). Predicting or measuring the effect of chronic exposure is reported as challenging because of the large number of parameters potentially influencing the outcome or simply because of the necessity to conduct monitoring over a long period of time.

A recent example of research dealing with this particular exposure is the work of Oliveira et al., who observed adverse reproductive effects on Daphnia magna of chronic exposure to chlorpromazine and propranolol using the OECD standard test (Oliveira et al., 2015). The compounds chlorpromazine and propranolol caused a significant decrease in fecundity, and the rate of population increase parameter suffered a significant decrease from 0.33 mg/L to 0.128 mg/L onwards, respectively.

Recent work also focuses on chronic impacts on microbial communities. For instance, a 2015 study reported that low levels of antihistamines impacted microbial activity in aquatic systems, leading to lower recycling rates of carbon and nitrogen nutrients (Jonsson et al., 2015). It was also shown that tetracycline exposure led to inhibitory chronic impacts on the growth of nitrifying bacteria (Katipoglu-Yazan et al., 2015).

In order to gain more information of the ecotoxicity of pharmaceuticals on vertebrates, data from human toxicology studies might help by providing read-across information on the potential effects. The read-across hypothesis stipulates that a drug will have an effect in non-target organisms if the molecular targets such as receptors and enzymes have been conserved (i.e. the mode of action of the pharmaceutical is similar in humans and in the non-target organism) and that similar blood plasma concentrations in humans and the non-target organism lead to similar concentrations at the target sites in both organisms. Although predictive models have been developed based on the Read-Across Hypothesis (the Fish Plasma Model, the VirtualToxLab and more recently models based on molecular docking), there is still much work to be done to ensure the applicability and robustness of those models in their extrapolations (Rand-Weaver, 2013) (Christen et al., 2010).

Substances with non-threshold effects

In order to gain a better understanding of the environmental hazards of pharmaceuticals, their ecotoxicologically relevant modes of action need to be better identified and clearly differentiated from the modes of action that are relevant in a human pharmacological and toxicological context (although, of course, there might be overlaps for certain groups of compounds). Sub-lethal endpoints must also be further investigated.

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46 PNECs can be derived from acute reference values (mainly EC_{50}) but usually with higher assessment factors
48 Those concentrations are above those already reported in the wild.
49 Higher than those thus far found in the field but still 100 times lower than the predicted no-effect concentration for fexofenadine.
51 www.biograf.ch
Compounds which are known to be active at very low concentrations, such as antineoplastic pharmaceuticals (Kümmerer et al., 2015), may have a PEC allowing them to “pass” the Phase I action limit of the ERA, while they would actually need further assessment under Phase II. This aspect has still to be further studied in order to be considered by institutions such as the EMA or the United States of America Food and Drug Administration (FDA).

- **Influence of pH on the toxicity of pharmaceuticals**

Environmental pH is likely to play an important role in the toxicity of pharmaceuticals. Indeed, around 80% of all pharmaceuticals are ionisable (Manallack et al., 2008), which means that aquatic environmental pH can affect their chemical speciation, i.e. the fraction of ionic or uncharged forms. The speciation may affect uptake and thereby toxicity (Stehly et al., 1990). Influence of aquatic pH on toxicity of ionisable chemicals has been demonstrated (Neuwohner et al., 2011; Nakamura et al., 2008; Valenti et al., 2009; Boström et al., 2015) and the fraction of the uncharged form, with its higher bioavailability, has been suggested as a driver of toxicity. Therefore, if toxicity is quantified at one pH only and knowledge of the pH-dependent relationship is lacking, risk assessments made may be more or less applicable for particular sites or protection goals (Boström et al., 2015).

Another example of the influence of pH can be found in the work of Freitas et al., who investigated the single and combined long-term impacts of carbamazepine (3.00 μg/L, control = 0) on clams (S. Plana), under conditions of ocean acidification (pH= 7.1, control=7.8), by looking at a set of oxidative stress markers. The authors found that the toxicity of carbamazepine on S. plana was synergistically increased under ocean acidification conditions (pH 7.1). The study’s findings thus indicate that ocean acidification may act to increase the toxicity of carbamazepine to marine organisms, which has clear implications for coastal benthic ecosystems suffering chronic pollution from pharmaceutical drugs (Freitas et al., 2016).

- **Ecotoxicity of transformation products, including metabolites**

With increasing evidence of the presence of pharmaceutical transformation products – including metabolites – in the environment, the ecotoxicity of those compounds is beginning to be investigated. Studies from the late 90’s already showed that the ecotoxicity of metabolites and transformation products varies compared to their parent compounds and that the potency of some of these residues may actually be higher than the latter (Halling-Sørensen et al., 2002; Nakamura et al., 2008; Buth et al., 2007). Increase in toxicity may be due to a number of reasons (Roig et al., 2009).

- Uptake of the transformation product into organisms is greater than for the parent compound, due to either an increase in lipophilicity or a change in dissociation or both;
- The transformation product contains the active moiety of the parent compound; and
- The transformation reaction results in the introduction of a toxic moiety which is not present in the parent compound.

According to recent studies, the toxicity of transformation products highly depends on the degradation stage considered. For instance, Diniz et al. showed that the toxicity of waters containing diclofenac increased after it was transformed by photolysis; however, toxicity decreased when the parent compounds investigated were atenolol and ketoprofen (Diniz et al., 2015). In the same way, during a 6-month exposure in a mesocosm study, enhanced ecotoxicity of diclofenac was observed and could be due to the presence of some phototransformation products and metabolites. Major effects of diclofenac and its

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53 Genotoxic compounds, i.e. alkylating and other DNA-damaging compounds, are active at any concentrations.
54 For instance, the action limit for human pharmaceuticals is set at 0.01 μg/L.
55 See section 4.2. for definitions of metabolites and transformation products in this report.
transformation products appeared only after one month of exposure, including direct
effects such as mortality, decrease in abundance of certain species and indirect effects
such as increase in abundance of certain species and taxa (Joachim et al. Personal
Communication).

ERAs conducted for the authorisation of pharmaceuticals in the EU do not consider
metabolites or other transformation products in the preliminary exposure assessment
(Phase 1), although they are likely to occur in the environment (see section 4.2). Although
relevant metabolites of pharmaceuticals undergoing a Phase II assessment must be
taken into account, no specific recommendations have been formulated in the relevant
CHMP and CVMP Guidelines.

- **Ecotoxicity of a mixture of pharmaceuticals**

The occurrence of a great number of pharmaceuticals in the environment (see section
4.1) implies that ecosystems are actually exposed to a combination of two or more of
these compounds. Yet it is only very recently that the focus of research has shifted to
tackle the effects of mixtures.

The effects of such mixtures on ecosystems can be described by three basic types of
action (SCHER, 2011):

- **Similar action (dose/concentration addition):** Occurs if chemicals in a mixture act by the same mechanism/mode of action, and differ only in their potencies. The effects can be estimated directly from the sum of the doses/concentrations, scaled for relative toxicity;

- **Dissimilar action (independent action):** Occurs if chemicals act independently from each other, usually through different modes of action that do not influence each other. The effects can be estimated directly from the probability of responses to the individual components (response addition) or the sum of biological responses (effects addition); and

- **Interaction:** Describes the combined effect of two or more chemicals as stronger (e.g. synergistic) or weaker (e.g. antagonistic) than would be expected on the basis of dose/concentration addition or response addition.

Two recent reviews by Vasquez et al. (2014) and Backhaus et al. (2014) provide a state-
of-knowledge on this issue and identify further needs for research (Vasquez et al., 2014;
Backhaus et al., 2014). In particular, Vasquez et al. provided an up-to-date compilation of
57 environmental and human toxicology studies published during 2000-2014 dealing with
the adverse effects of pharmaceutical mixtures. Different methodologies can be applied
to calculate the effects of mixtures that can either be conducted using complex
environmental samples or laboratory-generated mixtures. Yet, the review shows that the
prediction of synergistic and antagonistic effects is still very difficult based on the
available models and that additional methods to evaluate the combined risk of multi-
chemical exposure are urgently needed, given the complex mixtures existing in the
environment.

In ERA for human pharmaceuticals, no attention is given to cumulative or mixture effects.
Although the ecotoxicity assessment of veterinary mixtures is more extensive than for
human pharmaceuticals, joint occurrence with other pharmaceuticals or other pollutants
is not taken into account either\(^56\). More broadly, in the EU, there is still no consistent,
cross-sector approach to the risk assessment of mixtures. Nevertheless, guidance and
proposals for approaches were published at EU level for specific regulations\(^57\) and since
2010 it appears that much efforts are provided at EU level to develop a coherent

\(^{56}\) As inferred from the relevant CHMP and CVMP guidelines

\(^{57}\) REACH: Research project of the German Federal Environmental Agency "4M: Mixtures under REACH" (2014); Pesticides: EFSA’s Proposed cumulative risk assessment process (2008)

5.3. Illustration of suspected risks

ERAs conducted during recent monitoring studies highlight potential risks linked to pharmaceuticals for the environment at environmental concentrations\(^{58}\) (Godoy et al., 2015; Pereira et al., 2015; Liu et al., 2014; IWW, 2014).

For instance, the 2014 global review of pharmaceuticals in the environment (IWW, 2014) showed that the highest concentrations of diclofenac measured in surface waters have been above PNEC levels in 34 countries (Figure 9).

![Figure 9: Highest diclofenac concentration in surface waters in comparison to the PNEC of 0.1 µg/L](image)

As another example, Godoy et al. showed that some beta-blockers can pose, at measured environmental concentrations, a potential long-term risk for non-target organisms of both fresh and marine water species (Godoy et al., 2015), while Pereira et al. indicate that the environmental concentrations of ciprofloxacin, bezafibrate, gemfibrozil, simvastatin and diclofenac found in effluents from Portuguese WWTPs are expected to pose a threat\(^{59}\) to three trophic levels (algae, daphnids and fish) (Pereira et al., 2015).

Recently, Helwig et al. also showed that nine pharmaceuticals were identified as having a risk quotient greater than 1, of which four (the antibacterials piperacillin, tazobactam, flucloxacillin, and ciprofloxacin) had high hospital contributions and had not been highlighted previously in rankings based on community prescriptions (Helwig et al., 2016).

In Portugal, Pereira et al. showed that the ERA of eleven of the most consumed pharmaceuticals, belonging to several therapeutic classes were assessed in 15 WWTPs (waste water influents (WWIs) and waste water effluents (WWEs))\(^{60}\). Results showed that all samples were contaminated with at least 1, and up to 8 from the 11 targeted pharmaceuticals. The ERA posed by 7 of the selected pharmaceuticals presented a risk quotient higher than 1 to the three trophic levels (Pereira et al., 2016).

Table 7 below reports recent results of environmental risk quotients (RQ) calculated with measured concentrations. The lowest determined PNEC was chosen for each compartment\(^{61}\). Please note that the sample of pharmaceuticals reported is not representative of the range of pharmaceutical classes.

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58 Whether a substance poses risk or not depends on whether or not environmental concentrations are likely to trigger an adverse effect, not solely on its intrinsic hazard

59 Risk quotients were calculated as MEC/PNEC with the highest concentrations of pharmaceuticals in the effluent samples (to set in the worst-case scenario)

60 Monitoring from five different regions during one year (4 sampling campaigns). The highest concentrations observed were 150 and 33 µg L\(^{-1}\) for WWI and WWE, respectively.

61 As a result, some RQ were recalculated with reported MECs and the lowest PNEC found.
### Table 7: Examples of RQ for a selection of pharmaceuticals

<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Compartment, country</th>
<th>PNEC (ng/L)</th>
<th>RQ</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Saltwater, UK</td>
<td>0.006</td>
<td><strong>17,833</strong></td>
<td>(Godoy et al., 2015)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Freshwater, Spain</td>
<td>100</td>
<td><strong>110.2</strong></td>
<td>(Godoy et al., 2015)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Freshwater, Spain</td>
<td>120</td>
<td><strong>67</strong></td>
<td>(Godoy et al., 2015)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Saltwater, Belgium</td>
<td>10</td>
<td><strong>29.3</strong></td>
<td>(Godoy et al., 2015)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Saltwater, Belgium</td>
<td>24</td>
<td><strong>6.6</strong></td>
<td>(Godoy et al., 2015)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Freshwater, Germany</td>
<td>100</td>
<td><strong>5.9</strong></td>
<td>(Godoy et al., 2015)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Freshwater, Italy</td>
<td>27</td>
<td><strong>3.4</strong></td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Freshwater, Italy</td>
<td>70</td>
<td><strong>1.8</strong></td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Freshwater, Spain</td>
<td>70</td>
<td><strong>1.28</strong></td>
<td>(de Garcia et al., 2014)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Freshwater, Italy</td>
<td>150</td>
<td>0.59</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Freshwater, Italy</td>
<td>120</td>
<td>0.4</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Freshwater, Sweden</td>
<td>93</td>
<td>0.2</td>
<td>(Godoy et al., 2015)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Freshwater, Italy</td>
<td>27</td>
<td>0.19</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Freshwater, Italy</td>
<td>100</td>
<td>0.15</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Freshwater, Italy</td>
<td>70</td>
<td>0.1</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Freshwater, Italy</td>
<td>120</td>
<td>0.067</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Freshwater, Italy</td>
<td>150</td>
<td>0.046</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Freshwater, Spain</td>
<td>2620</td>
<td>0.031</td>
<td>(de Garcia et al., 2014)</td>
</tr>
</tbody>
</table>

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62 When two entries have the same reference and compartment/country, they refer to different sites.
<table>
<thead>
<tr>
<th>Pharmaceutical</th>
<th>Compartment, country</th>
<th>PNEC (ng/L)</th>
<th>RQ</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>Freshwater, Spain</td>
<td>9700</td>
<td>0.009</td>
<td>(de Garcia et al., 2014)</td>
</tr>
<tr>
<td>Propyphenazone</td>
<td>Freshwater, Italy</td>
<td>800</td>
<td>0.009</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Freshwater, Italy</td>
<td>9700</td>
<td>0.006</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Freshwater, Italy</td>
<td>2620</td>
<td>0.006</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Freshwater, Italy</td>
<td>2620</td>
<td>0.003</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Propyphenazone</td>
<td>Freshwater, Italy</td>
<td>800</td>
<td>0.002</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Freshwater, Italy</td>
<td>9700</td>
<td>0.001</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Freshwater, Italy</td>
<td>3900</td>
<td>0.001</td>
<td>(Al Aukidy et al., 2012)</td>
</tr>
</tbody>
</table>

As a result of ERAs, for the aquatic compartment, the Commission included in 2013 three active pharmaceutical ingredients into its watchlist - diclofenac, 17-beta-estradiol (E2), and 17-alpha-ethinylestradiol (EE2) - because of ecotoxicity concerns. In 2015, the watchlist also included macrolides antibiotics.

Recently, research work has focused on building upon the ERA methodology, as well as other approaches, in order to prioritise pharmaceuticals for monitoring purposes (Box 8).

**Box 8: Current trend – Use of ERAs for prioritisation purposes**

Daouk et al. developed a prioritisation methodology for the monitoring of APIs in hospital effluents. The application of the ERA methodology allowed prioritising APIs based on predicted concentrations and environmental toxicity data found in the literature for 71 compounds. Among high-priority compounds: ibuprofen, trimethoprim, sulfamethoxazole, ritonavir, gabapentin, amoxicillin, ciprofloxacin, raltegravir and propofol (Daouk et al., 2015). The authors highlighted the transposability of their approach to any other hospitals, which have the will to look at the contamination of their effluents.

Baumann et al. performed an ERA of clarithromycin and its two metabolites on 5 aquatic species in order to propose a freshwater quality standard for clarithromycin. The proposed value of 0.130 μg/L. takes into account the similar concentrations and comparable toxicity of the active metabolite of clarithromycin (a multiplication factor was applied). Therefore, single monitoring of clarithromycin may be sufficient, in order

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63 The ERA was used in combination with another approach: OPBT (Occurrence, Persistence, Bioaccumulation and Toxicity).
to reduce the number of substances listed for routine monitoring programmes (Baumann et al., 2015).

Booker et al (2014) prioritised anticancer drugs for environmental monitoring and risk assessment purposes. They used a methodology based on consumption, persistency and likelihood of occurrence in surface waters in order to draw a shortlist of 15 pharmaceuticals from 65 initially investigated (Booker et al., 2014).

The previous paragraphs have been focused on the release of authorised pharmaceuticals and their possible risks for the environment. Another subject of interest regards the potential risks posed by illicit drugs and their break-down products, which are also detected in surface waters throughout the world. This topic has been very little investigated so far, whereas a wide array of aquatic organisms, including bacteria, algae, invertebrates, and fishes, have receptors that make them potentially sensitive to these compounds (Rosi-Marshall et al., 2015).
5.4. Illustration of observed impacts

Numerous studies report the adverse effects of pharmaceuticals on biota, at concentrations encountered in the environment. Notably, the following effects were described: effects of the contraceptive ethinylestradiol on fish populations, impairing their reproduction (Nash et al., 2004); effects of benzodiazepine and oxazepam on the European perch (Brodin et al., 2013) and effects of the anti-parasitic Ivermectin on dung fauna (Liebig et al., 2010). It has also been proved that the residues of the veterinary non-steroidal anti-inflammatory drug diclofenac has been a major cause of the rapid declines in the Indian subcontinent of three species of vultures endemic to South Asia, due to an unanticipated route of exposure (vulture population declines of 80–99% per year in 2003-2004) (Swan, 2006; Green, 2007; Oaks, 2004). Vultures were exposed to diclofenac when scavenging on livestock treated with the drug shortly before death. Diclofenac caused kidney damage, increased serum uric acid concentrations, visceral gout, and death. It has been banned in India since 2006.

For instance, according to the review of Jechalke et al. a number of studies also revealed that veterinary antibiotics entering via manure into agricultural soil can affect the soil microbial community – and in particular the abundance, and diversity (Jechalke, 2014). Phytotoxic effects of antibiotics varying between plant species and antibiotic compounds have been reported (Du, 2012).

Adverse effects can be observed that were not necessarily anticipated in the risk assessments, as actual environmental concentrations may differ from predicted ones or the concentrations usually reported (see section 5.2).

In addition to ecotoxic effects on the biota, the development and maintenance of antimicrobial resistance in the environment is also a growing concern. The issue of the development of resistant bacteria due to their exposure to pharmaceuticals and its impacts will be developed in the next chapter (see section 6.3).

5.5. Focus on endocrine disruption, as a growing threat to the biota

The endocrine-disrupting effect of some pharmaceuticals which are released in the environment is subject to particular attention in the EU, in the context of growing concern about negative environmental impacts possibly caused by endocrine disruptors (Nohynek et al., 2013).

**Box 9: Endocrine-disrupting chemicals**

Endocrine-disrupting chemical (EDC) is defined as an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. The European Commission is currently working on a scientific criteria to determine endocrine disrupting properties. These substances may act like hormones and disturb the normal functioning of the endocrine system. The endocrine system is a network of glands and hormones that regulate quite a large number of body physiological activities such as reproductive processes like embryonic development, sex differentiation, and metabolic development (Flint et al., 2012). Endocrine disruptors are suspected of interfering with the production and performance of hormones.

- EDC have a negative impact on the biota

Endocrine disruptors are alternatively called environmental hormones that cause adverse effects on aquatic and terrestrial organisms through altering the metabolism of natural

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hormones, modifying hormones receptor in a cell, interference, or binding to receptors of the endocrine system (Jiao et al., 2008; Olujimi et al., 2010). Such effects have already been seen in animals, impairing reproduction, development or immunity. Their effects on aquatic organisms, at very low concentrations (e.g. ng), have been extensively described in scientific publications. e.g. (Frye, et al., 2012; Tyler, 2012; Amiard-Triquet & Amiard, 2014; Boer, Fritsche, Schoeters, & Kimber, 2015; J G Vos, 2000). Ever since, there has been increasing concern with regard to the likely impacts of exposure to chemical compounds with endocrine-disrupting activity in the environment (Segner, 2005; Sumpter et al., 2005; Game et al., 2006; Mauricio et al., 2006; Xue & Xu, 2006; Moder et al., 2007; Shin et al., 2007; Hecker & Giesy, 2008).

A recent study by Trasande et al. also aimed at estimating the costs of EDC exposures in the EU: EDCs are likely to contribute substantially to disease and dysfunction of living organisms with costs in the hundreds of billions of Euros per year at best (Trasande et al., 2015).

- Several pharmaceuticals have been identified as potential endocrine disruptors

In 2009, Claiman and Gaurilescu identified the pharmaceutical substances in the figure below as potential EDCs (Figure 10). However, the list of pharmaceuticals with potential endocrine-disrupting effects can be more or less extensive depending on the criteria considered (Claiman et al., 2009).

![Figure 10: Scheme of the potential endocrine disruption of pharmaceuticals products (Claiman et al., 2009)](image-url)

Although pharmaceuticals like 17 alpha-ethinylestradiol (EE2) have been subject to important focus recently for their endocrine-disrupting properties, they are a few substances amongst what is thought to be a significant pool of EDCs. EDCs include various chemicals in addition to pharmaceutical compounds, from pesticides to dioxins to plasticizers. According to Tijani et al. (2013), presently, more than 38,000 chemicals and potentially toxic elements have been identified, globally, as potential endocrine-disrupting chemicals and they claim this list is not complete since more than 87,000 new chemicals in the market have not been tested for their endocrine toxicity and new chemicals are being manufactured continuously (Tijani et al., 2013). On the other hand, DG ENV of
European Commission, which has been further investigating in the last 5 years how to assess risk of endocrine-disruption and establish priorities for further evaluation, ‘only’ identified ~200 substances out of ~550 substances as showing clear evidence of endocrine disrupting activity (~2/3) or presenting evidence suggesting such a risk (~1/3).

To date, lists of potential endocrine disruptors, based on available evidence and not constituting evaluations of individual substances to be carried out under the respective chemical legislations exist but these are incomplete because most of the new chemicals are being developed, manufactured and put on the market on a frequent basis. Moreover, if new criteria defining EDC are introduced, this list is likely to evolve again.

Information about the number and exposure to EDCs therefore remains incomplete and it is therefore very difficult to estimate at this stage the relative contribution of pharmaceuticals to endocrine-disruption.

Several EDC substances are being progressively phased out in the EU. However, their use in the EU and third countries, combined to their long-range transport and environmental persistence properties, impedes the reduction of their endocrine-disrupting effect. For instance, Trasande et al. reported that dichlorodiphenyldichloroethylene (DDE)-attributable obesity and diabetes could be prevented through further reductions in dichlorodiphenyltrichloroethane use globally. Its use in agriculture has been banned in several countries due to its known toxicity and its long-range transport and persistence in the environment. However, the current use of this chemical for malaria control cannot yet be halted because of the absence of relevant alternatives (Bouwman, 2011; van den Berg, 2009).
6. Pharmaceuticals might pose human health risks via indirect exposure

In brief

- This chapter highlights the latest state of knowledge about the risks and potential impacts on human health of environmental exposure to pharmaceuticals and their residues, through a selection of recent research findings (6.1). A focus is made on the phenomenon of anti-microbial resistance (AMR), which is subject to increasing concerns for human and animal health globally (6.3).

- Although health benefits brought by pharmaceuticals are unquestionable, exposure of humans (healthy or under treatment) to those same substances, via the environment, could potentially lead to adverse health effects. Exposure via the environment includes drinking water, residues in leaf crops, root crops, fishery products, dairy products, and meat.

- It is extremely challenging to establish a clear relationship between presence of pharmaceuticals in the environment and adverse health effects. This is due to the high number of compounds potentially involved, the long-time scales of contamination and the multiple routes possible.

- Possible risks are therefore less clear than for the environment, but there are concerns notably regarding certain type of molecules: antibiotics, anti-parasiticides, anti-mycotics and anti-cancer pharmaceuticals are especially intended to kill their target organism or target cells and might prove to be the most important pharmaceutical compounds affecting human health via indirect environmental exposure.

- The risks for human health due to environmental exposure to pharmaceuticals via drinking water have been considered unlikely in a number of risk assessment studies. Other studies point out possible risks related to other routes of exposure (handling of secondary sludge, agricultural disposal practices, extent of secondary sewage treatment, food consumption patterns). In any case, long-term effects of pharmaceuticals on human health cannot be ruled out with current knowledge especially with regard to more vulnerable populations and the increasing debate about the exposure and effects of mixtures.

- The development of AMR is of particular concern with regards to human and animal health and has received considerable attention in the last few years – including AMR arising from pharmaceuticals in the environment. Scientific literature offers increasing evidence of the development of AMR in microbial populations in manure and wastewater and in turn in the environment, especially in agricultural soils (due to the spreading of manure) and in the water compartment (due to the release of treated wastewater effluents). Yet, in most countries, there is still no monitoring or regulation of the release of antimicrobials or resistant genetic determinants into the municipal wastewater system and no monitoring of manure spread on the fields. Despite evidence of transfer of AMR between food and humans, it is still complex to establish a direct and indisputable link between the release of antibiotics (human or veterinary) in the environment and human health disorders due to resistant bacteria, namely because of other potential sources of AMR that exist.
Pharmaceutical authorisations are delivered when it is assessed that the benefits of using the pharmaceuticals to cure humans or animals or prevent sickness (in case of prophylactic use) outweigh the risks caused to the animal or human ingesting the substance. 'Risk' here refers to side effects which may be reported for target organisms at recommended doses – due to the fact that some pharmaceuticals may not suit all individuals. The presence of documented side-effects from regular administration must be distinguished from those related to non-targeted applications and environmental exposure of organisms (while healthy or already under treatment) to mixtures of chemical substances. Exposure to medicinal products may occur through drinking water and through residues in leaf crops, root crops, fishery products, dairy products, and meat (Schricks M et al., 2010; Debroux JF et al., 2012; Stuart ME, 2012). Direct soil ingestion is also a reported pathway (Hallling-Sørensen et al., 2002), in particular for children, while inhalation and skin absorption are more rarely considered (García-Santiago et al., 2016).

6.1.Risks to humans via drinking and other routes of exposure

The high number of compounds potentially involved in health risk, the long-time scales of contamination and the multiple routes make it extremely challenging to establish a clear relationship between presence of pharmaceuticals in the environment and adverse health effects. For humans, risks are therefore less clear than for the environment, but there are still concerns notably regarding certain types of molecules – in particular stemming from the results of European studies (BIO IS, 2014) – even if to date there is no clear evidence of short-term health effects on humans. The biological activity of antibiotics, anti-parasiticides, anti-mycotics and anti-cancer pharmaceuticals, which are pharmaceutical groups that are especially intended to kill their target organism or target cells, might notably affect human health via environmental exposure. The mode of action of pharmaceuticals with endocrine-disrupting properties is also of particular concern (see section 6.2).

Table 8 highlights the estimated risk likelihood from different exposure routes, based on a selection of recent work. According to Oldenkamp et al., the risks for human health due to environmental exposure to pharmaceuticals via drinking water have been considered unlikely in a number of risk assessment studies (Oldenkamp R., 2012). These results are in line with latest findings (e.g. (Houtman et al., 2014; de Jesus Gaffney et al., 2015; WHO, 2012)). By contrast, a number of studies still point out some human health risks related to specific routes of exposure, influenced e.g. by the local handling of secondary sludge, agricultural disposal practices, the extent of secondary sewage treatment, and local food consumption patterns. Oldenkamp et al. (2014) showed for instance that these factors were determinant for the impacts of two fluoroquinolone antibiotics (ciprofloxacin and levofloxacin) on the health of 0-1 yr old infants65 (Oldenkamp, Huijbregts, Hollander, & Ragas, 2014b). Paltiel et al. (2016) also showed that healthy individuals consuming reclaimed wastewater-irrigated produce excreted carbamazepine and its metabolite in their urine, while subjects consuming freshwater-irrigated produce excreted undetectable or significantly lower levels of carbamazepine (Paltiel et al., 2016).

Yet, risks for human health due to bioaccumulation of pharmaceutical in plants, through the application of manure / sludge or through irrigation with reclaimed water, are still rarely studied. Except the review from Oldenkamp et al. (2012) and recent research by Malchi et al. (2014), no other notable work on health risks due to residual pharmaceuticals in reclaimed water was detected66, although they would be valuable for the European Commission’s work related to the introduction of standards for water reuse.

65 estimated by the ratio of the dose taken in to the hazardous dose of pharmaceutical at which at least 50% of the individuals in 50% of mammalian species is affected.

66 However, there are publications studied bioaccumulation in plants not dealing with health risks, see Chapter 4.
Oldenkamp argues that risk assessment studies often lack differentiation (e.g. spatially or inter-individually), completeness (e.g. only exposure via drinking water), and/or specificity (e.g. the use of general dilution factors or general intake rates). In this context, this author developed as an example of possible improvement a methodology for assessing the possible different health and environmental impact of two therapeutically-equivalent pharmaceutical prescriptions (Oldenkamp et al., 2014). There is also a lack of recent research on the risks for vulnerable population – children (foetus, perinatal, infant, toddler, of school age, adolescent), pregnant women, the elderly, the sick, lower socio-economic groups and specific occupational groups – although concerns were first mentioned as early as 2007 (Collier, 2007).
### Table 8: Assessment of risks following different routes of environmental exposure

<table>
<thead>
<tr>
<th>Route of exposure</th>
<th>Documentation</th>
<th>Risk likelihood*</th>
<th>Selection of recent references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drinking water</strong></td>
<td>High</td>
<td>Unlikely</td>
<td>A monitoring study of 31 pharmaceuticals along Lisbon’s drinking water supply system showed that appreciable risks to the consumer’s health arising from exposure to trace levels of pharmaceuticals in drinking water are extremely unlikely.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Houtman et al., 2014) Houtman et al., which investigated risks linked to lifelong exposure of humans to drinking water containing pharmaceuticals (Netherlands), show that such exposure is not likely to pose a health risk to consumers, even when a combined exposure is considered (42 pharmaceuticals were monitored, covering several pharmaceutical classes (NSAID, antibiotics, psycholeptics, antidiabetics, anti-hypertension, antiparkinetics, beta-blockers, cytostatics, diuretics). Concentrations found in drinking water ranged from 0.05 ng/L to 26 ± 24 ng/L (metformin))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(WHO, 2012) The review conducted by the WHO in 2012, which indicated that adverse human health impacts are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in treated drinking-water (data from United Kingdom, the USA and Australia).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Oldenkamp R., 2012) This review shows that the risks for human health due to environmental exposure to pharmaceuticals have been considered unlikely in a number of risk assessment studies.</td>
</tr>
<tr>
<td><strong>Food consumption</strong></td>
<td>Low</td>
<td>Likely</td>
<td>Potential health risk through the ingestion of leaves of vegetables whose roots were irrigated with reclaimed wastewater, due to the presence of lamotrigine and 10,11-epoxycarbamazepine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Boonsaner et al., 2015) Transfer in plants from manure and potentially significant human exposure was studied for oxytetracycline in aquatic plants, and showed that uptake from aquatic plants should not be ignored when determining human exposure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Oldenkamp, Huijbregts, Hollander, &amp; Ragas, 2014b) Oldenkamp pointed out some risks related to specific routes of exposure, influenced e.g. by local food consumption. These factors are shown to be determinants for the impacts of two fluoroquinolones antibiotics (ciprofloxacin and levofloxacin) on the health of infants.</td>
</tr>
<tr>
<td>Route of exposure</td>
<td>Documentation</td>
<td>Risk likelihood*</td>
<td>Selection of recent references</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Handling of manure and sludge</td>
<td>Low</td>
<td>Likely</td>
<td>(Oldenkamp, Huijbregts, Hollander, &amp; Ragas, 2014b) Idem.</td>
</tr>
</tbody>
</table>

* based on available information
6.2. Human exposure to endocrine disruptors compounds (EDC)

There is no consensus on the relevance of some scientific aspects regarding the effect of human exposure to EDCs (EC, 2016):

- An extensive review conducted in 2012 showed substantial evidence that low doses of EDCs have adverse effects on human health. The weight of the available evidence suggests that EDCs affect a wide range of human health endpoints that manifest at different stages of life, from neonatal and infant periods to the aging adult (Vandenberg et al., 2012). Furthermore, several studies investigated in the aforementioned review indicate that EDCs can have additive or even synergistic effects/properties and thus these mixtures are likely to have unexpected significant effects – see also the work of Kortenkamp (Kortenkamp et al., 2012).

- Despite such evidence, it is very difficult to establish cause-effect relationships for EDC, due to a combination of low-dose effects and non-monotonic dose responses, which make it difficult to predict low-dose exposure from effects observed at high doses (Vandenberg et al., 2012).

- Some reviews have suggested that the association between exposure to low doses of chemicals and diseases is not supported by evidence, while other publications criticise the methodology used by the reviews supporting the existence of such an association (EC, 2016).

In particular it appears from existing literature, including the aforementioned review and other work such as Trasande et al., 2015; Sweeney et al., 2015; Kabir et al., 2015 that endocrine-disrupting pharmaceuticals such as EE2 or fluoxetine, are scarcely studied – as compared to other EDCs such as parabens, bisphenol-A or phthalates.

6.3. The issue of emergence of anti-microbial resistance (AMR) in the environment and its health implications

➢ The development and maintenance of AMR in the environment is a growing concern

AMR has received considerable attention in the last few years as it has been singled out as one of the global public health issues of great concern (WHO, 2014a; UK House of Parliament, 2013).

The term “microbes” in “anti-microbial resistance” refers to many types of micro-organisms: bacteria, viruses, fungi, and parasites. Although resistance of bacteria (e.g. E. coli or Salmonella) has been the most discussed\(^\text{67}\), resistance of viruses such as the HIV is also of utmost concern (WHO, 2014a).

Naturally occurring resistant micro-organisms exist in the environment, due to the transfer of genetic resistance determinants (resistome). Although development of AMR is a natural phenomenon, its development and spread is being accelerated by misuse of anti-microbial medicines, inadequate or non-existent programmes for infection prevention and control, poor-quality medicines, weak laboratory capacity, inadequate surveillance and insufficient regulation of the use of anti-microbial medicines (Finley, 2013; WHO, 2014a; Berkner et al., 2014). **Antimicrobial resistance in the environment is but one factor leading to global AMR.** The drivers contributing to the development of AMR are in particular misuse and overuse, both in humans and animals. Food is a possible

\(^{67}\) In particular, the first cases of AMR were identified for antibiotics (sulfonamides 1939, penicillin 1941) (No Pills in Water, 2015).
transfer route and can contribute to spread of AMR, through the poor handling and cooking of antimicrobial-contaminated food\textsuperscript{68}.

There are several possible origins of AMR in the environment and its spread within the environment is complex. Selective pressure from exposure to antimicrobial medicinal products in the environment is also considered an important factor for emergence of resistance. For instance, fluoroquinolones/quinolones are a group of antibiotics with very high potential to drive the development of resistance in the environment (Morris et al., 2015). In this context, Bell et al. also mention a process of co-selection, where the use of an antimicrobial provokes resistance to another one (Bell et al., 2014). Cross resistance can also be favoured by other categories of chemicals such as heavy metals or silver (nanoparticles). There still are uncertainties with regards to the drivers of AMR: genetic determinants as well as selective pressures appear to be the leading contributors of AMR development (Morris et al., 2015).

Evidence exists that antibiotic treatments of animals trigger the increase of resistance genes in microbiota. For example, Tian et al. has shown that the use of antibiotics (oxytetracycline) for 50 years in beekeeping in the United States of America has resulted in extensive tetracycline resistance in human gut microbiota (Tian, 2012).

Scientific literature offers increasing evidence of the development of AMR in microbial population in contaminating sources (manure and waste waters) and then in the environment, and especially in agricultural soils (due to the spreading of manure), and in the water compartment (due to the release of treated wastewater effluents). The following boxes summarise key new findings about AMR development, due to human or veterinary antibiotics uses, in manure and soils (see Box 10), and in water and waste water (see Box 11).

It appears that manure has become a reservoir of resistant bacteria and veterinary antibiotic compounds, and its application to agricultural soils significantly increases antibiotic resistance genes and selection of resistant bacterial populations in amended soils. This result is supported by substantial experimental and in situ evidence presented in rigorous scientific studies (see Box 10).

**Box 10: Summary of new scientific evidence of AMR development in manure and soils**

According to the review of Heuer (Heuer, 2011), the usage of antibiotics in animal husbandry has promoted the development and abundance of antibiotic resistance in farm environments. For example, the frequency of bacteria carrying anti-microbial resistant genes (to amoxicillin and tetracycline) is higher for pigs (which use high amounts of antibiotics) as compared to cattle or sheep. Moreover, a range of studies reviewed in (Heuer, 2011) demonstrated a correlation between manure amendment and resistance in soils. For example, the prevalence of sulfonamide resistant isolates was increased in a field soil after two years of application of antibiotic-containing pig slurry, compared to pre-application soil. Graham et al. found more β-lactam anti-microbial resistant genes in manured soils than inorganic fertilised field (Graham, 2016), consistent with Hartmann works (Hartmann, 2013).

A study investigated the changes in antibiotic resistance from agricultural soils over time (from 1940 to 2008), and found that levels of all studied resistant genes rose over time from the pre-antibiotic era (1940) to the present, and especially since the 1970s for tetracycline and β-lactam resistance elements, reflecting changes in agricultural practice and demonstrating the enrichment of resistant organisms with the modern use of antibiotics (Wright, 2010; Knapp, 2010).

The horizontal transfer of genes from manure to soil bacteria is an important factor in resistance dissemination, because bacteria from manure may not be well adapted to

\textsuperscript{68} http://www.cdc.gov/drugresistance/about.html
the soil environment: It has indeed been shown that bacterial communities of manure and soil are largely distinct, and ribotypes\textsuperscript{69} introduced into soil decline below detection level within months (Heuer, 2011).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of article</th>
<th>Compartment</th>
<th>AMR genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heuer, 2011</td>
<td>Review</td>
<td>Manure and amended soils</td>
<td>β-lactam anti-microbial resistant genes</td>
</tr>
<tr>
<td>Graham 2016</td>
<td>Research article</td>
<td>Manure and non-amended soils</td>
<td>beta-lactamase resistant genes</td>
</tr>
<tr>
<td>Hartmann 2012</td>
<td>Research article</td>
<td>Soils, cattle and farm environment</td>
<td>Sulfadiazine and sulphonamide resistance</td>
</tr>
<tr>
<td>Bibbal 2007</td>
<td>Research article</td>
<td>Faeces</td>
<td>Ampicillin resistance</td>
</tr>
<tr>
<td>Heuer 2007</td>
<td>Research article</td>
<td>Manure and amended soils</td>
<td>Sulfadiazine and sulphonamide resistance</td>
</tr>
<tr>
<td>Heuer 2008</td>
<td>Research article</td>
<td>Manure and amended soils</td>
<td>Sulfadiazine and sulphonamide resistance</td>
</tr>
<tr>
<td>Heuer 2011</td>
<td>Research article</td>
<td>Manure and amended soils</td>
<td>Sulfadiazine and sulphonamide resistance</td>
</tr>
<tr>
<td>Byrne-Bailey 2009</td>
<td>Research article</td>
<td>Pig slurry and manured agricultural soils</td>
<td>Sulfonamide resistance</td>
</tr>
<tr>
<td>Gosch 2007</td>
<td>Research article</td>
<td>Farm soil</td>
<td>Tetracyclines and sulfonamides resistance</td>
</tr>
<tr>
<td>Hölzel 2010</td>
<td>Research article</td>
<td>Manure and amended soils</td>
<td>Tetracycline an Sulfadiazine resistance</td>
</tr>
<tr>
<td>Enne 2008</td>
<td>Research article</td>
<td>Pigs, cattle and sheep</td>
<td>Tetracycline resistance</td>
</tr>
<tr>
<td>McKinney 2010</td>
<td>Research article</td>
<td>Livestock lagoons</td>
<td>Tetracycline resistance</td>
</tr>
<tr>
<td>Schwaiger 2009</td>
<td>Research article</td>
<td>Liquid manure</td>
<td>Tetracycline resistance</td>
</tr>
<tr>
<td>Peak 2007</td>
<td>Research article</td>
<td>Wastewater lagoons at cattle feedlots</td>
<td>Six tetracycline resistance genes</td>
</tr>
</tbody>
</table>

Regarding the contamination of the aquatic compartment by resistant bacteria, it also appears that the introduction of antibiotics into the water compartment from human and veterinary applications (from manure leaching or treated waste water) results in a strong AMR increase. Abundant scientific evidence exists on the AMR development in surface waters or sediments of river or estuaries (see Box 11). Discharge of effluents from WWTPs or Drug manufacturing plants are the main source of entry of antibiotic-resistant bacteria into the aquatic environment, including multidrug-resistant and highly multidrug-resistant bacteria, which survive in freshwaters.

**Box 11: Summary of new scientific evidence of AMR development in water and waste water**

Recently, research projects specifically investigated AMR abundance from different wastewater systems: (No Pills in Water, 2015) RiskWa/SauberPlus\textsuperscript{70}; COST Action\textsuperscript{71}.

According to the review of Marti et al., aquatic environments, including surface water and groundwater bodies, provide ideal settings for the horizontal exchange of mobile genetic elements encoding antibiotic resistance; and anthropogenic antibiotics act as promoters of antibiotic resistance (Marti, 2014). So the introduction of antibiotics into the water compartment from human and veterinary applications results in an AMR increase. For example (Wright et al., 2007) reported that AMR genes were more abundant in bacteria from contaminated riverine and estuarine microhabitats, and from metal- or antibiotic-amended freshwater microcosms, than in bacteria from reference riverine and estuarine microhabitats. A significant number of publications state the presence of Antibiotic Resistant Bacteria in the aquatic compartments or watershed (e.g. (Allen et al., 2010; Baquero et al., 2008; Novo et al., 2010; Schwartz et al., 2003; Wright et al., 2007) reported in NoPills, 2015). Harris et al. also reported that in Ireland for instance, the predicted levels of anti-microbial agents are such that they may plausibly contribute to the development and maintenance of antibiotic resistance in the environment, at least to some extent (Harris et al., 2012). Kristiansson et al. measured high levels of resistance and gene transfer elements in antibiotic-contaminated river sediments (Kristiansson, 2011); and Drudge et al. detected clinically important

\textsuperscript{69} A ribotype is the RNA component of the genetic material in an organism.

\textsuperscript{70} http://www.bmbf.riskwa.de/en/1282.php

\textsuperscript{71} http://www.cost.eu/COST_Actions/essem/TD0803
antibiotic resistant genes in bacteria from freshwater systems impacted by anthropogenic activities (Drudge, 2012).

Wastewater is considered to be the main source of entry of antibiotic-resistant bacteria into the aquatic environment, along with manure and sludge (Morris et al., 2015; No Pills in Water, 2015; Marti, 2014). Several studies (Rosenberg-Goldstein, 2012; Szczepanowski, 2009; LaPara, 2011; Marti E, 2013; Zhang Q.-Q., 2015; Wellington E, 2013) showed that AMR bacteria were abundant in activated sludge and the final effluent of a WWTP, and also downstream of the WWTP discharge. Waste water effluent is also a significant source of multi-resistant bacteria (Amos, 2014; Stalder et al., 2013; No Pills in Water, 2015). Multidrug-resistant and highly multidrug-resistant bacteria (resistance to more than 4 antibiotics) were detected in a river impacted by WWTP discharges (Sidrach-Cardona, 2014).

Morris et al. report that the numbers of both E. coli sensitive to antibiotics and those resistant to antibiotics are unequivocally reduced by wastewater treatment. However, significant numbers of these bacteria are still released into the environment in treated effluent (they are present in both primary and dried sludge), or the genetic material carrying resistance, even if the bacteria are killed. WWTPs were not originally designed to have a specific impact on resistant bacteria or anti-microbial residues, and their effects on these contaminants remains largely unknown (Harris et al., 2012). Hendricks et al. study showed that the effectiveness of the sewage treatment processes is not optimal, resulting in bacteria and antibiotic residues still discharged into the environment (Hendricks, 2012). Recent studies show that WWTP processing may actually increase the proportion of resistant bacteria, through selective pressure (based on a meta-analysis of 161 different research projects). For example, Bréchet et al. measured that the treatment at the WWTP led to the relative enrichment of resistant E. coli in the effluent. They estimated that more than 600 billion of resistant bacteria are released into the river per day and the sludge produced by the WWTP, used as fertilizer, contains a high concentration of those resistant bacteria (Bréchet, 2014). However, the effects of WWTPs on the removal of antibiotic-resistant bacteria appear to be highly variable and bacteria specific. It may depend on the effluent they receive, on the treatment process used, as well as the season and rainfall (Morris et al., 2015).

Along with WWTP, antibiotic production facilities contribute to the emergence and spread of antibiotic resistance in the environment (Larsson, 2014) (Larsson, 2009). According to Sidrach-Cardona et al., antibiotic-resistant faecal bacteria (E. coli, total coliforms and Enterococcus spp.) were detected in water and sediment samples from a river impacted by both antibiotic manufacturing facilities and urban WWTP discharges; with higher resistance to amoxicillin and cephalaxin after the manufacturing facility discharge point than after the WWTP effluent (Sidrach-Cardona, 2014). Marathe et al. also showed that waste water from multiple bulk drug manufacturers contained various strains of bacteria, of which a large majority (86%) were highly multi-drug resistant, i.e. resistant to 20 or more antibiotics (Marathe, 2013).

Contrary to a common assumption, hospital effluent may not be the main factor influencing the overall resistance prevalence (e.g. review by Morris et al.), given the large use of antibiotics outside hospitals. Bacteria resistant to widely used antimicrobials are already present in high proportions throughout municipal wastewater systems and in WWTPs, which decrease the influence of hospital effluents. Morris et al. showed that the effect of hospital effluent containing anti-microbial residues varies for each anti-microbial and resistant bacteria complex: for some anti-microbials (e.g. ampicillin and streptomycin), the release of hospital effluent does not significantly affect the rate of resistance, but for other anti-microbials, such as ciprofloxacin, tetracycline and sulphonamide, the release of hospital effluent significantly impacts on the prevalence of resistant bacteria (Morris et al., 2015). In the NoPills project (2012-2015), an experience on hospital effluents showed for instance that up to 80% of E. coli bacteria could present resistance to ampicillin. E. coli resistant to newer classes of anti-microbials, such as quinolones (ciprofloxacin), second-generation cephalosporins (cefoxitin) and third-generation cephalosporins (ceftaxime) have been detected in low proportions in hospital effluent but can survive the wastewater treatment process and...
are released into the environment in treated effluent.

- **The AMR concern needs to be evaluated, monitored and managed**

According to Allen et al., monitoring for antibiotic resistance in natural environment has been infrequent and incomplete (Allen et al., 2010). Despite the growing evidence base of the increase of AMR genes in the environment due to human or veterinary antibiotics release, in most countries, there is still no monitoring or regulation of the release of antimicrobials or resistant genetic determinants into the municipal wastewater system and no monitoring of manure spread on the fields. Although there is in the scientific literature a continued reporting of the global spread of resistance in the environment associated with its known human and environmental risks, monitoring or regulation is actually not a legal requirement in many countries (Morris et al., 2015). According to Port et al. (Port, 2014), the idea of a lack of data and uncertainty regarding risk and risk metrics can explain why environmental monitoring of antibiotic resistance has still not been formalised into public health surveillance or water quality management decision frameworks.

Further research is needed to understand better the relationship between anti-microbial consumption, wastewater treatment/manure spreading and resistance within the environment. In particular, further research is needed to understand what drives the development of resistance in effluent or in the manure and what helps to maintain it; and the correlation, if any, that exists between the presence of sub-inhibitory levels of antimicrobials in the environment and the selection of bacteria resistant to them (Morris et al., 2015). The development of a harmonised tool to prioritise monitoring is also needed. A first attempt has been made by Port et al. through the metagenomic surveillance of antibiotic resistance determinants in the environment: they developed a screening tool for establishing baseline levels that can be used to inform and prioritise decision making regarding management of antibiotic resistance determinants sources and human exposure routes (Port, 2014).

According to Berendonk et al., key measures required to reduce the risks posed by antibiotic resistance genes that occur in the environment include the identification of critical points of control, the development of reliable surveillance and risk assessment procedures, and the implementation of technological solutions that can prevent environmental contamination with antibiotic resistant bacteria and genes (Berendonk, 2015). More work is also needed to identify management options for reducing the spread of antibiotics and antibiotic-resistance determinants via environmental pathways. Pruden et al. examined management options with respect to limiting agricultural sources; treatment of domestic, hospital, and industrial wastewater; and aquaculture (Pruden, 2013). They concluded that environmental releases of antibiotics and antibiotic-resistant bacteria can in many cases be reduced at little or no cost. They identified several options, such as nutrient management, runoff control, and infrastructure upgrades and highlighted the importance of monitoring and validating effectiveness of management strategies.

- **AMR in the environment has been singled out by the WHO as one of the most concerning public health issue globally** (WHO, 2014a)

Antibiotic resistance has become a global public health concern because the organisms that cause infections are becoming resistant to the most commonly prescribed antibiotic treatments, resulting in prolonged illness and greater risk of death (Marti E, 2013). Infections caused by AMR bacteria are associated with excess mortality, prolongation of hospital stay, and increased costs (Huijbers, 2015). The following box (see Box 12) proposes some examples of health impacts among the world of AMR.

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**Box 12: The health impacts of AMR contamination**

The WHO report on anti-microbial resistance surveillance (WHO, 2014a) reported very high rates of resistance, observed in all WHO regions, in common bacteria (for example, *E. coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*) that cause common health-care associated and community-acquired infections (urinary tract infections, wound infections, bloodstream infections and pneumonia). It also highlighted the growing multidrug-resistant *Mycobacterium tuberculosis* and
**Plasmodium** resistance to artemisinin for malaria.

AMR leads to increased number of treatment failures of bacterial diseases. The consequences are increased morbidity and mortality but also associated costs (Chomarat, 2014), in NoPills, 2015). This can be particularly observed in third countries, where the growing prevalence of drug-resistant strains of Tuberculosis, Malaria and HIV is well documented (O'Neill, 2014). For instance, for Tuberculosis, there were an estimated 480,000 new cases of multidrug-resistant Tuberculosis in 2013 (3.5% of total Tuberculosis worldwide) – of which 30% went untreated (WHO, 2014b). On average, an estimated 9.0% of patients with multidrug-resistant Tuberculosis had extensively drug-resistant disease. According to WHO, if all notified TB patients (6.1 million, new and previously treated) had been tested for drug resistance in 2013, an estimated 300,000 cases of multidrug-resistant Tuberculosis would have been detected (but only 45% have really been diagnosed and notified), more than half of these in three countries alone: India, China and the Russian Federation (WHO, 2014b).

A UK Government-funded review on AMR suggests that AMR bacteria would already claim 700,000 lives a year globally (as a low estimate) in 2014 and estimates this value up to 10 million in 2050 (O'Neill, 2014). All countries exposed to one or more of these three diseases will be particularly exposed to a rise in AMR, with consequences on morbidity and costs for society (particular countries at risk include India, Nigeria and Indonesia for malaria, and Russia for tuberculosis). Drug-resistant malaria could constrain the economic progress achieved by some countries in Asia, and also wreck the efforts undertaken by China and Brazil to eradicate the disease. In addition, malaria and HIV drug resistance threatens Africa as a continent, along with the debilitating impacts of HIV and TB co-morbidity already seen in many of the poorest parts of the world (O'Neill, 2014). Overall, Asia and Africa will be the most concerned by mortality related to AMR, with respectively 4.7 and 4.1 million deaths per year. Preliminary estimates on a subset of 3 drug-resistant bacteria (**Klebsiella pneumonia**, **E. coli** and **Staphylococcus aureus**) and 3 broader public health issues for which resistance is a concern (HIV, tuberculosis, malaria), project about 300 million premature deaths over the next 35 years and a reduction of 2% to 3.5% in Gross Domestic Product (GDP), which would cost the world up to 100 trillion USD (O'Neill, 2014).

According to recent data from the ECDC and EMA, every year approximately 25,000 European citizens (5.1 per 100,000 inhabitants) die from infections caused by bacteria that have developed resistance towards anti-microbials. For countries in the OECD, the cumulative loss of economic output by 2050 will amount to between USD 20 and 35 trillion along with a 1 to 4.5% reduction in GDP (O'Neill, 2014). In Europe, the ECDC estimates that AMR results in 25,000 deaths and related costs, resulting from healthcare expenses and productivity losses, of over €1.5 billion annually. O'Neill et al. projected a 15-fold increase in morbidity by 2050 in Europe, with 390,000 deaths per year. For instance, in 15 European countries more than 10% of bloodstream **Staphylococcus aureus** infections are caused by methicillin-resistant strains, with several of these countries seeing resistance rates closer to 50% (EARS-NET data for 2013, reported in O'Neill, 2014).

At a larger scale, increasing global trade and travel favours the spread of AMR between countries and continents. For instance, the resistant bacteria carrying the genetic code New Delhi Metallo-beta-lactamase-1 (NDM-1) that was first identified in India in 2006 has already been found in 35 countries in a short period of time, for example in Kenya in 2007, Canada in 2009, Japan in 2010 and France in 2011 (Berrazeg et al., 2014). In most cases, infected people had connections with the Indian subcontinent or Balkan countries: they were originally from these areas, had either spent time (infection from food or environment) and/or been hospitalised there.

72 [http://www.ecdc.europa.eu/]
It must be noted that the values presented in Box 12 are related to general contamination by resistant bacteria, not only environmental resistant bacteria (e.g. they also include infection through medical procedures, inappropriate treatment, person-to-person transmission of disease, etc.). The scientific evidences of the issue of health impacts due to the emergence of AMR in the environment is much scarcer.

After WWTP processing and environmental release in the water and the soil compartment, there is potential for human exposure to resistant bacteria, via contaminated drinking water for example or food ingestion (including crops, livestock, and seafood); recreational activities such as swimming; or direct contact with organisms carrying antibiotic resistant bacteria (Port, 2014; Wellington E, 2013). Human contact with these resistant bacteria in the agricultural environment, or ingestion of resistant bacteria through the consumption of uncooked vegetables and fruits, might increase the chance of exchanging resistance determinants between the human and environmental microbiome – and consequently may contribute to the threat of incurable infections in humans (Jechalke, 2014).

This exposure may in turn result in the dissemination of resistance genes among the gastrointestinal bacteria of exposed individuals and may, therefore, introduce resistance to the human population. According to Doyle et al. and Woolhouse et al., the transfer of anti-microbial-resistant bacteria from food animals to humans is well documented; and farmers may be at a greater occupational risk of acquiring anti-microbial resistant bacteria from the environment (Doyle, 2006; Woolhouse, 2015).

However, despite evidence of transfer of AMR between food and humans, it is difficult to prove upstream steps of the contamination chain. It is still complex to establish a direct and indisputable link between the release of antibiotics (human or veterinary) in the environment and human health disorders due to resistant bacteria, although such a link is highly plausible. This is due to the potential other sources of AMR that exist (naturally or not) in the environment. The following box (see Box 13) presents examples of this scientific debate.

**Box 13: Linking environmental antibiotic release to human health is still not scientifically proven**

A study quantified the number of human deaths from bloodstream infections caused by third generation cephalosporin-resistant *E. coli* that were due to the use of antibiotics, mainly the third-generation cephalosporins, in poultry production (Collignon, 2013). The study extrapolated from Dutch data that 1,518 additional deaths and an associated increase of 67,236 days of hospital admissions would be counted in the EU as a result of cephalosporin and other antimicrobial drug use in poultry. However, Singer et al. contested those results, arguing that the authors neglected the relative importance of diverse potential other causes that can have a contribution to the emergence, amplification, persistence and dissemination of AMR, and used linear and simplistic assumptions that do not reflect non-linear and interconnected systems (Singer, 2014). According to Singer et al., linking agricultural antibiotic use to human health through resistant bacteria is complex and will require application of complex systems methodologies from various fields to the epidemiology of AMR. One of these tools can be the human health risk assessments that focus on the role of the environment in the failure of antibiotic treatment caused by antibiotic-resistant pathogens (Ashbolt, 2013).

Huijbers et al. conducted a review to establish a possible role for the natural environment in the transmission of clinically relevant AMR bacteria to humans (Huijbers, 2015). AMR bacteria were detected at exposure-relevant sites, including recreational areas, drinking water, ambient air, shellfish, and in fresh produce; environmental compartments including wildlife, water, soil, and air/dust; and contamination sources including wastewater and manure. The abundance of AMR bacteria at exposure-relevant sites suggests risk for human exposure; however, no direct evidence was found for transmission of AMR bacteria to humans through the environment. Regarding the transmission of AMR bacteria from food-producing animals to humans, the review from ECDC/EFSA/EMA reported positive associations between occurrence of cephalosporins and fluoroquinolones resistance in
indicator *E. coli* originating from food-producing animals and the occurrence of resistance in *E. coli* from humans. Positive associations were also noted for consumption of macrolides in food-producing animals and the occurrence of resistance in *Campylobacter spp.* from cases of human infection, and for consumption of tetracyclines and the occurrence of resistance in *Salmonella spp.* and *Campylobacter spp.* However, no associations were observed between the consumption of 3rd- and 4th-generation cephalosporins in food-producing animals and the occurrence of resistance to this sub-class in selected bacteria from humans, as well as for fluoroquinolones and the occurrence of resistance in *Salmonella spp.* and *Campylobacter spp.* from cases of human infection (JIACRA, 2015).
Conclusions

Health care as practised in the EU heavily relies on the consumption of pharmaceuticals, as reflected by the continuous growth of the European market for medicines for human and veterinary use. Contamination of the environment by pharmaceuticals can occur all along their life cycle, from their manufacturing to their disposal, in their original form (APIs) or as metabolites or other transformation products. In particular, recent studies make direct links between consumption patterns and the presence of pharmaceuticals in the environment, to the extent where consumption data can be used as a proxy for estimating environmental concentrations. Most emissions of pharmaceuticals indeed result from the use phase, namely through human and animal excretions but also through e.g. improper disposal of products in the sinks. As a consequence, many recent studies have investigated further the possible shortcomings of wastewater treatments (at municipal- or hospital-scale), which have been shown to contribute significantly to the discharge of pharmaceuticals in the environment, or the effect of sludge, reclaimed water or manure reuse in agricultural productions. Still considered negligible less than 5 years ago, the contribution of manufacturing facilities to environmental pollution hotspots is also receiving increasing attention.

As a result of their continuous emission to the environment and despite their degradation to a certain extent, pharmaceuticals of all categories (antibiotics, antineoplastics, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, antidiabetics, etc.) have been detected in the environment, including products put on the market several decades ago and no longer on the market. Few studies in general have focused so far on the occurrence of metabolites excreted by humans or animals, although some recent research work showed that they could be detected on the same order or even higher than those of the parent compound and that they could often be more persistent in the environment. The topic is now receiving increasing attention in the scientific literature.

Although the presence of pharmaceuticals in fresh surface water is quite documented (with an increased interest in the last few years in the contamination of resources dedicated to drinking purposes and of marine areas), information about their occurrence in other environmental compartments such as soils, groundwater and biota is still not well described. Yet, emissions to all environmental compartments remain of concern, due to the ability of pharmaceuticals to transfer from one compartment to another.

Based on previous studies and the complements of most recent work, it is becoming increasingly clear that some pharmaceuticals, in particular anti-parasiticides, antibiotics and pharmaceuticals with endocrine-disrupting effects, pose environmental risks in specific exposure scenarios. Despite the implementation of ERA procedures, the information regarding the environmental risk is still not sufficient for the majority of pharmaceuticals currently on the EU market, either because of the limited knowledge on environmental occurrence or because of the insufficient publically available data on the ecotoxicology of many pharmaceuticals. In some cases, data exist but remain scattered across sectors, heterogeneous between studies and little accessible (no consolidation and centralisation for the different APIs or relevant metabolites). In other cases, key challenges are yet to be tackled by the scientific community, such as how to determine the risks associated with chronic exposure to pharmaceuticals at low doses, metabolites and transformation products, pharmaceutical mixtures in environmentally realistic settings. The emphasis was until very recently on the assessment of acute effects of pharmaceuticals applied in isolation. Only recently has the focus been shifted to chronic exposure and to the assessment of cocktail effects.

Nonetheless, several studies have already reported the common use of human pharmaceuticals with risk quotients (PEC/PNEC) > 1, including some commonly sold over the counter, thanks to the development of research work on pharmaceutical consumption. Other studies have confirmed previous findings about the critical adverse effects of some pharmaceuticals at concentrations encountered in the environment (e.g.
case of diclofenac and xenoestrogens). Although it is commonly accepted that maintaining human health thanks to pharmaceuticals will always remain a priority over environmental considerations, this calls for considering possible options for a more sustainable use of pharmaceuticals and consideration of their risk-benefits.

Although health benefits brought by pharmaceuticals are unquestionable, exposure of humans (healthy or under treatment) to those same substances, via the environment, could potentially lead to adverse health effects. It remains extremely challenging to establish a clear relationship between presence of pharmaceuticals in the environment and adverse health effects. Although several studies report unlikely risks on human health of pharmaceuticals at environmental concentrations, in particular via drinking water, long-term effects of pharmaceuticals on human health cannot be ruled out with current knowledge especially with regard to more vulnerable populations and the increasing debate about the exposure and effects of mixtures. In particular, evidence of the development of AMR in manure and wastewaters raises particular concern with regards to human health and has received considerable attention in the last few years. Although trends in consumption of antimicrobials have been decreasing in the EU, the expected growth of the market of antimicrobials globally is likely to further contribute to the issue.

As exposed above, several studies and reviews published in the last five years investigate further the issue of pharmaceuticals in the environment and provide new evidence on a number of topics such as: contribution of manufacturing activities and WWTPs to environmental contamination; consumption data of pharmaceuticals with a high-risk profile; occurrence of pharmaceuticals in drinking water and marine areas; occurrence, fate and ecotoxicity of metabolites and transformation products; impacts of chronic exposure on non-standard endpoints in laboratory conditions and with predictive models; adverse effects related to pharmaceuticals in the environment; development of AMR in microbial population in potentially contaminating sources (manure and waste waters), etc.

Although a wealth of information has been collected and produced in the last few years, resulting data remain often scattered across individual studies, heterogeneous, incomplete and of difficult access at the EU level. Several research needs remain to be tackled, e.g.:

- continue developing predictions or monitoring of environmental concentrations based on the latest consumption and occurrence data, in particular for veterinary pharmaceuticals (including pets), antimicrobials and AMR microorganisms (bacteria);
- further investigate the presence of pharmaceutical products in reclaimed wastewater and manure to be reused on agricultural fields and risks of bioaccumulation, as well as long-term impacts of landfills
- further develop the modelling of the transfer of pharmaceuticals between environmental compartments;
- continue developing intelligent testing strategies for chronic toxicity assessment (e.g. based on mode of action) and increasing knowledge on the ecological relevance of sub-lethal responses to pharmaceutical exposure and in particular the relevance of non-standard endpoints;
- further develop read-across, modelling and extrapolation approaches to overcome ecotoxicological and toxicological data gaps as well as lack of information on fate and behaviour of substances
- further investigate the significance of the effects of metabolites and transformation products;
- further investigate how mixture effects could be assessed, and identifying priority mixtures;
- further investigate the link between the release of anti-microbials, AMR microorganisms and determinants in the environment and the development of human and animal health disorders due to resistant bacteria;
- further assess health effects on vulnerable human groups of environmental exposure to pharmaceuticals;
- further monitor concentrations of illicit drugs in areas of production and high use, environmental fate of these compounds, and effects of these compounds on aquatic ecosystems at the concentrations that typically occur in the environment; and
- develop collaborative work to share the environmental information about pharmaceuticals in a harmonised and accessible way.

This state-of-the-art of the issue of pharmaceuticals in the environment calls for fostering research and collaborative work in order to share and capitalise on the environmental information about pharmaceuticals in a more harmonised and accessible way at the EU level. Other leverages to mitigate the risks posed by pharmaceuticals can be promoted at the EU level. They will be developed in the following task of this study, as support for an EU public consultation.


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Annex 1. Methodological details of relevance about the ERA

1.1. Assessment of exposure: prediction of environmental concentrations

The table below highlights the ERA requirements for PECs data, for the different phases of the ERA, for human or veterinary products.

**Table 10: Use of PECs in the ERA of human and veterinary pharmaceuticals**

PECs are identified by the compartment they relate to

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Phase of ERA</th>
<th>Calculation method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Phase I (Human)</td>
<td>Simple formula using the maximum daily dose consumed per inhabitant, the fraction of market penetration, the amount of wastewater per inhabitant per day and a dilution factor</td>
</tr>
<tr>
<td></td>
<td>Phase II Tier A (Human)</td>
<td>Refinement of the estimation of Phase I with information on the sales forecast of the product</td>
</tr>
<tr>
<td></td>
<td>Phase II Tier B (Human)</td>
<td>Further refinement of the estimation of Phase II Tier A with information from Sewage Treatment Plant (STP) modelling (adsorption and biodegradability)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Phase of ERA</th>
<th>Calculation method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterinary</td>
<td>Surface water</td>
<td>Refinement of the estimation of Phase I with information on the sales forecast of the product</td>
</tr>
<tr>
<td></td>
<td>Groundwater</td>
<td>Further refinement of the estimation of Phase II Tier A with information from Sewage Treatment Plant (STP) modelling (adsorption and biodegradability)</td>
</tr>
</tbody>
</table>

The different modelling methods for estimating PECs in the ERA procedure for the authorisation of pharmaceuticals in the EU are provided in Table 11. They are outlined in the ERA Guidelines drafted by the Committee for Medicinal Products for Human Use at EMA (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP) and based on the TGD.

**Table 11: Methods for estimating pharmaceutical PECs, depending on the compartment, phase of ERA and nature of the pharmaceutical**

73 Guideline on the environmental risk assessment of medicinal products for human use (CHMP, 2006) and Environmental Risk Assessment for Veterinary Medicinal Products other than GMO containing and Immunological Products (CVMP, 1998)
The guidelines suggest a few methods for estimating concentrations that may reach surface waters by run-off:

- Adapting public domain models developed for pesticides or for industrial chemicals;
- Determining the distribution between soil and surface waters by calculating the adsorption factor $K_{oc}$ thanks to adsorption studies or QSAR (Quantitative structure–activity relationship); and
- Determining the concentration in soil water (interstitial pore water) which, along with the amount of rainfall, conditions the concentration in surface water.

For the specific case of PEC estimates for fish medicines used in freshwater, reported concentrations in the effluent from fish farms should be used.

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Phase of ERA</th>
<th>Calculation method</th>
</tr>
</thead>
</table>
| Phase II Tier A (Veterinary) | The guidelines suggest a few methods for estimating concentrations that may reach surface waters by run-off:  
- Adapting public domain models developed for pesticides or for industrial chemicals;  
- Determining the distribution between soil and surface waters by calculating the adsorption factor $K_{oc}$ thanks to adsorption studies or QSAR (Quantitative structure–activity relationship); and  
- Determining the concentration in soil water (interstitial pore water) which, along with the amount of rainfall, conditions the concentration in surface water.  
For the specific case of PEC estimates for fish medicines used in freshwater, reported concentrations in the effluent from fish farms should be used. |
| Groundwater | Phase II (Human) | PEC for surface water divided by 4 |
|             | Phase I (Veterinary) | The guidelines suggest using models available for the evaluation of pesticides. These models use the soil degradation parameter $DT_{50}$ and the soil sorption characteristic $K_{oc}$ as main parameters. |
| Soil        | Phase I (Veterinary) | The estimations are mainly based on doses, excreta production, percentage of animals treated, degradation during storage, slurry application rates and soil density. |
|             | Phase II Tier B (Human) | Modelling |
| Sediment    | Phase II Tier B (Human) | Water sediment study (OECD 308) |
| Aeration tank | Phase II Tier B (Human) | STP modelling |
1.2. Assessment of ecotoxicity: derivation of PNECs

The table below highlights the assessment factors used to derive PNEC values for the aquatic compartment.

**Table 12: Assessment factors to derive a PNEC for the aquatic compartment**

<table>
<thead>
<tr>
<th>Available data</th>
<th>Assessment factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one short-term L(E)C50 from each of three trophic levels of the baseset (fish, <em>Daphnia</em> and algae)</td>
<td>1000</td>
</tr>
<tr>
<td>One long-term NOEC (either fish or <em>Daphnia</em>)</td>
<td>100</td>
</tr>
<tr>
<td>Two long-term NOECs from species representing two trophic levels (fish and/or <em>Daphnia</em> and/or algae)</td>
<td>50</td>
</tr>
<tr>
<td>Long-term NOECs from at least three species (normally fish, <em>Daphnia</em> and algae) representing three trophic levels</td>
<td>10</td>
</tr>
<tr>
<td>Species sensitivity distribution (SSD) method</td>
<td>5-1 (to be fully justified case by case)</td>
</tr>
<tr>
<td>Field data or model ecosystems</td>
<td>Reviewed on a case by case basis</td>
</tr>
</tbody>
</table>

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