

The environmental and health impacts caused by emissions of APIs to the environment

The impact of pharmaceuticals has been underestimated for many years, but the issue needs to be addressed just as much as the impact of other chemicals, such as pesticides, biocides or industrial chemicals which have a known impact on the environment and human health. The discovery of estrogens in sewage effluents as a cause of the feminisation of fish in the late 1990s sparked increased interest in the issue of pharmaceuticals in the environment. In 2007, the German Advisory Council on the Environment (SRU, 2007) recommended examining the possibility of including pharmaceuticals in the list of priority hazardous substances¹ under the Water Framework Directive. However, in 2018 there is still no pharmaceutical included as a priority substance although it was already proposed by the Expert Group on Review (SG-R) of the Priority Substances in 2009. Alongside other identified relevant substances some pharmaceuticals are now included or proposed to be included on a Watch List to receive more monitoring data.

Most of these identified substances are hormonally active substances and antibiotics. This is not surprising because pharmaceuticals include active ingredients that are designed to be biologically active so they have a therapeutic effect and thus may cause effects in other living organisms. In addition, excipients are also recognised to be toxic.

An excipient is a substance formulated alongside the active ingredient of a medication to improve e.g. the physical properties of the pharmaceutical ingredient. Among others, phthalates are used as functional excipients in a large number of oral pharmaceutical formulations. These substances are suspected endocrine disrupting chemicals and show adverse reproductive and/or developmental effects (EMA, 2014).

Human and veterinary medicinal products are consumed for preventive, diagnostic, nutritional and/or treatment purposes. In terms of market presence, around three thousand active pharmaceutical ingredients (APIs) are currently authorised on the EU market as a whole, even if the APIs authorised at national level vary significantly (BIO Intelligence Service, 2013). The annual worldwide consumption of APIs is estimated at 100 000 tonnes (KNAPPE, 2008). Regarding human medicinal products, EU consumption of medicine accounts for 24% of the world total, ranked second after the United States (55%), the third place occupied by Japan (14%) (BIO Intelligence Service, 2013).

EMISSIONS TO THE ENVIRONMENT

The key steps (from an environmental perspective) in the life cycle of a medicinal product are manufacturing, consumption and waste disposal.

¹ 'Hazardous substances means substances or groups of substances that are toxic, persistent and liable to bio-accumulate, and other substances or groups of substances which give rise to an equivalent level of concern. Priority (hazardous) substances means substances identified in accordance with Water Framework Directive (WFD) Article 16 and listed in Annex X.

Manufacturing

A very substantial share of pharmaceutical production now takes place overseas. This is particularly the case for antibiotics and other generic medicines that are produced in Asia but are also sold to Europe and the United States. China produces 80-90 % of antibiotic APIs and Indian companies lead the production of finished dose antibiotics. In many cases, the product is finalised in Europe on the basis of imported APIs and hence can be labeled as made in EU (Changing Markets, 2016).

Despite the statement that with the exception of accidental releases the production of medicinal products seems to play a minor role in their discharge into the environment, a systematic monitoring of emissions during manufacturing at the EU level is presently missing and thus the amount of API releases from production facilities is largely unknown. Moreover, possible downstream pollution from manufacturing plants has been observed in the EU and other parts of the world while monitoring specific sites: APIs have already been monitored in some manufacturing plants' effluents in Asia (notably in India) and in Europe (Main, Rhine) (BIO Intelligence Service, 2013). An on-the-ground investigation in India has revealed extremely high levels of antibiotic resistance at pharmaceutical manufacturing sites, while detailed research and an investigation in China have uncovered failings in the GMP² inspection system and a potential risk from the spread of antibiotic residues on soil in the form of fertiliser (Changing Markets, 2016). Another study, conducted by a microbiologist from the University of Leipzig, found "excessively high" concentrations of clinically relevant antibiotics and antifungal agents in water samples taken at sites in Hyderabad and a high level of drug-resistant bacteria in more than 95% of samples (Luebbert et al. 2017). These high levels of resistance can easily transmit to pathogenic bacteria that can threaten the health of the local population and spread antimicrobial resistance around the world through travel and trade. Furthermore, the vast majority of antibiotic factories where high levels of resistance were detected are producing for global markets, including the EU, which makes this issue a supply chain problem (Changing Markets, 2016).

Consumption

In Europe and the United States the consumption phase is considered to be the biggest contributor to the emissions of medicinal products into the environment, notably through excretions and incorrect disposal of unused medicines through sinks and toilets. Between 30% and 90% of an orally administered dose is generally excreted as an active substance in the urine of animals and humans. Significant amounts can also be excreted in faeces (up to 75% in animal faeces) (BIO Intelligence Service, 2013). Therefore, animal farms (in particular, large intensive animal farms) can become large sources of anti-microbial resistance. Medicinal products can also directly enter the environment through feed surplus, notably in the case of aquaculture (BIO Intelligence Service, 2013).

Waste management

According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), unused medicinal products destined for humans represent 3 to 8% of the medicinal products sold. Other estimates are more pessimistic and are as high as 50% in France and the United Kingdom. However, in the majority of EU Member States, a big share of unused medicinal products (from 50% up to 90%) are

2 GMP: Good Manufacturing Practice

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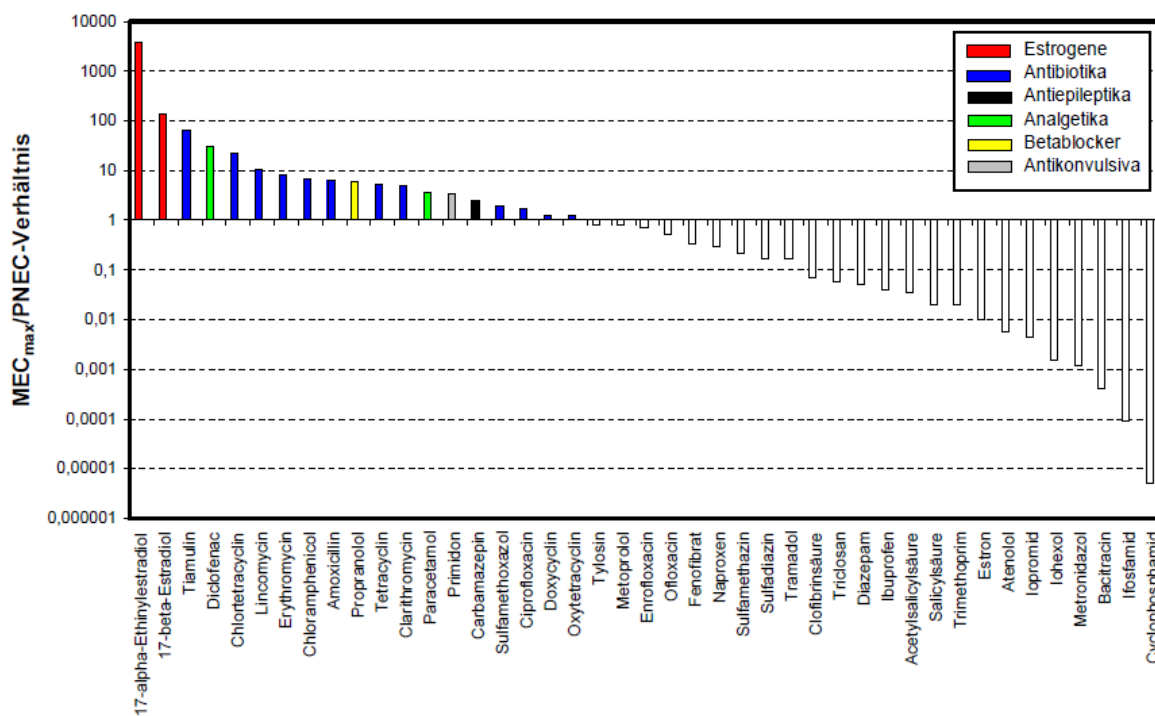
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not collected or returned to pharmacies and may contribute to environmental pollution (BIO Intelligence Service, 2013). Medical waste includes unused medicinal products (human or veterinary) and contaminated materials (e.g. packaging) and liquids (Castensson, 2008) generated during manufacturing and administration.

Studies have shown that medicinal products are especially present in water bodies. They are often filtered ineffectively by wastewater treatment plants which are not designed to manage them (BIO Intelligence Service, 2013).

The following figure shows maximum measured environmental concentrations (MEC) compared to predicted no-effect concentrations (PNECs). The measured concentrations are up to more than 1000 times higher than the no effect concentrations.



Risk quotients in Germany for a range of medicinal products (BIO Intelligence Service, 2013)

A global review found that 713 pharmaceuticals (of which 142 are transformation products) have been looked for in the environment and 631 (of which 127 are transformation products) have been found above their detection limits (CHEM Trust, 2014). In 71 countries, pharmaceuticals have been detected in the environment.

Name	Therapy Group	Number of Countries with Positive Detection in Surface Water, Groundwater, Drinking Water					
		African Group	Asia Pacific Group	EEG	GRULAC	WEOG	global
Diclofenac	Analgesics	3	8	13	3	23	50
Carbamazepine	Antiepileptic drugs	3	6	13	2	24	48
Ibuprofen	Analgesics	3	8	10	2	24	47
Sulfamethoxazole	Antibiotics	5	9	10	2	21	47
Naproxen	Analgesics	2	8	10	2	23	45
Estrone	Estrogen	1	10	6	2	16	35
17-beta-Estradiol	Estrogen	2	9	4	2	17	34
17-alpha-Ethinylestradiol	Estrogen	1	8	3	2	17	31
Trimethoprim	Antibiotics	2	9	3	2	13	29
Paracetamol	Analgesics	1	6	4	3	15	29
Clofibrac acid	Lipid-lowering drugs	1	3	5	2	12	23
Ciprofloxacin	Antibiotics	1	5	1	2	11	20
Ofloxacin	Antibiotics	1	4	1	1	9	16
Estriol	Estrogen	1	1	2	1	10	15
Norfloxacin	Antibiotics	1	4	1	2	7	15
Acetylsalicylic acid	Antibiotics	1	4	1	2	7	15

In the EU, veterinary medicinal products are used in smaller quantities than human medicinal products. They are extensively used in farming for therapeutic and metaphylactic purposes. A growing segment of the veterinary products market is for companion animals, or pets. Antibiotics account for a large part of the veterinary market (BIO Intelligence Service, 2013).

PHARMACEUTICALS IN THE ENVIRONMENT

Once in the environment, medicinal products are transformed and transferred through different parts of the environmental 'host compartments' (i.e. water, air, or soil), depending on the nature of the compounds and the characteristics of the host compartment. The detected concentrations could be in the range of sub-ng/L levels to more than several µg/L. In drinking water medicinal products could usually be detected at low concentrations (ng/L range). The molecules most often detected in Germany, France and Finland are non-steroidal anti-inflammatory medicinal products (NSAIDs). Progestagens and androgens seemed to be the more resistant to drinking water treatments (BIO Intelligence Service, 2013).

Due to the observed concentrations, risks are more related to possible cumulative effects of long-term low-dose exposures than to acute health effects (BIO Intelligence Service, 2013).

Examples of ecotoxicological effects of medicinal products include the contraceptive Ethinylestradiol, which impairs the reproduction of exposed fish populations in laboratory experiments; the effects of various antibiotics on environmental bacteria and algae; the impacts of the Benzodiazepine anxiolytic drug oxazepam on European perch; and the effects of the anti-parasiticide ivermectin on dung fauna. The decline of vulture populations on the Indian sub-continent due to poisoning with Diclofenac, a non-steroidal painkiller, is a good example of how unexpected exposure pathways – feeding on carcasses – can lead to severe ecotoxicological effects. Antibiotics, anti-parasitides, anti-mycotics and anti-cancer medicinal products are pharmaceutical groups that 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 environmental exposure. Chronic low-level exposure to medicinal products can occur through drinking water and through residues in leaf crops, root crops, fishery products, dairy products, and meat (BIO Intelligence Service, 2013).

In addition, there is growing concern that combined exposure (mixtures) to chemicals from different sources may have adverse effects on human health, even if each individual substance is below its own risk limit. Carvalho et al (2014) showed that complex chemical mixtures where all single substances were introduced in a concentration which is considered to be safe for the environment (EQS) showed toxicity in several ecotoxicological test systems (BIO Intelligence Service, 2013).

MOST RELEVANT PHARMACEUTICALS FOR THE ENVIRONMENT

Three of the most relevant pharmaceuticals, hormonally active drugs (like EE2, which is present in the birth control pill), antibiotics and anticancer medicinal products, are briefly described in the following sections.

Endocrine disrupting chemicals

A particular focus is suggested to be placed on endocrine disrupters (COM, 2012, BIO Intelligence Service, 2013). These substances act like hormones and disturb the normal functioning of the endocrine system. Hormones are substances involved in cell signalling in humans and animals. They are biologically active at low doses and as medicinal products they are used as natural, nature identical and synthetic substances. As contaminants in the ecosystem, hormones have already been shown to disrupt biological signal pathways. Two hormones are included in the EU surface water Watch list of emerging pollutants, estradiol (E2) and ethinylestradiol (EE2), however monitoring data of these substances is still scarce due to lack of measurements undertaken with sufficient analytical capacity to quantify these substances.

Thanks largely to the extensive work done by researchers in the United Kingdom, the scale of the problem with E2 and EE2 is well described. Measured mean concentrations of EE2 along the main rivers appear to exceed the proposed Environmental Quality Standards (EQS) at all sampling sites and modelling has shown that in 40 % of 21,452 km river reaches in England and Wales, concentrations can be expected to exceed levels causing effects (Jobling et al, 2006; Williams et al, 2009 and 2012, Gardner et al, 2012).

Antibiotics

Antibacterial medicinal products are compounds that kill or inhibit the growth of bacteria. Antibiotics have been used in human and veterinary medicinal products for several decades. Antimicrobial resistance (AMR) is nowadays a widely recognised and growing problem. Without effective antimicrobials, infections become more difficult to treat, while medical and surgical procedures (such as gut surgery, caesarean sections, joint replacements, and treatments that depress the immune system, such as chemotherapy for cancer) could become too dangerous to perform (O'Neill, 2016). They can become high-risk interventions, leading to prolonged sickness, disability and death.

AMR already causes more than 700,000 deaths each year worldwide (Access to Medicine Foundation, 2018). The European Centre for Disease Prevention and Control has estimated that in 2007 in Europe 25,000 deaths were as a result of AMR and health care expenses and productivity losses as a result of AMR are in the region of over 1.5 billion EUR. This is an underestimation as it refers to only seven antibiotic-resistant bacteria, hence not providing the complete picture. Projections estimate a 15-fold increase in morbidity in Europe by 2050 with 390,000 deaths (Background document for public consultation on pharmaceuticals in the environment, 2017).

As mentioned before antibiotics can reach the environment through manufacturing, consumption and waste disposal. Pharmaceutical manufacturing and production processes can contribute to antimicrobial resistance through two key routes: by releasing waste that includes antibiotics into the environment; and by manufacturing antibiotics with sub-therapeutic levels of the active antibiotic ingredient (BIO Intelligence Service, 2013). Antibiotics can contaminate soil, crops and water sources and encourage the development of drug resistance amongst the pathogens with which they interact (O`Neill, 2016).

It is important to note that even trace amounts of antibiotic residues can put selective pressure on bacteria to develop resistance (Sandegren L., 2014). What is more, scientists have shown that bacteria present in the environment can develop resistance factors which, through the transfer of genetic elements to human pathogens, can render antibiotic treatment “useless” (Fick, 2009). Indeed, a 2014 study reported that “there is increasing evidence that the resistance we see in pathogens did not initially appear in the clinical setting, but that environmental bacteria have contributed to the resistance gene pool shared among pathogens today.” (Bengtsson-Palme, J., 2014).

The increasing resistance to antimicrobial medicinal products represents one of the major emerging threats to human health. The development of AMR is by far the largest risk for humans of having medicinal products residues in the environment.

Anticancer medicinal products

Anticancer medicinal products are optimally designed to kill/inhibit malignant tumour cells at doses that allow enough unaffected cells in critical tissues with high cell proliferation rates to survive so that recovery can occur. Different substance groups with specific mechanisms of actions are used in anticancer chemotherapy; however, most are generally genotoxic, mutagenic and reprotoxic substances already at relatively low concentrations. An unintended human exposure of anticancer medicinal products via drinking water (which are detected in drinking water) or food could be problematic (BIO Intelligence Service, 2013). Kümmerer et al (2009) have proposed these substances to be subject to an environmental risk assessment. No safe threshold can be assumed for these substances, even at very low concentrations.

REGULATION IS NEEDED

In general, pharmaceuticals should not be treated differently to all other substances. An obligation to reduce and/or phase out their emissions does not necessarily mean that marketing these products is no longer possible. What is unacceptable however is when uncertainty about the measures that may be taken to tackle the problems caused by certain substances are used as grounds to simply continue ignoring the problem. Uncontrolled emissions of pharmaceuticals in the environment do not only harm ecosystems, but can even undermine the working of these same pharmaceuticals for the benefit of humanity. For this reason it is of paramount importance that the EU takes regulatory actions in line with precautionary principle.

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