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Joint Statement

Europe must align policies to tackle Pharmaceuticals in the Environment and Antimicrobial Resistance

The signatories urge European policymakers to ensure that Europe's response to the threat posed by the presence of pharmaceuticals in the environment (PiE) is taken seriously, and that present and future European action will be timely, resolute and coordinated in all relevant policies.

Especially in light of the looming and severe public health crisis posed by antimicrobial resistance (AMR) fuelled by, *inter alia*, pollution caused by pharmaceuticals throughout their life-cycle, we underline that only a multi-sectoral, multi-stakeholder approach can generate the required results for the continued health of people, animals and ecosystems, in Europe and globally.

The European Commission is set to release the long-awaited strategic approach to PiE, which will contain a series of measures to alleviate pollution and other damage caused by pharmaceutical residues released into the environment. The strategic approach follows the Commission's 2017 follow-up Action Plan against AMR, which we regret falls short on the environmental side, and ignores clear evidence on the extent of pharmaceutical pollution.

European policies need to recognise that the increased presence of pharmaceuticals in the environment and the effects are entirely preventable – if Europe accepts its leadership responsibility to address the root causes and makes available dedicated resources.

Pharmaceutical active substances are currently excluded from EU environmental legislation, which is untenable in light of the risk that pharmaceutical pollution poses to the environment and to human and animal health. We therefore urge the European Commission to seize a number of important policy opportunities which, in combination, will mitigate the crushing effects of PiE and AMR.

Recommendations

Based on the evidence presented in the Annex and the background documents to the Commission's consultation on PiE, the signatories of this statement propose the following recommendations:

- Revise the Good Manufacturing Practices (GMP) to include compulsory environmental standards

- Include medicinal and veterinary products under all of REACH titles in order to ensure adequate information and transparency on environmental occurrence and impacts of APIs.
- Introduce an EU monitoring system for the mandatory, routine collection of data on antimicrobials and AMR microorganisms in the environment.
- Introduction of legally binding concentration limits and standards for residues of pharmaceutical substances in water.
- Revise relevant Best Available Techniques (BAT) reference documents (BREFs) in the Industrial Emissions Directive (IED) to take into account environmental emissions of pharmaceutical ingredients during the manufacturing of pharmaceutical products, and on intensive rearing of poultry and pigs.
- Ensure that ERA results are systematically considered in the risk-benefit analysis of marketing authorisation decisions for new human medicinal products, coupled with compulsory ERAs for products put on the market before 2006.
- Set up public procurement in EU member states to favour human and veterinary medicinal products with low environmental impacts.
- Ensure extended producer responsibility for full life-cycle of products placed on the market.
- Support research into the various transmission dynamics of AMR via the environment.
- Task the EU One Health Network on AMR with ensuring policy coherence and alignment between AMR, PiE, water legislation and other relevant environmental strategies.
- Define criteria for veterinary pharmaceuticals that are especially hazardous to the environment, implement a system of comparative assessment and establish a process that denies authorisation for such APIs with no or strictly limited derogation.
- Develop comprehensive data collection for all antibiotics used in human medicine as well as in animal breeding and husbandry, and make those accessible to the public.
- Initiate EU-wide measures to improve animal welfare, livestock conditions and animal husbandry practices as important precaution measures to secure animal health and reduce the need for medication.

Changing Markets Foundation
 European Environmental Bureau
 European Public Health Alliance
 Healthcare Without Harm
 PAN Germany

Annex: Pharmaceuticals in the Environment and Antimicrobial Resistance

Introduction

In spring 2018, the European Commission is set to release the long-awaited strategic approach to PiE, which will contain a series of measures to alleviate pollution and other damage caused by pharmaceutical residues released into the environment during their life-cycle, i.e. during production, consumption and disposal.

The strategic approach follows the 2017 release of the Commission's follow-up Action Plan against AMR, which emphasises the importance of taking a holistic One Health approach in reducing the prevalence of AMR, curbing irresponsible uses of antimicrobials and raising further awareness of prudent use practices and behaviours. It outlines important policy measures to be taken in healthcare environments and in livestock farming, including by establishing explicit links with implementing acts of the legislative proposals on Veterinary Medicinal Products and Medicated Feed, as well as the so-called Animal Health Law. **However, the Action Plan falls short on the environmental side, as it ignores clear evidence on the extent of pharmaceutical residues in the environment and the health risk it poses.** A balanced One Health approach should consider the recent scientific studies that have showed that antibiotic waste from manufacturing sites doesn't just pollute the environment but is also a reservoir of resistant microbes.

Complementing the AMR Action Plan, the upcoming Commission Communication on Improving Health Security in the EU will also adopt a One Health approach in order to counteract the growing global threat emanating from infectious diseases and build a comprehensive European public health emergency preparedness and response strategy.

One important vector for the spreading of PiE is water. We should take advantage of all opportunities to tackle the twin problems of PiE and AMR, e.g. by setting binding limits on the amount of pharmaceutical residues in water, and by ensuring that API present in waste water are effectively treated and destroyed before further release.

In the face of a powerful cross-border phenomenon like AMR, it is vital that Europe exploits its full regulatory mandate in all applicable areas if it wishes to avoid the alarming scenarios described in the 2016 UK Review on AMR¹ and by the OECD², which involve hundreds of thousands of deaths at a massive cost to Europe's social fabric and its economy.

Importantly, European policies need to recognise that the increased presence of PiE and the effects are entirely preventable – if Europe accepts its leadership responsibility to address the root causes and makes available dedicated resources.

Pollution from drugs manufacturing

The extent of pollution caused by active pharmaceutical ingredients (APIs) during the manufacturing process of pharmaceutical drugs is well documented, in particular in India and

¹ O'Neill J (2016) Tackling drug-resistant infections globally: Final report and recommendations. The review on antimicrobial resistance.

² Cecchini M & Lee S (2017) "Low-value health care with high stakes: Promoting the rational use of antimicrobials", in *Tackling Wasteful Spending on Health*, OECD Publishing, Paris

China where most APIs are manufactured. A number of studies³ and documentaries⁴ have lifted the veil on the devastating impacts of uncontrolled manufacturing discharges on water bodies, as well as on the people and animals who have come into contact with resistant bacteria in the environment. The most recent evidence from Hyderabad (India) reveals the presence of toxic chemicals at extremely high concentrations, exceeding maximum regulatory limits or safe exposure levels.⁵

The effects of pollution from pharmaceutical production are not only a local or national problem. The global spread of resistant bacteria is facilitated by international travel and tourism, trade in foodstuffs and other forms of mobility. In other words, resistance that may evolve in far-flung places can easily be imported to Europe and present a major challenge to our health systems, if the latter lack the resources, capacity or expertise to safeguard patient safety (e.g. via strict hospital screening procedures, infection prevention and control, hand hygiene, antimicrobial stewardship).

In addition, there is some evidence of increased AMR in antibiotic manufacturing effluent in Europe.⁶ It should be ensured that manufacturing plants located within the EU avoid emissions of pharmaceutical ingredients.

Agriculture pollution

Resistant bacteria from livestock farming can pose a threat to humans given their ability to spread via contaminated meat, direct contact with animals and the environment.

Worryingly, in many European countries, last-line antibiotics⁷ are still commonly used in livestock farming, which not only exacerbates drug resistance but also leads to further pollution. Oral doses of antibiotics used in animals are only partially metabolised or degraded by animal body and as a result, active ingredients are being excreted unchanged and enter the environment, whereas farm effluents are polluting surface and ground waters. The Veterinary Medicinal Products Directive and Animal Health Law provide important opportunities to curb unnecessary administration of antibiotics and to ensure better alignment between policies targeting AMR, pharmaceuticals in the environment and species-appropriate husbandry.

The behaviour of pharmaceuticals in the environment is complex and depends on many factors (farming system, climate, combination of drugs used, etc.). Farm effluents pose a significant risk to surface and ground waters given that many antibiotics are soluble and easily dispersed. It is thus crucial to ensure that animal keepers and veterinary professionals become

³ Changing Markets (2016) Impacts of pharmaceutical pollution on communities and environment in India.

Larsson J, de Pedro C, Paxeus N (2007) Effluent from drug manufacturers contains extremely high levels of pharmaceuticals, in *Journal of Hazardous Materials*, 148

Larsson J (2014) Pollution from drug manufacturing: review and perspectives, in *Philosophical Transactions of the Royal Society B: Biological Sciences*, 369

Lübbert C, Baars C, Dayakar A et al. (2017) Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens, in *Infection*, 45(4)

⁴ Zembla (2018) The real price of cheap medicine <https://zembla.bnnvara.nl/nieuws/the-real-price-of-cheap-medicine>

Norddeutsche Rundfunk (NDR) (2018) Auf der Spur der Superkeime

<https://www.ndr.de/nachrichten/niedersachsen/Gefaehrliche-Keime-in-Baechen-Fluessen-und-Seen,keime302.html>

⁵ Larsson J (2014) Pollution from drug manufacturing: review and perspectives, in *Philosophical Transactions of the Royal Society B: Biological Sciences*, 369

Changing Markets (2018) Hyderabad's pharmaceutical pollution crisis.

⁶ Gonzalez-Plaza J, Simatovic A, Milakovic M et al. (2018) Functional repertoire of antibiotic resistance genes in antibiotic manufacturing effluents and receiving freshwater sediments, in *Frontiers in Microbiology*

⁷ World Health Organization (2017) 20th WHO Model List of Essential Medicines

more aware of the effects of PiE and AMR. This can further lead to curbing unnecessary use of antibiotics in farming, e.g., through restricting their metaphylactic use.⁸ While the data on veterinary use of antibiotics are much more comprehensive than in healthcare, they do not include dairy farms, aquaculture and many other types of livestock operations. Data on the use of other veterinary pharmaceuticals like hormones and antiparasitics are still missing for many livestock operations, though these pharmaceuticals have proven to affect the environment. These gaps need to be tackled.

A successful strategy to tackle environmental pollution by veterinary pharmaceuticals must include efforts to identify and limit the placing on the market of substances which are specifically hazardous to the environment, including substances covering PBT, vPvB and EDC properties (PBT = substances which are at the same time persistent, toxic and accumulate in living organisms, vPvB = substances which are very persistent and very bio-accumulative, EDCs = substances with endocrine disrupting properties).

Healthcare pollution

The use of antibiotics and other pharmaceutical agents in different types of healthcare environments – which also includes people's homes - is difficult to measure and reliable data are scarce. Many actors are involved, from healthcare professionals to patients and carers. It is unacceptable that in some European countries it is still possible to obtain prescription drugs without much effort, and much remains to be done to educate all stakeholders about the legitimate use of antimicrobial drugs. Irresponsible use and disposal, e.g. by flushing pharmaceuticals down the toilet or sink, remain common, thereby increasing the amount of residues that enter the environment coming from healthcare settings.

Given that patients rely on functioning antibiotics in these very settings, Europe needs to ensure that sweeping changes are being implemented as quickly as possible: everybody is a patient, and AMR does not discriminate. The growing problem of healthcare-associated infections in many European countries provides another warning signal, again fuelled by the excessive use of antibiotics.

That drug resistance can quickly become an international challenge has been proven by the transfer of victims of the Colectiv night club fire in Romania, many of whom displayed multi-drug resistance.⁹

Water pollution

Water is a key vector for the diffusion of pharmaceuticals in the environment at all stages of the drug life-cycle. Antibiotics and other hazardous contaminants often enter local water bodies where they pollute surface and ground waters, sediment and soil, and this can bring lasting effects on entire ecosystems. For example, the negative impacts of pharmaceutical residues in the environment have been demonstrated on algae, fish, earthworms, birds, insects, plants and crops, to name but a few. These impacts are even stronger where different harmful substances are able to mix.

Another corollary of this is that the quality of Europe's drinking water supply – dependent on uncontaminated groundwater - is increasingly at risk. Given the transnational geography of many major rivers and lakes, the consequences of PiE and AMR know no borders. Even

⁸ PAN Germany (2018) Antibiotics in livestock farming. What can be done to reduce environmental threats and avoid the development of antibiotic resistance?

⁹ European Public Health Alliance (2017) In the red zone. Antimicrobial resistance: lessons from Romania

countries that have successfully implemented best practices and restricted the use of antimicrobial drugs can thus be affected.

In almost all countries, wastewater sewage plants are not equipped to filter out most pharmaceutical residues. As it is costly to invest in such infrastructure, it is crucial to take a precautionary approach.

Joining the dots between pharmaceutical pollution, the environment and health

Clearly, humans and animals rely on functioning pharmaceutical drugs, which are crucial for treating diseases and enabling many of the key functions of modern medicine.

As the above paragraphs show, people, animals and the environment are closely intertwined. If one part is suffering, the others will automatically also be affected.

From a public health perspective, the pollution that occurs due to lack of scrutiny during the life-cycle of pharmaceuticals also amplifies the negative effects of other developments affecting population health. For example, a recent WHO report warns that growing numbers of people die as a result of air pollution. If current trends continue, millions of people in Europe will rely on functioning antibiotic treatments to treat lung cancer and chronic obstructive pulmonary disease (COPD). The rise of chronic, non-communicable diseases in an ageing European society, and the rising threat posed by infectious diseases calls for a preventive approach that does not have to be costly but involves investments in building an effective safety net against PiE and AMR.

AMR from environmental pollution was recognised recently as one of the biggest emerging health threats by the United Nations Environmental Programme (UN Environment).¹⁰ Urgent action is required globally, and the signatories of this statement urge Europe to lead by implementing our recommendations.

¹⁰ UN Environment (2017) Antimicrobial resistance from environmental pollution among biggest emerging health threats, says UN Environment