Health Care Without Harm
The campaign for environmentally responsible healthcare

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6th September 2018

RE: Important considerations regarding the upcoming debate on the 'Report on the European One Health Action Plan against Antimicrobial Resistance', Monday 10th September 2018

Dear Member of the European Parliament,

Next Monday, 10th September in Strasbourg, you will be engaged in a discussion on the Report on the European One Health Action Plan against Antimicrobial Resistance (AMR),[1] presented by MEP Karin Kadenbach. In light of the upcoming debate on this report, we call upon MEPs to raise the following issues when assessing the importance of urging the European Commission to take further action to combat AMR.

We also call on MEPs to highlight the lack of certain provisions (listed in the accompanying Annex, sections 3.1 and 4) in the report and to consider these in future debates on the issue.

The problem

Described by England's Chief Medical Officer as a "catastrophic threat", AMR is estimated to cause 700,000 deaths per year globally.[2,3] Whilst a key aim of the EU One Health Action Plan against AMR is to make the EU a "best practice region", the European Commission (EC) is failing to protect both European and global citizens from drug-resistant infections through a lack of effective legislation. The EC grossly underestimates the scale of the problem - continually stating that AMR is responsible for approximately 25,000 deaths per year in the EU[4] – an out-dated figure from 2007 based on data for only five drug-resistant bacteria. Researchers estimate that drug-resistant infections cause half of those deaths (12,500) annually in France *alone.*[5]

In preparation for the debate on the ENVI report on the One Health Action Plan, we would like to bring your attention to the manifold aspects of this serious problem, particularly highlighting the role pharmaceutical pollution plays in the emergence and spread of AMR.

Lack of adequate legislation to tackle AMR

In 2001, the EC proposed far more ambitious actions and measures[6,7] to tackle AMR compared to the EU One Health Action Plan against AMR proposed in 2017. Using the EC's own very conservative estimates,[8] over 400,000 deaths could have been caused by drug-resistant infections in Europe since 2001 - evidently, the loss of human life is not an

adequate motivator for action on tackling AMR (for more information, please see Annex, section 1).

The 2017 Action Plan ignores clear evidence on the extent of pharmaceutical pollution's role in AMR. Pharmaceutical effluent is released into the environment during manufacturing and active pharmaceutical ingredients (APIs) are excreted from both humans and animals during consumption. Most of the world's APIs and finished dose antibiotics are manufactured in China and India, and then sold in bulk to European pharmaceutical companies. This allows European companies to profit not only from cheap labour, but also weak environmental regulations. Many drug manufacturers do not adequately treat their pharmaceutical waste, resulting in the dangerous excretion of APIs and finished dose antibiotics into the environment, polluting soil, crops, and water systems and encouraging the development of AMR (for more information, please see Annex, section 2.1).

The EC should have proposed the Strategic Approach to address the pharmaceutical pollution of water by **13 September 2015**.[9] Three years later, the Commission appears to be unconvinced of the urgency of the matter and the necessity of the approach. Recent media reports[10] demonstrate a shocking removal and weakening of key measures from early drafts. Particularly alarming is the removal of proposals to include environmental criteria in the Good Manufacturing Practices (GMP) framework - a legislative measure that would force pharmaceutical companies supplying the European market to tackle polluting practices throughout their supply chains (Annex, section 2). **The EC's lack of action on this long-delayed Strategic Approach on pharmaceuticals in the environment appears to demonstrate maladministration, which would warrant an investigation by the European Ombudsman.** We especially implore you to consider this important factor in the upcoming discussion and debate on the report on the Action Plan.

Furthermore, the EC was supposed to develop a legislative proposal on minimum quality requirements for water reuse in agricultural irrigation and aquifer recharge by the end of 2017. When reviewed by SCHEER (the Scientific Committee on Health, Environmental and Emerging Risks), the European Commission Joint Research Centre's report was described as "deficient in key details" (including the way pharmaceuticals in the environment and AMR are addressed) and that "the [proposed] minimum quality requirements provide insufficient protection both to environmental and human health".[11,12] The EC appears to be lacking initiative when it comes to regulating water reuse (for more information, please see Annex, section 3.2)

Continued overuse of medically important and last-resort antibiotics in animal husbandry not only accelerates the development and spread of AMR, but also contributes to pharmaceutical pollution of the environment. Whilst the new Medicated Feed and Veterinary Medicinal Product Regulations introduced long-overdue and necessary restrictions on antimicrobial use in animal husbandry, there are multiple, further important steps that could be taken to reduce inappropriate use of antimicrobials in livestock.[13,14] More comprehensive surveillance on antimicrobial-resistant pathogens from animals, along with more extensive data collection on the sales and use of antimicrobials would increase the understanding of the relationship between antibiotic use and the rise of resistance.

Introducing targets for veterinary antimicrobial use along with the taxation of certain antimicrobials used in animal husbandry could help to decrease the use of antimicrobials (for more information, please see Annex, section 4).

Finally, the EC has also failed to publish any report on the progress of the Innovative Medicines Initiative's €650 million public-private programme, *New Drugs 4 Bad Bugs* (ND4BB), [15] or detail how public money has been spent. The lack of a report raises serious questions about the success of this initiative and whether the money could have been better spent (for more information, please see Annex, section 5).

Time to act

Europe's response to the threat posed by pharmaceuticals in the environment, proven to fuel the public health crisis posed by AMR, must be taken seriously. Present and future European action must be timely, resolute, and coordinated across all relevant policies. We commend the important steps already taken by multiple MEPs: proposing amendments on pharmaceutical pollution in the ENVI Report and calling for the EC to appropriately address the issue by proposing effective measures to tackle this serious problem.

We hope you find the attached Annex useful in your preparation for Monday's debate on the Report on the European One Health Action Plan against AMR, and that you will consider the points we have raised in the upcoming debate. Please do not hesitate to contact us if you require further information or to request a meeting – we remain at your disposal.

Yours sincerely,

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About HCWH Europe:

HCWH Europe is a non-profit European coalition of hospitals, healthcare systems, healthcare professionals, local authorities, research/academic institutions and environmental and health organisations. It currently has 84 members in 26 countries from the WHO European region, including 17 EU member states. HCWH Europe works to transform the healthcare sector worldwide so that it becomes more ecologically sustainable and a leading advocate for environmental health and justice across the globe. We bring the voice of healthcare professionals to the European policy debate about key issues such as chemicals, climate change and health, green building, sustainable procurement, pharmaceuticals, sustainable food and waste management. www.noharm-europe.org

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[1] Report on a European One Health Action Plan against Antimicrobial Resistance (AMR). Committee on the Environment, Public Health and Food Safety. http://www.europarl.europa.eu/sides

[2] https://www.gov.uk/government/news/antimicrobial-resistance-poses-catastrophic-threat-says-chief-medical-officer--2

[3] The Review on Antimicrobial Resistance. (2016) *Tackling Drug-Resistant Infections Globally: final report and recommendations*. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf

[4] European Commission. (2017) A European One Health Action Plan against Antimicrobial Resistance (AMR). https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf

[5] Colomb-Cotinant M, Lactoste J, Brun-Buisson C, *et al.* (2016). Estimating the morbidity and mortality associated with infections due to multidrug-resistant bacteria (MDRB), France, 2012. *Antimicrobial Resistance & Infection Control.* https://www.ncbi.nlm.nih.gov/pubmed/27999665

[6] Communication from the Commission on a Community Strategy Against Antimicrobial Resistance of 2001. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52001DC0333&from=en

[7] Opinion of the Scientific Steering Committee On Antimicrobial Resistance 1999. https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_ssc_out50_en.pdf

[8] European Centre for Disease prevention and Control (2009). The bacterial challenge: time to react.. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

9 Directive 2013/39/EU of the European Parliament and of the Council of 12th August 2013. https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32013L0039

[10] The Guardian (2018). https://www.theguardian.com/environment/2018/jun/01/antibiotic-apocalypse-eu-scraps-plans-to-tackle-drug-pollution-despite-fears-of-rising-resistance

[11] European Commission Joint Research Centre (JRC) (2017). Minimum quality requirements for water reuse in agricultural irrigation and aquifer recharge. http://publications.jrc.ec.europa.eu/repository/bitstream/JRC109291/jrc109291_online_08022018.pdf

[12] Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) (2017). Proposed EU minimum quality requirements for water reuse in agricultural irrigation and aquifer recharge. https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_010.pdf

[13] Proposal for a Regulation of the European Parliament and of the Council on the manufacture, placing on the market and use of medicated feed and repealing Council Directive 90/167/EEC. COM(2014) 556. http://ec.europa.eu/transparency/regdoc/rep/1/2014/EN/1-2014-556-EN-F1-1.Pdf

[14] European Commission - DG Health and Food Safety. *Revision of the legal framework for veterinary medicinal products*. http://www.consilium.europa.eu/en/policies/animal-medicines-health-package/veterinary-medicinal-products/

[15] Innovative Medicines Initiative (IMI). New Drugs 4 Bad Bugs (ND4BB) https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb

Annex to letter: 'Important considerations regarding the upcoming debate on the 'Report on the European One Health Action Plan against Antimicrobial Resistance', sent 6th September 2018

1. Failure of the European Commission to implement the recommendations made in the 1999 Scientific Steering Committee Opinion on Antimicrobial Resistance

In 1998, the European Commission (EC) recognised the gravity of the implications of antimicrobial resistance (AMR) for the treatment of infectious diseases in both animals and humans, and consulted its Scientific Steering Committee (SSC) on this issue. The SSC was requested to evaluate factors contributing to the development of AMR and to make recommendations based on scientific evidence. The SSC subsequently set up a Working Group and adopted an Opinion on Antimicrobial Resistance[1] in 1999. This document proposed precise recommendations to limit the emergence and spread of AMR. The SSC stated that action needed to be "taken promptly to reduce the overall use of antimicrobials in a balanced way in all areas: human medicine, veterinary medicines, animal production, and plant protection".[1]

The SSC's recommendations included:[1]

- Tighter controls on the sale, supply, and distribution of antimicrobials by enforcing the legal classification mechanisms of individual EU Member States
- Eliminating incentives, especially financial, that encourage inappropriate use of antibiotics
- Planned and coordinated phase-out of antimicrobials used for growth promotion as soon as possible
- Replacing antimicrobials used for growth promotion with non-antimicrobial alternatives whilst introducing changes in animal husbandry practices to maintain animal health and welfare during the phase-out process
- Restricting herd treatment use of antimicrobials to only when alternatives are unavailable. Additionally, such cases should be regarded as a failure of preventative measures and require evaluation and investigation
- Cooperation and coordination between academic departments, the pharmaceutical industry, and medical and veterinary research bodies to promote necessary and appropriate research to develop truly novel agents and effective alternatives to antimicrobials, as well as preventive therapies

Furthermore, in the 2nd Opinion on Antimicrobial Resistance,[2] published in 2001, the SSC highlighted new evidence indicating that "the persistence in the environment of certain

[1] Opinion of the Scientific Steering Committee On Antimicrobial Resistance 1999. https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_ssc_out50_en.pdf
[2] 2nd Opinion on Antimicrobial Resistance Opinion of the Scientific Steering Committee On Antimicrobial Resistance 2001. https://ec.europa.eu/food/sites/food/files/safety/docs/sci-com_ssc_out203_en.pdf

antimicrobials, whatever their origin, and the pressure they create on the environment are not speculative." This document stated that the SSC wished to "encourage the Commission urgently to act on all of the other recommendations made in its opinion of 28 May 1999 and to pay special attention to implications of antimicrobial resistance to environmental microbial ecology."

Many of these proposals have not yet been adopted almost two decades later and, arguably, those that have been are not fully implemented. Despite the EU-wide ban on the use of antibiotics as growth promoters in animal feed that was introduced in 2006, antibiotic use in livestock animals has not dramatically decreased[3] - antibiotics are still being used for purposes other than treating disease, thus contributing to the public health threat posed by AMR. A recent epidemiological study carried out in China has shown a positive correlation between the presence of colistin resistance gene in people and their overall consumption of meat.[4] This suggests that the spread of this resistance gene stems from the overuse of colistin in animal husbandry.

Furthermore, the EU One Health Action Plan against AMR (2017) lacks the specific, basic, and measurable policy recommendations proposed in the 1999 SSC report. Based on the Commission's own conservative estimate of 25,000 deaths per year[5] due to AMR - 400,000 people have died from drug-resistant infections in Europe in the 16 years between the publication of the 2001 Communication from the Commission on a Community Strategy Against Antimicrobial Resistance[6] and the 2017 EU Action Plan against AMR. A considerable proportion of these deaths could have been prevented if the Commission had urgently implemented all of the recommendations put forward by its own SSC.

2. Considerable delay in the publication of the Strategic Approach to Pharmaceuticals in the Environment

The threat that pharmaceutical pollution poses to ecosystems and human health globally is increasingly recognised - pharmaceuticals can enter the environment at all stages of their life cycle (production, use, and disposal), meaning they can end up in drinking water as well as accumulate in vegetables and fish. In June 2018, the European Commission was set to release the long-awaited strategic approach to Pharmaceuticals in the Environment (PiE), which was hoped to contain a series of measures to alleviate the damage caused by the release of pharmaceutical residues into the environment during their life-cycle.

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[3] European Medicines Agency (EMA) (2017). Sales of veterinary antimicrobial agents in 30 European countries in 2015. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2017/10/WC500236750.pdf

[4] Shen Y, Zhou H, Xu J, Wang Y, *et al.* (2018) Anthropogenic and environmental factors associated with high incidence of mcr-1 carriage in humans across China. Nature microbiology. https://doi.org/10.1038/s41564-018-0205-8

[5] European Centre for Disease prevention and Control (ECDC). The bacterial challenge: time to react. 2009. https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

[6] Communication from the Commission on a Community Strategy Against Antimicrobial Resistance of 2001. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52001DC0333&from=en

The publication of this document was due almost three years ago "the Commission shall, as far as possible within two years from 13 September 2013 develop a strategic approach to pollution of water by pharmaceutical substances" - Article 8c of Directive 2013/39/EU.[7] The article also states that "In the framework of that strategic approach, the Commission shall, where appropriate, by 14 September 2017 propose measures to be taken at Union and/or Member State level, as appropriate, to address the possible environmental impacts of pharmaceutical substances".[7]

After an initial delay, the strategic approach was later intended to follow the 2017 release of the EU One Health Action Plan against AMR - emphasising the importance of a holistic One Health approach to reduce the prevalence of AMR, curb irresponsible use of antimicrobials, and raise further awareness of prudent use practices and behaviours. This Action Plan outlines important policy measures to be taken in healthcare environments and in livestock farming, such as establishing explicit links with implementing acts of the legislative proposals on Veterinary Medicinal Products[8] and Medicated Feed,[9] as well as the "Animal Health Law".[10] **The Action Plan falls short on the environmental side, however, as it ignores clear evidence of the health risk that pharmaceutical pollution in the environment poses.**

A balanced One Health approach should consider the recent scientific studies[15] showing that antibiotic waste from manufacturing sites doesn't just pollute the environment, but has been linked to antibiotic resistance. Given that the link between antibiotics in the environment and the rise of AMR was recognised by the Commission itself in 2001, it is inconceivable that a "One Health" action plan from the Commission does not place limits on pharmaceutical discharges into the environment or include environmental criteria for the Good Manufacturing Practices (GMP) framework. Omitting these points undermines the EC's plan, rendering it ineffectual.

Two reports published by Deloitte for the European Commission (in 2013[11] and 2016[12]) present detailed scientific evidence that even low concentrations of pharmaceuticals can have harmful effects on animals, plants, and may also affect humans. These studies provide the basis for developing the strategic approach by providing details and documentation for

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[7] Directive 2013/39/EU of the European Parliament and of the Council of 12th August 2013. https://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A32013L0039

[8] European Commission - DG Health and Food Safety. Revision of the legal framework for veterinary medicinal products. http://www.consilium.europa.eu/en/policies/animal-medicines-health-package/veterinary-medicinal-products/

[9] Proposal for a Regulation of the European Parliament and of the Council on the manufacture, placing on the market and use of medicated feed and repealing Council Directive 90/167/EEC. COM(2014) 556. http://ec.europa.eu/transparency/regdoc/rep/1/2014/EN/1-2014-556-EN-F1-1.Pdf

[10] Regulation (EU) 2016/429 of the European Parliament and of the Council of 9 March 2016 on transmissible animal diseases and amending and repealing certain acts in the area of animal health ('Animal Health Law'). OJ L 84, p. 1–208. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0429&from=EN

[11] https://ec.europa.eu/health/sites/health/files/files/environment/study_environment.pdf

[12] https://ec.europa.eu/info/sites/info/files/study_report_public_consultation_pharmaceuticals_environment.pdf

options that could address the issue. These reports also show that active pharmaceutical ingredients (APIs) in the environment cause reproductive failure, growth inhibition, and behavioural changes in organisms, and even collapse populations.[11,12] APIs are designed to be biologically active and resistant to metabolic degradation, meaning they persist and remain active in the environment as an unintended consequence.

The UN Environment report *Frontiers 2017: Emerging Issues of Environmental Concern* from UN Environment links growing AMR to the discharge of drugs and particular chemicals into the environment and identifies this as one of the most worrying health threats today.[13] Experts view the promotion of antibiotic resistant bacteria as "the greatest human health concern" posed by the presence of pharmaceutical residues in the environment and note that, in addition to fostering the spread of resistant pathogens, antibiotic residues can also turn harmless environmental bacteria into carriers of resistance.[14]

2.1. Pharmaceutical pollution – a reservoir for AMR

Several studies and documentaries have shown the devastating impacts of uncontrolled manufacturing discharges on water systems, as well as on the people and animals that have come into contact with resistant bacteria found in the environment, especially in India and China - where most APIs are manufactured.[15,16] Recent studies from Hyderabad (India) reveal excessively high concentrations of pharmaceuticals that exceed maximum regulatory limits or safe exposure levels.[17] Since the production of both APIs and finished dose antibiotics is concentrated in specific locations, point-source pollution can take place, resulting in incredibly high concentrations, which encourages the development of drug

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[13] UN Environment (2017). Frontiers 2017: Emerging Issues of Environmental Concern. . https://www.unenvironment.org/resources/frontiers-2017-emerging-issues-environmental-concern

[14] Ågerstrand M, Berg C, Björlenius B, Breitholtz M, Brunstrom B, Fick J, Gunnarsson L, Larsson DGJ, Sumpter JP, Tysklind M, Rudén C (2015). Improving environmental risk assessment of human pharmaceuticals. https://www.ncbi.nlm.nih.gov/pubmed/25844810

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Larsson J (2014) Pollution from drug manufacturing: review and perspectives. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 369. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213584/

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. *Infection*, 45(4). https://www.ncbi.nlm.nih.gov/pubmed/28444620

Al Jazeera (2016) What is killing India's babies? https://www.aljazeera.com/indepth/features/2016/08/killing-india-babies-160810134404255.html

[16] 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

[17] Larsson J (2014) Pollution from drug manufacturing: review and perspectives. *Philosophical Transactions of the Royal Society B: Biological Sciences.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213584/

resistance. This practice has a detrimental impact on vulnerable populations living near manufacturing facilities and wastewater treatment plants in these countries.

A recent study suggests that in Hyderabad, exposure to an environmental source of antimicrobial drugs is placing pregnant women from low-income backgrounds at a higher risk for community acquired-antimicrobial resistance.[18] Contamination of water sources with antimicrobial drugs (combined with mass misuse of antibiotics and poor sanitation) has had grave consequences in India, where an estimated 58,000 new-borns die from multidrug-resistant infections every year.[19]

3. Steps needed to tackle pharmaceutical pollution

Pharmaceutical pollution from drug manufacturing is a global problem with global solutions. Increased travel and international trade facilitate the spread of resistant bacteria, allowing for the introduction of resistant bacteria into Europe, challenging our health systems and putting human lives at risk. Pharmaceutical pollution cannot be seen as simply an issue for the countries that produce the most pharmaceuticals (such as China and India) - the EU must accept its leadership responsibility and introduce the necessary legislation to protect citizens both in Europe and worldwide.

Recent evidence shows that antibiotic resistance genes are also present in antibiotic manufacturing effluent in Europe.[20] Prof Ramanan Laxminarayan, Director of the Center for Disease Dynamics, Economics & Policy (CDDEP), who addressed the European Parliament on the subject in June 2017, has studied how multidrug-resistant bacteria can travel around the world in a very short time.[21]

Furthermore, a Swiss study demonstrated that 75% of 38 tourists travelling to India returned home with antibiotic-resistant bacteria in their guts.[22] In addition, 11% of tourists had bacteria resistant to the last-resort antibiotic colistin.[22] **This highlights the immediate danger for the entire world if the pharmaceutical pollution issue is not immediately and effectively addressed.**

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[18] Aslan M, Kammili N, Lakshmi J, *et al.* (2018) Poverty and Community-Acquired Antimicrobial Resistance with Extended-Spectrum β-Lactamase–Producing Organisms, Hyderabad, India. *Emerging Infectious Diseases*. https://wwwnc.cdc.gov/eid/article/24/8/17-1030_article

[19] Laxminarayan R, Duse A, Wattal C, *et al.* (2013) Antibiotic resistance – the need for global solutions. *The Lancet*. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2813%2970318-9/abstract

[20] Gonzalez-Plaza J, Simatovic A, Milakovic M, *et al.* (2018) Functional repertoire of antibiotic resistance genes in antibiotic manufacturing effluents and receiving freshwater sediments. *Frontiers in Microbiology*. https://www.ncbi.nlm.nih.gov/pubmed/29387045

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[22] Bernasconi O, Kuenzlei E, Pires J, Tinguely R, et al. (2016) Travelers Can Import Colistin-Resistant Enterobacteriaceae, Including Those Possessing the Plasmid-Mediated mcr-1 Gene. *Antimicrobial Agents and Chemotherapy*. https://www.ncbi.nlm.nih.gov/pubmed/27297483

At the EU level, Pharmaceuticals in the environment (PiE) are mainly addressed in legislation on veterinary medicinal products but not fully tackled in legislation on medicinal products for human use. The EC's long-awaited Strategic Approach on pharmaceuticals in the environment is meant to cover this legislative gap, but it is increasingly unclear if this long overdue approach will be published under the current Commission, despite a call for its swift publication in a letter co-signed by environment officials from ten different countries. **The failure of the Commission to produce this document within the timeframe, combined with the lack of transparency concerning the decision to remove key measures from the strategic approach, appears to constitute a case of maladministration by the Commission. There are therefore grounds to file a complaint with the European Ombudsman.**

Thankfully, the European Parliament seems to have a better understanding of the seriousness of the problem and the urgent need to implement effective legislation. One of the adopted amendments to the ENVI Committee's Own Initiative Report on the EU Action Plan Against AMR states that the European Parliament "Deplores the fact, in this context, that the Commission did not propose a strategic approach to the pollution of water with pharmaceuticals sooner, as required by Directive 2013/39/EU; urges the Commission and Member States therefore, without delay, to draw up a European strategy for tackling drug residues in water and the environment, devoting sufficient attention to monitoring, data collection and better analysis of the impact of AMR on water resources and the aquatic ecosystem; draws attention to the usefulness of an integrated chain approach to drug residues and antimicrobial resistance in the environment."[23]

The Commission has therefore not only failed to act in the interests of the European Parliament and Member States, it has also failed to act in the interest of public health.

3.1 Recommendations for the strategic approach to pharmaceuticals in the environment

HCWH Europe has been working to tackle pharmaceuticals in the environment (PiE) for the past six years: supporting their safe production, management, and disposal, whilst reducing negative impacts upon environment and health impact throughout their life cycle. HCWH Europe aims to foster innovations for green products as part of the only EU-wide campaign dealing with the presence of PiE: Safer Pharma.[24] The main objective of the Safer Pharma campaign is to make the EU the first region to legislate on pharmaceutical pollution. The organisation and its members seeks to achieve this through encouraging pharmaceutical companies to clean up their production, raise awareness among healthcare professionals of the impact of PiE, and promote better medicine disposal practices amongst the public.

[23] Report on a European One Health Action Plan against Antimicrobial Resistance (AMR). Committee on the Environment, Public Health and Food Safety. http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+REPORT+A8-2018-0257+0+DOC+PDF+V0//EN

[24] www.saferpharma.org

To advocate for the publication of the strategic approach to PiE, HCWH Europe maintains a dialogue with important stakeholders in the process, such as Commissioners and policy-makers from DG Environment and DG SANTE. Most recently, HCWH Europe sent a letter to President Jean Claude Junker, urging for the publication of the Strategic Approach before the summer recess and presenting a number of recommendations that it would like to see included.[25]

To most effectively combat the issue of pharmaceutical pollution, HCWH Europe proposes the following recommendations:

- Revise the Good Manufacturing Practices (GMP) to include compulsory environmental standards
- Include medicinal and veterinary products under all 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
- Introduce legally binding concentration limits and standards for residues of pharmaceutical substances in water
- Increase investment in the development of rapid diagnostic tools for use in human and animal health, to decrease the inappropriate use of antibiotics
- 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 the intensive rearing of poultry and pigs
- Ensure that Environment Risk Assessment (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
- Develop public procurement initiatives 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
- Establish an EU AMR Emergency Committee that develops platforms and modes of action if an outbreak of pandrug-resistant bacteria occurs, as referred to by former WHO Director-General Dr Margaret Chan[26]

[25] Letter to President Jean-Claude Juncker, 2 July 2018 http://changingmarkets.org/wp-content/uploads/2018/07/Letter-to-President-Jean-Claude-Juncker.pdf
[26] WHO Director-General briefs UN on antimicrobial resistance http://www.who.int/dg/speeches/2016/antimicrobial-resistance-un/en/

3.2 Policies dealing with wastewater and water supply

Water is a key route for the diffusion of pharmaceutical into the environment at all stages of the drug life-cycle. Hazardous contaminants, including antibiotics, often enter local water bodies where they pollute surface and ground waters, sediment, and soil, which leads to lasting effects on entire ecosystems. As a consequence, the quality of the Europe's drinking water supply, which depends on uncontaminated groundwater, is increasingly at risk.

Given that many major rivers and lakes cross borders, the consequences of pharmaceutical pollution and AMR can even affect countries with successfully implemented best practices and restricted use of antimicrobial drugs. In addition, due to the high costs, wastewater sewage plants are not equipped to filter out most pharmaceutical residues. It is therefore crucial to take a precautionary approach - policies should tackle the twin problems of PiE and AMR, for example by setting binding limits on the amount of pharmaceutical residues in water and ensure that APIs present in wastewater are effectively treated and destroyed before further release.

4. European Commission's actions regarding tackling antibiotic use in animal husbandry

In 2013, 73% of all antimicrobials sold globally were used in animals.[27] Many of these same antimicrobials are also used to treat infections in humans and this is of considerable concern in light of the threat of AMR.[27] Antimicrobial use in animal husbandry has not only been linked to drug-resistant infections in animals and humans, but also leads to further pharmaceutical pollution of the environment[21] - oral doses are only partially metabolised, and APIs are excreted and enter the environment, polluting surface and ground water. The overuse of antimicrobials in animal husbandry is therefore an incredibly serious problem.

Promisingly, there has been recent progress on the prevention of inappropriate use of antimicrobials in animal husbandry, with the recent Veterinary Medicinal Products[8] and Medicated Feed Regulations.[9] These interrelated regulations introduce restrictions on the use of certain antimicrobials in animals, reserving them for the treatment of human infections; they also include rules prohibiting prophylaxis (preventive administration of antimicrobials to animals, when a disease has not been diagnosed). These new rules, however, will only apply three years after the entry of these regulations into force, and there are still multiple gaps in the data on veterinary use of antimicrobials, outlined below.

In September 2008, the EC adopted an Action Plan for the implementation of the EU Animal Health Strategy. This document states: "in the light of European Food Safety Authority (EFSA) opinion, the Commission may decide to strengthen its policy as regards the surveillance and control of antimicrobial resistance (AMR) in zoonotic agents caused by the

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[27] Van Boeckel T (2017). A global plan to cut antimicrobial use in animals. *Center for Disease Dynamics, Economics & Policy*. *https://cddep.org/blog/posts/global-plan-cut-antimicrobial-use-animals/*

use of antibiotics in animals."[28] Following this, the Animal Health Law[10] adopted in March 2016 states that "A computerised interactive information system for the effective collection and management of surveillance data should be established at Union level for listed diseases and, when relevant, for emerging diseases or antimicrobial-resistant pathogens." This is in spite of the fact that there are still major gaps in reporting across Europe: the 2016 European Union summary report on AMR in zoonotic and indicator bacteria highlights that the monitoring of some multidrug-resistant bacteria is voluntary and only a limited number of countries report data.[29]

Aside from the rules in the Veterinary Medicinal Product and Medicated Feed Regulations, there are a number other measures that could be used to encourage the prudent use of antimicrobials in livestock. To better understand the relationship between the use of antimicrobials and the spread of AMR, and to decrease reliance on the use of antimicrobials, HCWH Europe recommends the following:

- Developing extensive publically accessible data collection for all antibiotics used in human medicine and animal husbandry
- Enforcing comprehensive data collection across all Member States for antimicrobial-resistant bacteria from animals
- Initiating EU-wide measures to improve animal welfare, livestock conditions, and animal husbandry practices - important precautions to secure animal health and reduce the need for medication. This includes the research, development, and authorisation of feed additives to reduce the need for antibiotics as growth promoters
- Introducing an EU-wide system of taxes for the sale of antibiotics used in animal husbandry (as already practiced in Denmark and in Belgium)[30] and use the revenues to fund prudent use policies, data collection and analysis

5. Weaknesses in antibiotic research funded by the Commission

The Innovative Medicines Initiative (IMI) public-private programme, New Drugs 4 Bad Bugs (ND4BB),[31] was set up in 2013 to develop new antibiotic drugs to combat certain pathogens. The programme now encompasses eight projects, such as the ENABLE[32] project for potential antibiotics in the early stages of drug discovery. Five years later, no report has been published on the progress of the research studies and on how exactly the money has been spent.

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[28] https://ec.europa.eu/food/sites/food/files/animals/docs/ah_policy_strategy_action-plan_2007-13_20080910.pdf
[29] https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2018.5182
[30] Lhermie G., Gröhn Y. and Raboisson D (2016). Addressing Antimicrobial Resistance: An Overview of Priority Actions to Prevent Suboptimal Antimicrobial Use in Food-Animal Production. *Frontiers in Microbiology*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5216048/
[31] Innovative Medicines Initiative (IMI). New Drugs 4 Bad Bugs (ND4BB). https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb
[32] http://nd4bb-enable.eu/

6. Conclusions

Europe's AMR burden in terms of morbidity, healthcare costs, and productivity losses is much greater than currently available statistics suggest. Recent projections estimate a 15-fold increase in morbidity in Europe by 2050 due to AMR, with 390,000 deaths every year as a result of drug-resistant infections.[33] The EU has the opportunity to urgently seize a number of important policy opportunities that would reduce the development and spread of AMR, both in Europe and on a global scale. Without essential legislation such as an effective strategic approach on PiE, there will be no pressure on pharmaceutical companies to ensure that third-party suppliers are properly disposing of antibiotic waste. There is a pressing need for action before the "post-antibiotic apocalypse" becomes a reality.[34]

[33] Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, URL: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20- %20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf

[34] https://www.gov.uk/government/news/antimicrobial-resistance-poses-catastrophic-threat-says-chief-medical-officer--2