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Environmental risk assessment of antibiotics: predicted no-effect concentrations for resistance selection in the aquatic environment

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To assess the risk that chemicals pose to the environment, Predicted No-Effect Concentrations (PNEC) are used. If environmental concentrations lie below the PNEC, we do not expect a risk of adverse effects. PNECs are used to assess water quality and they are called Environmental Quality Standards (EQS) if derived according to the EU Technical Guidance Document on EQS [1] and used for retrospective assessment of surface water bodies. In Switzerland, EQSs for some substances are set as legal thresholds in the Water Protection Ordinance (see Chapter 11).

The protection objective of environmental risk assessment is the health of organisms living in the environment. In the case of antimicrobials, however, it is not only the health of organisms that is of concern, but also the potential adverse effects on human health. Indeed, high concentrations of antimicrobial substances in the environment can lead to the selection of pre-existing or the emergence of new antimicrobial resistances in environmental bacteria. Selection of pre-existing resistances leads to a greater abundance of antimicrobial-resistant bacteria, and the potential for infection with such bacteria rises. The emergence and subsequent appearance of new types of antimicrobial resistance carries the risk that these resistances will spread to human pathogens and, in the event of infection, increase the likelihood of treatment failure due to resistance. While emergence events can potentially have serious consequences for the antimicrobial resistance landscape in humans, it is exceptionally difficult to quantify the risk of such events because of their probabilistic nature. Quantifying the relationship between antimicrobial concentrations and selection pressure, however, is much more palpable. PNECs derived for this purpose will be indicated as $PNEC_{res}$ (*res* for resistance selection).

Minimum Inhibitory Concentrations (MIC) – the concentration of a specific antimicrobial at which bacterial growth is inhibited – can be conceptualized as the upper limit of a concentration at which selection occurs. At antibiotic concentrations below the MIC, the growth of bacteria sensitive to antibiotic treatment is slowed, whereas bacteria resistant to antibiotic treatment will continue to thrive, thus creating conditions in which a selection for the survival of resistant bacteria occurs. The lowest concentration at which we expect a selection for resistance in the bacterial population is called the Minimum Selective Concentration (MSC).

MSCs can be experimentally measured with methods such as competition experiments with isogenic bacteria. The downsides of experimental approaches include the high amount of time, effort, and expertise required, as well as conclusions being limited to the bacterial species tested. One approach to estimating MSCs beyond a single species relies on the experimentally tested relationship between MIC and MSC – it uses the available MIC to estimate the MSC. For this purpose, databases containing the MIC of numerous antibiotics and different bacterial species, such as the EUCAST (European Committee on Antimicrobial Susceptibility Testing) database, are used. From the MIC distributions, the 1% percentile is chosen to account for the precautionary principle, and a factor is applied to estimate the MSC from this concentration. This method, developed by Bengtsson-Palme and Larsson [2], is currently the most widely used methodology for deriving $PNEC_{res}$ in the aquatic environment. Limitations include the fact that derivation is possible only for antibiotics for which extensive MICs are available. Since the EUCAST database is designed for use in human medicine, and it is difficult to find corresponding MIC data for antibiotics used in veterinary medicine, the derivation of $PNEC_{res}$ for such antibiotics with the Bengtsson-Palme and Larsson method [2] is challenging.

Swiss surface water concentrations of antibiotics compared to Environmental Quality Standards (EQS) and Predicted No-Effect Concentrations for resistance selection ($PNEC_{res}$)

For four antibiotics, surface water concentrations measured from 2018 to 2022 lie above their respective EQS, indicating a possible risk for adverse effects on aquatic organisms (Figure XIV). However, the extent to which EQSs are exceeded varies widely. EQS exceedances for clarithromycin, erythromycin and sulfamethoxazole lie within a factor of 1 to 1.5. For azithromycin, however, this factor lies between 1 and more than 50, indicating a higher risk for aquatic organisms. If we compare the EQS with the $PNEC_{res}$, we find that for all substances except trimethoprim, EQSs are lower than $PNEC_{res}$ (Figure XIV). In these cases, we can assume that EQS values are protective not only for adverse effects on aquatic life, but also against the selection for antimicrobial resistance.

For four of the five antibiotics for which $PNEC_{res}$ are available (clarithromycin, erythromycin, sulfamethoxazole, and trimethoprim), environmental concentrations do not exceed these values (Figure XIV). Azithromycin is the only substance for which the $PNEC_{res}$ is exceeded in the measurement period 2018–2022, albeit only in a low number

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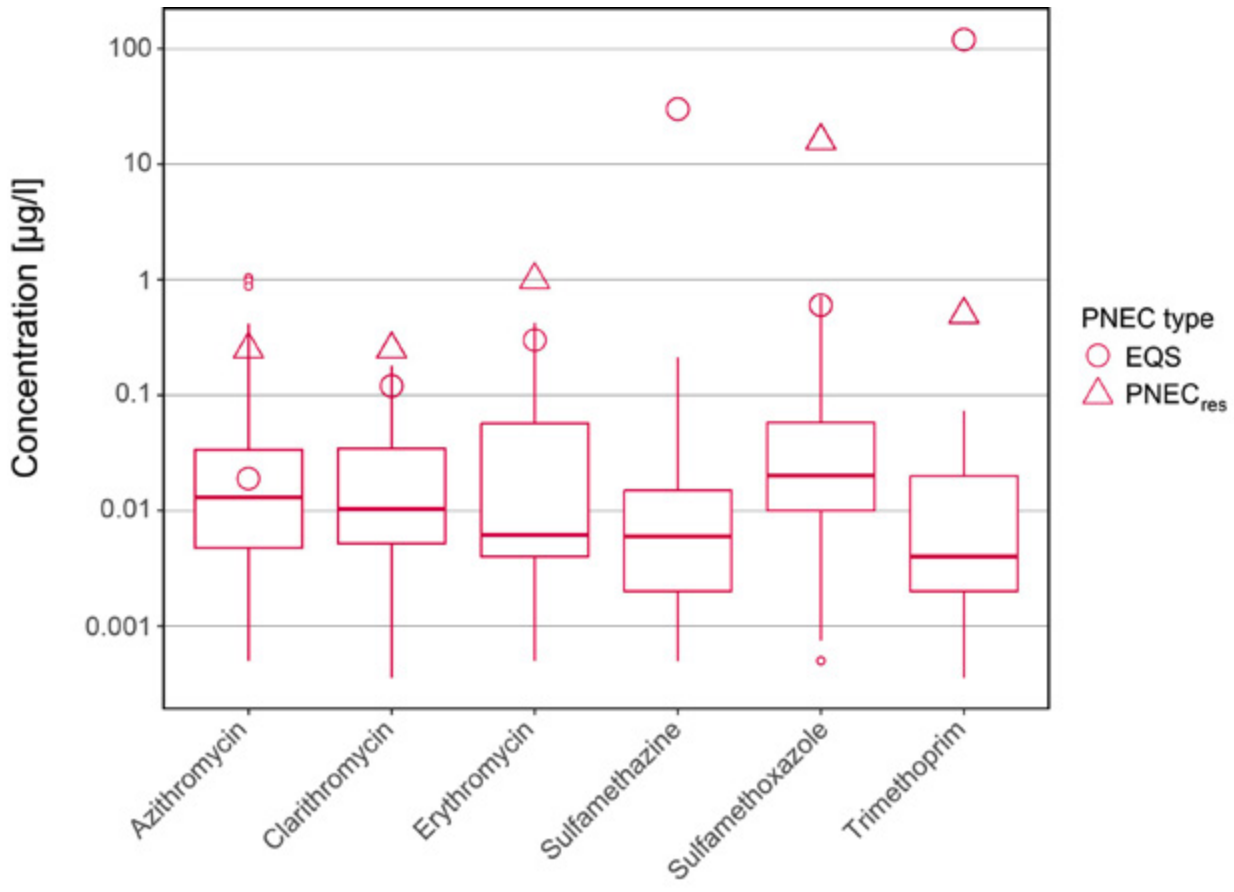
of samples. However, no exceedances occurred in 2022 (data not shown). Hence, we can assume that there is currently no risk of antimicrobial resistance selection in Swiss surface water.

No $PNEC_{res}$ is available for sulfamethazine. This is because it is only used in veterinary medicine, and the database used to derive $PNEC_{res}$ is for antibiotics used in human medicine. A new derivation of $PNEC_{res}$ was not possible, since corresponding MIC data could not be found. Although the sulfamethoxazole metabolite acetyl-sulfamethoxazole was the second most frequently detected antibiotic in surface water after its mother substance, neither a $PNEC_{res}$ nor an EQS value is available for it. For the former, this is because the human medicine database used to derive $PNEC_{res}$ only offers data on the antibiotics, and not their metabolites, since it is intended for clinical use. An EQS derivation was not possible due to a lack of ecotoxicological data. The insufficient data availability makes risk assessment of antibiotic metabolites challenging.

Figure XIV: Environmental Quality Standards (EQS) and Predicted No-Effect Concentrations for resistance selection ($PNEC_{res}$) compared to environmental concentrations of the antibiotics azithromycin, clarithromycin, erythromycin, sulfamethazine, sulfamethoxazole and trimethoprim measured in Swiss surface water between 2018 and 2022.



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Applications and outlook

Selection of antimicrobial resistance is mostly a concern in places where high concentrations of antibiotics can occur, for example in hospital wastewaters or in pharmaceutical manufacturing wastewaters. To tackle the issue of wastewater management in pharmaceutical manufacturing, the World Health Organisation produced a draft guidance [3], and the AMR industry alliance also published a guidance document, the Antibiotic Manufacturing Standard [4]. Both guidance documents suggest concentrations of antimicrobials in receiving surface water should remain below both EQS and $PNEC_{res}$ values to ensure no adverse effects on aquatic life, and no selection for antimicrobial resistance. If no $PNEC_{res}$ is available for a substance, a default value of 50 ng/l is suggested, based on a statistical evaluation of available $PNEC_{res}$ data [3,4].

In the derivation of EQS, the antibiotic resistance selection risk is currently not considered in the methodology. However, it has been considered both for EQS derived by the Swiss Centre for Applied Ecotoxicology [5] and the University of Stockholm, and in new proposals for EQS of antibiotics under the Water Framework Directive of the European Union. Currently, considerations of $PNEC_{res}$ need to happen on a case-by-case basis, with expert judgment complementing traditional methodology. Given that EQSs are part of ordinances in many European countries, comparability and transparency in the derivation are of great importance. Therefore, a revision of the guidance, including methodology for $PNEC_{res}$, would be an important next step.

The multifaceted problem of antimicrobial resistance poses challenges that go beyond what traditional environmental risk assessment encompasses. New perspectives in substance-based risk assessment are essential to tackle the challenge of antimicrobial resistance. This further highlights the importance of the environment in the cycle of antimicrobial resistance under a One Health approach.

References

[1] European Commission (2018). Technical Guidance for Deriving Environmental Quality Standards Environment, Guidance Document No. 27, Updated version 2018, Document endorsed by EU Water Directors at their meeting in Sofia on 11-12 June 2018.

[2] Bengtsson-Palme, J., Larsson, D. G. J. (2016): "Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation". Environment International 86: 140–149.

[3] World Health Organisation (2023). "Guidance on waste and wastewater management in pharmaceutical manufacturing with emphasis on antibiotic production (Draft for public consultation)". https://cdn.who.int/media/docs/default-source/wash-documents/burden-of-disease/guidance-on-waste-and-wastewater-management-in-pharma-manufact-pub-consult-20240110ecd72653-d3c5-4dcb-a044-d455d6e4c27a.pdf?sfvrsn=e35f97c9_5

[4] AMR industry alliance (2023). "Minimizing risk of developing antibiotic resistance and aquatic ecotoxicity in the environment resulting from the manufacturing of human antibiotics". https://www.amrindustryalliance.org/wp-content/uploads/2022/06/AMRIA_Antibiotic-Manufacturing-Standard_June2022.pdf

[5] Ferrari, G., Junghans, M., Korkaric, M., & Werner, I. (2019): "Antibiotikaresistenzbildung in der Umwelt. Herleitung von UQK für Antibiotika unter Berücksichtigung von Resistenzbildung". Aqua & Gas 99(6): 52-58.