BIOCIDE: Antibacterial biocides in the water cycle – an integrated approach to assess and manage risks for antibiotic resistance development

Aquatic Pollutants

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The BIOCIDE consortium

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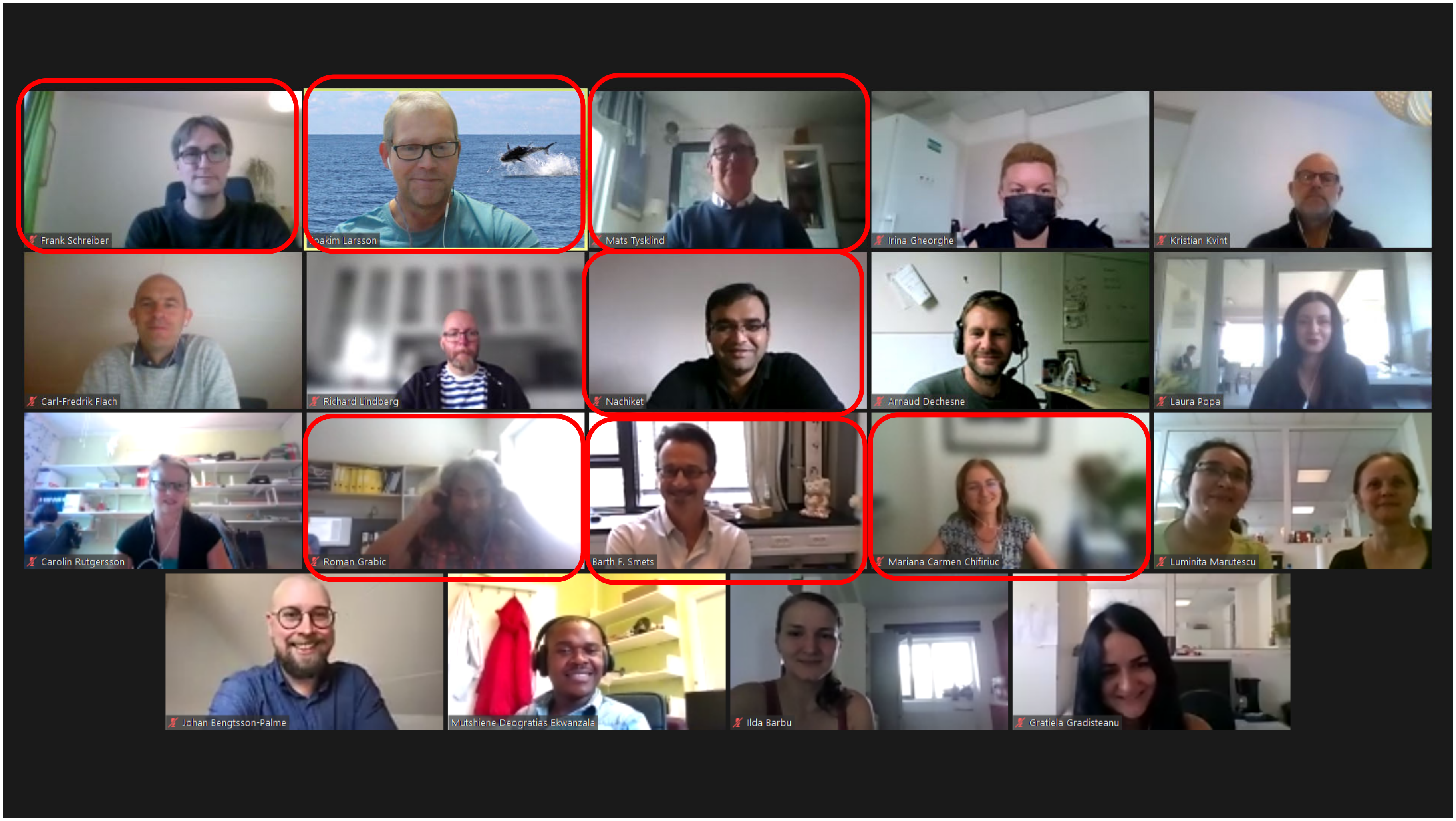
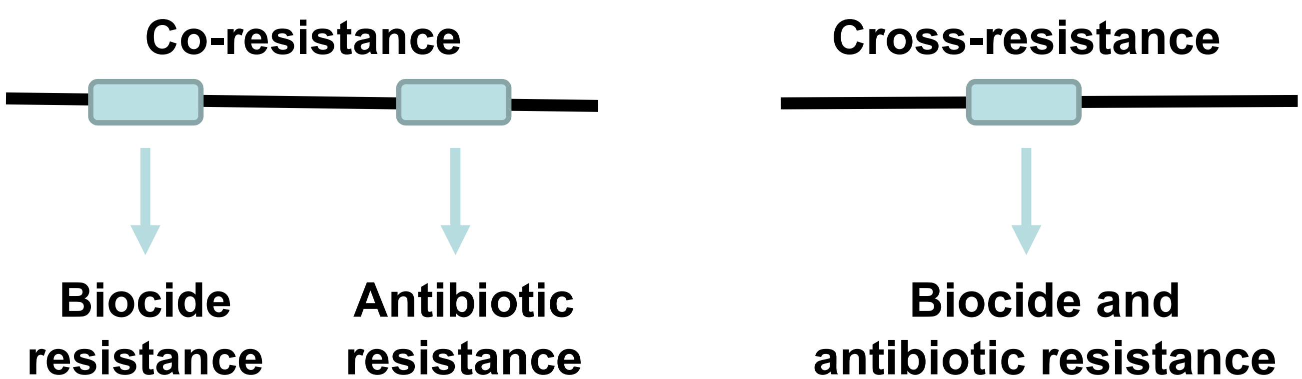


Antibacterial biocides – chemicals that have an intended or unintended antibacterial effect but are not antibiotics (i.e. used as medicines)

The two main genetic mechanisms behind co-selection



Some of our previous work on the links between antibacterial biocides and antibiotic resistance

Pal C, Bengtsson-Palme J, Rensing C, Kristiansson E, Larsson DGJ. (2014) BacMet: antibacterial biocide and metal resistance genes database. Nucleic Acids Res, 42:D737.

Pal C, Bengtsson-Palme J, Kristiansson E, Larsson DGJ. (2015) Co-occurrence of resistance genes to antibiotics, biocides and metals reveals novel insights into their co-selection potential. BMC Genomics. 16:964.

Pal C, Bengtsson-Palme J, Kristiansson E, Larsson DGJ. (2016). The structure and diversity of human, animal and environmental resistomes. Microbiome. 4:54.

Östman M, Lindberg RH, Fick J, Björn E, Tysklind M. (2017). Screening of biocides, metals and antibiotics in Swedish sewage sludge and wastewater,Water Research 115: 318-328,

Pal C, Asiani K, Arya S, Rensing C, Stekel DJ, Larsson DGJ, Hobman JL. (2017). Metal resistance and its association with antibiotic resistance. Adv Microb Physiol. 70:261 ISBN: 9780128123867.

Flach CF, Pal C, Svensson CJ, Kristiansson E, Östman M, Bengtsson-Palme J, Tysklind M, Larsson DGJ. (2017). Does antifouling paint select for antibiotic resistance? Sci Total Environ. 590–591:461

Hao X*, Li X*, Pal C*, Hobman J, Rosen BP, Larsson DGJ, Saquib Q, Alwathnani HA, Zhu Y-G, Rensing C. (2017). Bacterial resistance to arsenic protects against protist killing. Biometals. 30:307.

Jutkina J, Marathe NP, Flach C-F, Larsson DGJ. (2018). Antibiotics and common antibacterial biocides stimulate horizontal transfer of resistance at low concentrations. Sci Total Environ. 616-617:172.

Östman, M.; Fick, J.; Tysklind, M. (2018). Detailed mass flows and removal efficiencies for biocides and antibiotics in Swedish sewage treatment plants. *Science of the Total Environment*, 640 : 327-336.

Wang, HJ, Mustafa, M, Yu, G, Östman, M,, Cheng, Y, Wang, YJ, Tysklind, M. (2019). Oxidation of emerging biocides and antibiotics in wastewater by ozonation and the electro-peroxone process. *Chemosphere* 235, 575-585.

Östman, M.; Björlenius, B.; Fick .Tysklind M. (2019) Effect of full-scale ozonation and pilot-scale granular activated carbon on the removal of biocides, antimycotics and antibiotics in a sewage treatment plant. *Science of the Total Environment*, 649 : 1117-1123,.

Varadarajan, A.R., Allan, R., Valentin, J., Castañeda Ocampo, O.E., Somerville, V., Pietsch, F., Buhmann, M.T., West, J., Skipp, P.J., van der Mei, H.C., Ren, Q., Schreiber, F., Webb, J.S., Ahrens, C.H. (2020). An integrated model system to gain mechanistic insights into biofilm-associated antimicrobial resistance in Pseudomonas aeruginosa MPAO1. npj Biofilms and Microbiomes 6:46.

Pietsch, F., O'Neill, A., Ivask, A., Jenssen, H., Inkinen, J., Kahru, A., Ahonen, M. and Schreiber, F. (2020). Selection of resistance by antimicrobial coatings in the healthcare setting.. Journal of Hospital Infection 6(1):115-125.

Norholt, N., Kanaris, O., Schmidt, S., and Schreiber, F. (2021). Persistence against benzalkonium chloride promotes rapid evolution of tolerance under periodic disinfection. Nature Communications 12:6792

Pietsch, F., Heidrich, G., Nordholt, N., and Schreiber, F. (2021). Prevalent synergy and antagonism among antibiotics and biocides in Pseudomonas aeruginosa. Frontiers in Microbiology 11:615618

https://www.gu.se/en/biocide

Some major knowledge gaps

- For most antibacterial biocides, **environmental exposure data** is lacking/scarce

- For most antibacterial biocides, we do not know **to what extent they can co-select for antibiotic resistance or induce horizontal gene transfer**

- For most antibacterial biocides, we do not know **what concentrations are needed** select for antibiotic resistance or for inducing horizontal gene transfer

- **Risks** for co-selection of antibiotic resistance is **not considered** during authorization of new products or as part of environmental regulations

Our aim is to determine how and to what extent antibacterial biocides contribute to the development and spread of antibiotic (AB) resistant bacteria in different freshwater/marine ecosystems, and to inform and enable measures that ultimately protect human health and provide safe water resources for all.

More specifically, we have the following objectives/tasks:

WP1 Exposure

√ 1.1 Prioritize antibacterial biocides to be investigated based on existing databases on sales, uses and detection in aquatic environments

1.2. Develop state-of-the art chemical analysis protocols for a range of antibacterial biocides, applicable to different sample types

1.3. Generate screening data for the presence and levels of antibacterial biocides from a set of different aquatic ecosystems in Europe and Africa

WP2 Effects

2.1. Generate a dose-response matrix for a large number of biocides and bacterial species in order to Predict No Effect Concentrations (PNECs) for growth that will also be protective against AB resistance co-selection

2.2. Directly assessing co-selection by competition experiments in complex aquatic communities using a subset of biocides

2.3. Investigate the potency of selected biocides to induce horizontal transfer of AB resistance genes via conjugation and transformation

WP3 Mechanisms

3.1. Investigate the incidence and mechanisms of AB resistance driven by metal-based antifouling agents used in international maritime traffic and marine aquaculture

3.2. Provide a first description of the predominant co- and cross-resistance mechanisms in bacterial isolates from aquatic ecosystems in Europe and Africa

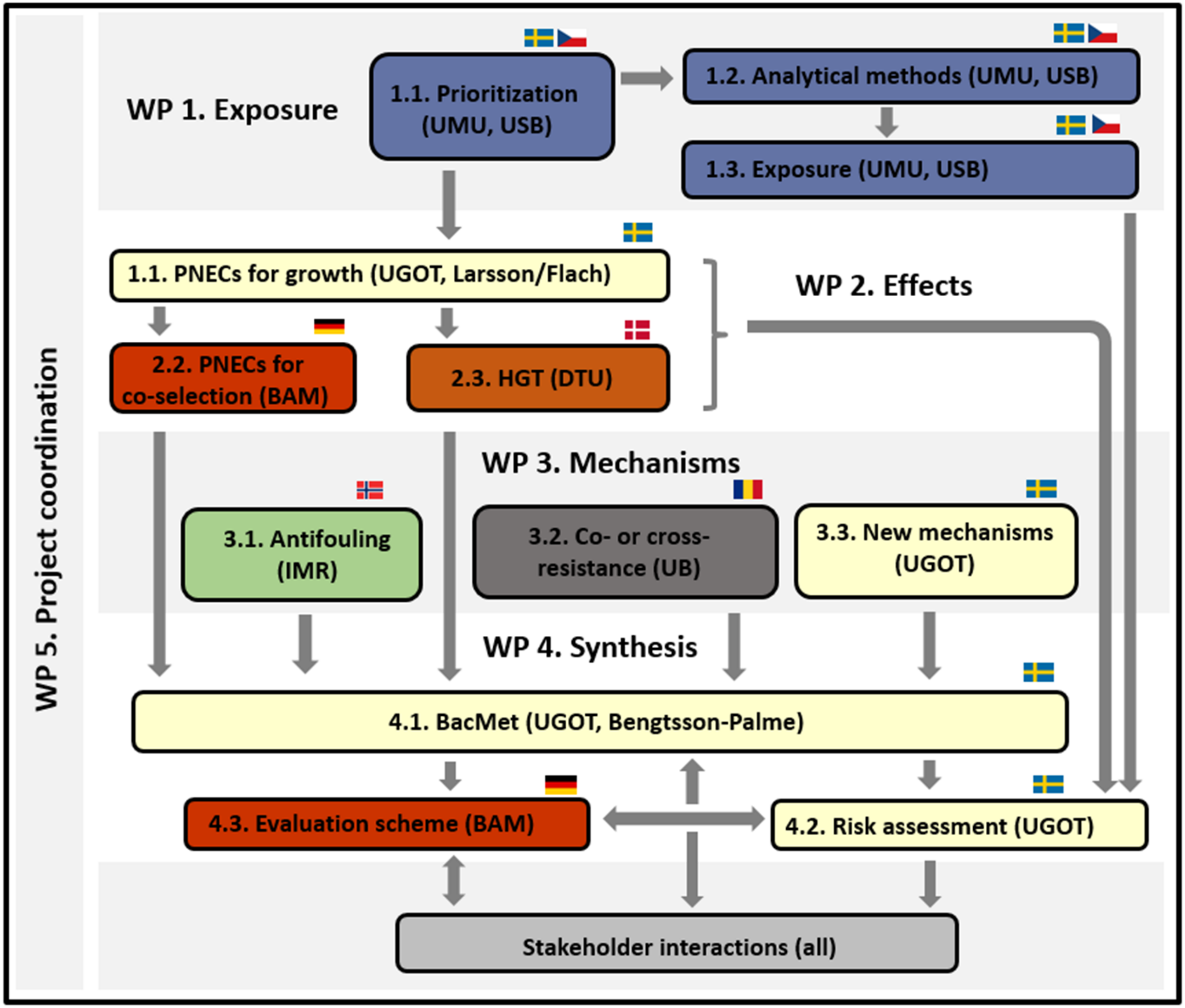
3.3. Identify the genetic context and basis for resistance to several biocides using a functional metagenomics approach combined with exploration of public genomic data

WP4 Synthesis

4.1. Incorporate extensive data on selective concentrations and co-selection opportunities into the BacMet database to make it useful for practical risk assessment and management

4.2. Perform a preliminary assessment of risks for biocides to promote AB resistance in aquatic environments based on generated exposure and effect data

4.3. Produce an evaluation scheme in collaboration with relevant authorities on how resistance risks formally could be incorporated in existing regulatory frameworks


WP 1. Exposure
1.1. Prioritization (UMU, USB)
1.2. Analytical methods (UMU, USB)
1.3. Exposure (UMU, USB)
1.1. PNECs for growth (UGOT, Larsson/Flach)
WP 2. Effects
2.2. PNECs for co-selection (BAM)
2.3. HGT (DTU)
WP 3. Mechanisms
3.1. Antifouling (IMR)
3.2. Co- or cross-resistance (UB)
3.3. New mechanisms (UGOT)
WP 4. Synthesis
4.1. BacMet (UGOT, Bengtsson-Palme)
4.3. Evaluation scheme (BAM)
4.2. Risk assessment (UGOT)
Stakeholder interactions (all)
WP 5. Project coordination

Who do we think this research primarily would be relevant for?

- Regulators of chemicals – e.g. market authorization
- Regulators of chemical pollution – e.g. water quality standards
- Health agencies with antibiotic resistance on their agenda
- Companies/sectors that produce or use antibacterial agents
    - Marine shipping sector – antifouling
    - Aquaculture sector - antifouling
- Water sector – e.g. sewage treatment

6TH INTERNATIONAL SYMPOSIUM ON THE ENVIRONMENTAL DIMENSION OF ANTIBIOTIC RESISTANCE – EDAR6

September 22 – 27, 2022
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And do not miss our monthly, count-down webinars – next on March 23 !