The PEPCY Project:

Toxic and bioactive peptides in cyanobacteria

Cyanobacterial peptides (cyanopeptides) are among the most ubiquitously found potentially hazardous substances in surface waters used by humans. Though these substances are natural in origin, sewage and fertilisers reaching water-bodies cause massive cyanobacterial proliferation throughout Europe. Cyanopeptides occur with unnatural frequency and concentration. Some cyanotoxins (i.e. the microcysins) have been known for 2-3 decades and are rather well-studied, but a much wider range of structurally-related substances – particularly peptides – are found in cyanobacteria, but little is known about their toxicity and occurrence.

Objectives

- The central objective of PEPCY was to improve cyanotoxin risk assessment and risk management;
- For this purpose, PEPCY aimed to clarify the extent to which the previously poorly understood cyanopeptides are important for public health because of (i) their toxicity; and (ii) the frequency and concentrations with which they occur. This included developing an understanding of the factors determining cyanopeptide occurrence, optimising methods for detection and analysis and contributing to the development of appropriate risk management policies;
- During the project, the World Health Organisation developed a new approach for ensuring drinking-water quality, and PEPCY aimed to integrate cyanopeptide risk assessment and risk management into this approach. PEPCY further aimed to disseminate information for identifying potential hazards to end-users and the general public.

Key findings and conclusions

- PEPCY identified an enormous range of cyanopeptides, which belong to several major cyanopeptide classes. Few specific peptides proved typical for specific cyanobacteria so that these peptides can be used as markers for the occurrence of these species;
- PEPCY identified the gene clusters responsible for the synthesis of most of the major cyanopeptide classes. Interestingly, field populations of a given cyanobacterial species usually proved to consist of genotypes with the gene for the production of a given cyanopeptide and genotypes without this gene;
- Physiological experiments conducted in PEPCY with producer-genotypes for a large range of cyanopeptides showed that environmental conditions (light, nutrients and temperature) have a minor impact on the amount of the peptide produced by the organism. Rather, the share of producer- versus non-producer genotypes determines the peptide levels in water-bodies;

- PEPCY screened 13 peptides from a range of peptide classes for toxicity, using cellular bioassays intended to indicate toxicity to humans, and found almost no effects (other than for microcystins, as was previously known) in these bioassays. Thus, the results suggest that microcystins are indeed the key cyanopeptides of human health concern. A caveat remains in face of the huge number of variants within each class and the variability of specific bioactivities: the results can neither exclude more pronounced toxicity of cyanopeptides not isolated and tested in PEPCY, nor toxicity to specific types of cells with specific transporter systems;
- Similar to drugs, cyanobacterial peptides can only be specifically cytotoxic if they can reach the enzymes that they inhibit, e.g. phosphatases, tyrosinases, elongases, proteases. Most of the cyanobacterial peptides appear not to be able to enter cells without being actively transported via (un)specific transporting systems. Therefore, knowledge on the ability of transporting peptides, such as the organic anion cyanobacterial transporting polypeptide family to transport peptides into the cytosol of various organs, is very helpful for understanding toxicity;
- PEPCY obtained results with microcystins as model peptides using transfected cell lines for studying this transport. The inhibition of proteases, such as trypsin and trypsin-like enzymes in Daphnia, via a number of peptides produced by frequently occurring cyanobacteria (i.e. Planktothrix, Microcystis and Anabaena) was found frequently from some of the peptides when tested in isolation, and from water samples.

Relevance and contribution to EU policy

Research carried out by PEPCY on cyanobacterial peptides produced a comprehensive understanding of cyanopeptides, i.e. mechanisms governing production, occurrence in nature, and impact on other biota. The project further systematically developed methods and produced materials necessary for cyanopetide research. In addition to this scientific outcome, PEPCY developed and promoted a risk-based and setting-specific approach to protecting public health from cyanotoxins which is in line with the current approach of the WHO for drinking-water quality and the EU Bathing Water Directive.

Dissemination materials produced by PEPCY will help the general public and water sector stake¬holders to better perceive hazardous situations, particularly for recreation, and to avoid exposure. The now more comprehensive assessment of the health hazards caused by cyanobacteria and the new, more effective risk management strategy will directly benefit regulators developing European legislation and practitioners in public health authorities involved in implementation. Results will be relevant for further develop¬ment of WHO guidance on cyanotoxins hazard assessment and risk management. PEPCY thus improved the protection of public health.

Toxic and other bioactive peptides in Cyanobacteria

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