

Transcriptomics and bioconcentration studies in fish to identify pharmaceuticals of environmental concern

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

- I. **Diclofenac in fish: Blood plasma levels similar to human therapeutic levels affect global hepatic gene expression**
Filip Cuklev, Erik Kristiansson, Jerker Fick, Noomi Asker, Lars Förlin, D.G. Joakim Larsson
Environmental Toxicology and Chemistry. 2011. 30(9):2126–2134
- II. **Does ketoprofen or diclofenac pose the lowest risk to fish?**
Filip Cuklev, Erik Kristiansson, Marija Cvijovic, Jerker Fick, Lars Förlin, D.G. Joakim Larsson
Submitted
- III. **Global hepatic gene expression in fish exposed to sewage effluents: A comparison of different treatment technologies**
Filip Cuklev, Lina Gunnarsson, Marija Cvijovic, Erik Kristiansson, Carolin Rutgersson, Berndt Björleinius, D.G. Joakim Larsson
Submitted
- IV. **Waterborne beclomethasone dipropionate affects fish while its metabolite beclomethasone is not taken up**
Bethanie Carney Almroth, Filip Cuklev, Jerker Fick, Lina Gunnarsson, Erik Kristiansson, D.G. Joakim Larsson
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Transcriptomics and bioconcentration studies in fish to identify pharmaceuticals of environmental concern

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Abstract

Pharmaceuticals are frequently found in the aquatic environment. As they are most often highly biologically active, quite persistent and may accumulate in aquatic organisms, i.e. bioconcentrate, they may pose a risk to non-target organisms.

Current knowledge on environmental fate and effects of pharmaceuticals are limited, and traditional risk assessment strategies are insufficient to capture all substances posing risks for wildlife. In this thesis we explored the potential of two additional approaches to assist in the identification of substances of environmental concern. The first involved read-across between therapeutic plasma concentrations in humans and measured plasma levels of pharmaceuticals in exposed fish, in order to predict the risks for pharmacological effects in the fish. The second involved microarray analyses of gene expression to confirm pharmacological interactions, find potential biomarkers and assess the mode of action of pharmaceuticals in exposed fish.

We could show that waterborne diclofenac affects hepatic gene expression in exposed fish at water concentrations reported in treated effluents and surface waters. Pharmacological responses, resembling those found in mammals, were observed in fish at blood plasma concentrations similar to human therapeutic plasma levels, indicating a similar potency and mode of action in fish and humans. In contrast to some other reported results, the bioconcentration factor of diclofenac in fish was found to be stable across exposure concentrations.

Exposure of fish to ketoprofen at concentrations about 100 times higher than those found in treated sewage effluents resulted in plasma concentrations below 1% of human therapeutic plasma levels, suggesting low risk for effects in fish. Accordingly, no effects on hepatic gene expression could be confirmed. However, exposure of fish to complex effluents indicates a higher bioconcentration potential of NSAIDs than does exposure to single substances. Thus, laboratory experiments may underestimate risks in the environment.

Microarray analyses revealed several differentially expressed genes after exposure to conventionally treated effluents. These included estrogen-responsive genes and a biomarker for dioxin-like exposure. Further results included indications of general stress after exposure to all studied ozone treated effluents. Effluents treated with activated carbon resulted in the least responses in exposed fish.

Exposure to the glucocorticoid beclomethasone-dipropionate affected plasma glucose levels and caused oxidative stress in fish. Effects observed in fish resembled effects in humans, supporting read-across between species. Exposure to free beclomethasone did not result in any observed effects, most probably due to its inability to bioconcentrate.

Taken together, both read-across and microarray analyses have proven useful in identifying pharmaceuticals of environmental concern.

Keywords: fish, microarray, bioconcentration, pharmaceuticals, wastewater treatment, environment

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