

# ON THE USE OF GENOMICS TO ASSESS ENVIRONMENTAL RISKS OF PHARMACEUTICALS

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## ABSTRACT

Many drugs are found in the aquatic environment and are therefore a cause for concern. Low concentrations of active ingredients from human pharmaceuticals reach the environment via sewage treatment plants, mainly as a result of excretion. However, other routes, such as incorrect disposal and direct releases from manufacture, could also be of importance.

The effects of residual drugs in the environment are not well understood. This thesis addresses the issue by using different genomic techniques. The evolutionary conservation of 1,318 human drug targets were predicted in 16 species from different taxonomic groups. We show that the majority of the drug targets are conserved in aquatic vertebrates, while invertebrates and plants lack orthologs to many of the targets. The presented predictions can serve as a basis for identifying potentially sensitive (and insensitive) species that are used for the environmental risk assessment of pharmaceuticals.

The effects on fish of exposure to a single pharmaceutical (ethinylestradiol) as well as a complex industrial effluent that contains high levels of many drugs were explored using microarray analysis. We identified two sensitive and potentially robust biomarkers of estrogen exposure by performing a meta-analysis that combined our results with data from the literature. The identified biomarkers were also used to evaluate the ability of different sewage treatment technologies to remove estrogenic substances. Several treatment technologies reduced the levels of estrogenic substances, but ozonation was required to remove all measured biological effects. The fish that were exposed to a high dilution of the industrial effluent showed increased hepatic Cyp1a enzyme activity and altered expression of several genes that are involved in the detoxification of chemicals and drugs. Although the gene expression pattern did not clearly point to any specific group of substances, it could serve as a basis for hypothesizing mechanisms of toxicity and possible causative agents in the effluent.

More research is needed to understand the risks of residual drugs in the environment, and the presented results show that genomic approaches are useful for this purpose.

**Keywords:** comparative pharmacology, ecotoxicology, fish, microarray, genomics, wastewater treatment

**ISBN 978-91-628-7749-1**

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Akademisk avhandling

som för avläggande av medicine doktorexamen vid Göteborgs universitet kommer att försvaras offentligt i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, torsdagen den 7 maj 2009, kl. 13.00

av

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Avhandlingen baseras på följande arbeten:

- I Evolutionary Conservation of Human Drug Targets in Organisms used for Environmental Risk Assessments.**  
*\*Gunnarsson L, \*Jauhiainen A, Kristiansson E, Nerman O, Larsson, D G J. Environ Sci Technol. 2008. 42(15):5807-5813. \*equal contribution*
- II Sensitive and Robust Gene Expression Changes in Fish Exposed to Estrogen - a Microarray Approach.**  
*Gunnarsson L, Kristiansson E, Förlin L, Nerman O, Larsson D G J. BMC Genomics. 2007. 8(149).*
- III Comparison of six different sewage treatment technologies - reduction of estrogenic substances and gene expression changes in exposed fish.**  
*Gunnarsson L, Adolfsson-Erici M, Björlenius B, Rutgersson C, Förlin L, Larsson D G J. Submitted*
- IV Pharmaceutical industry effluent diluted 1:500 affects global gene expression, Cyp1a activity and plasma phosphate in fish.**  
*Gunnarsson L, Kristiansson E, Rutgersson C, Sturve J, Fick J, Förlin L, Larsson D G J. Submitted*



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