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Chemical mixtures and interactions with detoxification mechanisms and biomarker responses in fish

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Dissertation Abstract

Several classes of anthropogenic chemicals are present as mixtures in the aquatic environment. However, information of how wildlife species, including fish, are affected by exposures to chemical mixtures is limited. Chemicals interactions, due to shared elimination pathways or receptor interactions, can result in possible adverse outcomes in animals. This thesis investigates how detoxification mechanisms are affected by exposure to chemicals alone or in mixtures. Cytochrome P450 (CYP) enzymes and efflux pumps have key roles in the detoxification and elimination pathways of many structurally different chemicals and are therefore targets for chemical interactions. Induction of the CYP1A isoform and the egg-yolk precursor vitellogenin in fish are two established biomarkers used to assess exposures to aromatic hydrocarbons and estrogens in the environment.

This thesis focuses on regulation of these biomarkers, with emphasis on regulation and function of CYP1A, in fish or cultured fish liver cells exposed to different classes of chemicals alone and in mixtures. This thesis shows that structurally different chemicals can interact on regulation of CYP1A gene expression and/or on catalytic function. A synergistic mixture effect on the CYP1A biomarker response was demonstrated in the *Poeciliopsis lucida* hepatocellular carcinoma cell line, upon combined exposure to β-naphthoflavone (BNF) and different azoles. The synergistic mixture effect is caused by inhibition of the CYP1A catalytic function. An antagonistic mixture effect on the vitellogenin biomarker was demonstrated in primary cultures of rainbow trout hepatocytes upon combined exposure to BNF, which activates the aryl hydrocarbon receptor (AhR), and the synthetic estrogen 17α-ethinylestradiol, which activates the estrogen receptor (ER). The antagonistic mixture effect is caused by an inhibiting AhR-ER cross-talk. A cross-talk between the AhR and the pregnane-X-receptor (PXR) was also suggested in livers of the PCB-resistant killifish population from the New Bedford Harbor, Massachusetts, USA. These fish have reduced AhR-CYP1A signaling but respond to exposure to PCBs in the laboratory by increased PXR, CYP3A and efflux pump mRNA levels.

This thesis shows that these biomarkers are affected, in fish or in fish liver cells, exposed to chemical mixtures. This can have adverse effects on their detoxification mechanisms and can also lead to misinterpretation of biomarker data in biomonitoring programs in the aquatic environment.

Keywords:
Fish, AhR, CYP1A, PXR, chemical mixtures, chemical interaction, biomarker