TRANSCRIPTOMIC INSIGHTS INTO ENDOCRINE DISRUPTION OF DDE, DEHP, AND PFOA IN 5 DPF ZEBRAFISH

T. Papageorgiou[1,2], I. S. Frydas[1,2], D. Schultz[1,2], H. Le Mentec[4,5], D. Lagadic-Gossmann[6], N. Podechard[6], S. Karakitsios[1,2], D. Sarigiannis[1,2,3,7]*

[1]HERACLES Research Center – CIRI, Aristotle University of Thessaloniki, Greece

[2]Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, Greece

[3]Environmental Health Engineering, School for Advanced Study IUSS, Pavia, Italy

[4]Institut National de la Santé et de la Recherche Médicale (INSERM), Institut de Recherche en Santé, Environnement et Travail (IRSET-INSERM UMR 1085), 35000 Rennes, France,

[5]Université de Rennes 1, Faculté des Sciences Pharmaceutiques et Biologiques, Structure Fédérative de Recherche Biosit UMS CNRS 3480/US INSERM 018, 35043 Rennes, France

[6]Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail)-UMR_S 1085, University of Rennes, F-35000 Rennes, France. norman.podechard@univ-rennes1.fr.

[7]National Hellenic Research Foundation, 48 Vasileos Constantinou Ave., Athens 11635 Greece

(*sarigiannis@auth.gr)

ABSTRACT

Zebrafish (*Danio rerio*) are well-recognized vertebrate models for investigating the mechanisms of action of environmental toxins and their related diseases in humans. p,p'-Dichlorodiphenyldichloroethylene (DDE), the main metabolite of the banned pesticide dichlorodiphenyltrichloroethane (DDT), is commonly found in the food chain and has been detected in all tissues of many living organisms. DDE is associated with metabolic diseases by acting as an endocrine disruptor. Di-2-ethylhexyl phthalate (DEHP) is a lipophilic plasticizer belonging to the phthalates family and is considered a possible human reproductive and developmental toxicant. Perfluorooctanoic acid (PFOA) is a long-chain perfluorinated compound that has shown carcinogenic, reprotoxic, and immunotoxic features, as well as the capability of affecting thyroid and lipid metabolism in animals. The objective of this study was to assess gene expression responses of 5 days post fertilization (5 dpf) zebrafish embryos exposed to two different concentrations of DDE, DEHP, and PFOA and connect them with endocrine disruption and associated metabolic disorders. Transcriptomic analysis was performed using the one-color microarray-based gene expression analysis protocol provided by the supplier and was followed by an in-house statistical analysis pipeline. More specifically, scan results underwent quality control, background correction, and normalisation, followed by batch effect correction, using the R package limma. In order to identify the differentially expressed genes (DEGs), statistical analysis was performed on weighted array values using a moderated t-test with a Benjamin Hochberg FDR multiple testing correction. A fold change cut-off of 1.3 and adjusted p-value cut-off of < 0.05 were applied. The resulting DEGs underwent pathway analysis to identify the biochemical pathways in which they participate, with the use of KEGG and WikiPathway databases. GO analysis was also performed, indicating that the DEGs participate in primary and cellular metabolic processes. The PPAR signalling pathway, Oxidation phosphorylation, and Electron transport chain was affected by all three chemicals. Additionally, DDE and PFOA exposure revealed a perturbation of the Glycolysis and Gluconeogenesis pathway. Overall, microarray analysis provided important insights into potential biomarkers and the relevant toxicity of DDE, DEHP, and PFOA in zebrafish.

KEYWORDS: *Danio rerio*, developmental toxicity, microarray, EDCs, metabolic disorders