**PRENATAL EXPOSURE TO METALS IN THE EXHES COHORT STUDY: AN UNTARGETED METABOLOMICS ANALYSIS**

**F. Nikiforou1,2, N. Papaioannou1,2, C. Gabriel1,2, S. Karakitsios1,2,3, D.A. Sarigiannis1,2,3**

1 Aristotle University of Thessaloniki, Department of Chemical Engineering, Environmental Engineering Laboratory, University Campus, Thessaloniki 54124, Greece

2 HERACLES Research Center – KEDEK, Aristotle University of Thessaloniki, Greece

3 Environmental Health Engineering, Institute of Advanced Study, Palazzo del Broletto -Piazza della Vittoria 15, 27100 Pavia, Italy

*\* sarigiannis@auth.gr*

**ABSTRACT**

Mapping the human exposome becomes a challenge as it is constantly changing and varies according to the stage of an individual's life. However, exposome studies could make us understand the connection between environmental exposure and human health and help us discover the causes of various diseases. In the framework of the EU project HEALS we developed a multi-disciplinary and holistic approach to access prenatal exposure to metals and gain insight into their early childhood development effects. The present study is an untargeted metabolomics analysis. It was applied on 173 plasma samples of pregnant women at delivery collected in the HEALS pilot European Exposure and Health Examination Survey (EXHES). The metabolic profile analysis was performed using ultra‐high-performance liquid chromatography‐high resolution mass spectrometry (UPLC‐HRMS). The data pre-processing was carried out using the Bioconductor R - based packages XCMS and CAMERA. Then, the identification of the detected metabolites was performed, followed by the pathway analysis, using the Mass Profiler Professional platform of GeneSpring v.14.9 software. Out of the 2415 detected metabolites, the metabolite identification results pointed out that the total number of annotated metabolites in the plasma samples was 740. The total number of the pathways in which the detected metabolites are involved was 190. Finally, the results from the pathway analysis revealed the association between plasma biomarkers, such as citric acid, L-tyrosine, L-glutamine and L-phenylalanine and prenatal exposure to lead (Pb), copper (Cu), manganese (Mn), mercury (Hg), cadmium (Cd) and arsenic (As). Subsequently, the metabolic pathways mostly associated with exposure to metals were the TCA cycle, L-tyrosine biosynthesis, glucose homeostasis and purine metabolism. These metabolites have been found to be associated with adverse health outcomes, such as neurodevelopmental disorders in children, decreased levels of thyroid hormones and breast cancer development, as well as with mechanisms associated with multiple endpoints such as elevated oxidative stress. In conclusion, this study is of particular importance for environmental health; it provides useful insights into the related mechanisms of toxicity of metals and their impact on the human metabolome. This information, combined with other omics technologies, could contribute to developing new methods for precise prevention and public health protection.

**KEYWORDS:** Prenatal exposure to metals, Metabolomics, Untargeted metabolomics analysis, Environmental health