EARLY LIFE CO-EXPOSURE TO PLASTICIZERS AND METALS DYSREGULATES UREA CYCLE AND CHOLINE METABOLISM WITH ADVERSE EFFECTS ON NEURODEVELOPMENT: A HIGH DIMENSION BIOLOGICAL ANALYSIS PARADIGM

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ABSTRACT

This study was part of the largest project on the exposome (i.e. the totality of exposures an individual goes through over his/her lifetime) globally, HEALS, which proposes the functional integration of cross–omics data to derive exposome-wide causal associations with adverse health outcomes. Untargeted metabolomics of 600 urine and plasma samples from two cohorts (Repro_PL and PHIME) running in Poland, Slovenia, Croatia, Greece and Italy, which studied the environmental causation of neurodevelopmental disorders in neonates and children across Europe.

The aim of this study was to obtain mechanistic insight into how co-exposure to phthalates and heavy metals causes neurodevelopmental dysregulation coupling human data with in vitro assays. Specifically, HepaRG cells were exposed to mixtures of DEHP, DiNP, and BBzP phthalates, methylmercury and total mercury. These were the most abundant pollutants in the REPRO PL and PHIME cohorts. The effective in vitro concentrations of the chemicals were estimated through estimation from human biomonitoring data using internal dosimetry modeling on the INTEGRA computational platform.

High dimension pathway analysis of transcriptomics and proteomics data revealed that co-exposure to endocrine disrupting compounds such as phthalates and metals leads to dysregulation of the urea cycle due to alterations in the expression levels of arginase-1 and -2, argininosuccinate synthase, carbamoyl-phosphate synthase, ornithine carbamoyltransferase, and argininosuccinate lyase. Co-mapping proteomics and metabolomics data showed that their common drivers are responsible for the allostasis of metabolic pathways related to choline, phosphatidylcholine, phospholipases and triacylglycerol metabolism. The identification of the urea, phosphatidylcholine biosynthesis I and phospholipases metabolic pathways is of particular interest since these pathways have been also identified in human samples from the REPRO PL and PHIME cohorts using untargeted metabolomics analysis as being associated with impaired psychomotor development in children at the age of three to six. Our work reveals that co-exposure to plasticizers and metals disturbs biochemical processes related to mitochondrial respiration during critical developmental stages that are clinically linked to neurodevelopmental perturbations.