ALTERATION IN THE LIVER METABOLOME OF MICE, AFTER PERINATAL EXPOSURE TO A MIXTURE OF ENDOCRINE DISRUPTORS (MIXTURE G1) - A NMR-BASED METABOLOMICS STUDY

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Perinatal exposure to Endocrine Disrupting Chemicals (EDCs) triggers adverse health effects related to reproductive, developmental and metabolic processes to offsprings in their later life. Most of studies follow a single-substance approach, underestimating the risk of real-exposure to complex mixtures in daily life. A fundamental birth cohort conducted in Sweden during the period 2007-2010, SELMA (1), was focused on early life exposure to EDCs. 14 derivatives (Mixture G1) out of 41 EDCs analyzed in SELMA, were selected for a thorough investigation in animal models, contributing to a novel approach for risk assessment of chemical mixtures associated with endocrine disruption.
Female 2 month-old C57/BL6 mice, 1 day after mating, were divided into 3 groups based on perinatal dose exposure to Mixture G1: Control Group (daily exposure to DMSO vehicle), Low dose exposure group (daily exposure to 0.5*SELMA) and High dose exposure group (daily exposure to 500*SELMA). Male offsprings (n=20: Control n=5, 0.5*SELMA n=6, 500*SELMA n=9) were sacrificed at day 100, polar metabolites were extracted from their liver tissues and profiled using 1H NMR Spectroscopy. Multivariate (PCA, PLS-DA, OPLS-DA) and univariate analysis were performed, to investigate the metabolic effects of Mixture G1 on the offsprings' liver metabolome.
Spectra annotation resulted in 52 observed metabolites. According to 1H NMR profiling, both doses, despite the concentration difference (two different magnitudes), had comparable effects on liver metabolome. The levels of Uridine Diphosphate compounds (UDP- Glucose and/or Glucuronate), were found upregulated in the exposed groups, suggesting the suppression of glucuronidation process, a major phase II detoxification process. Hepatic metabolic fingerprint was also characterized by increased 3-Hydroxybutyrate (3HB) after exposure, indicative of elevated β-oxidation. Exposure to EDCs is known to upregulate fatty acid translocase (CD36) resulting in liver uptake of free fatty acids (2) and consequent increase of β-oxidation process. Finally, hepatic Uridine and Inosine were elevated in exposed offsprings, which may be associated with DNA methylation.
A more detailed metabolome mapping, applying an analytical technique of higher sensitivity and the investigation of additional intermediate EDC doses, will be of crucial importance and valuable for the risk assessment and management of EDCs and mixtures in health.

(1) Bornehag C-G et al "The SELMA Study" Paediatr Perinat Epid, 2012; doi: 10.1111/j.1365-3016.2012.01314.x
(2) Su et al "Long-term chronic exposure to di-(2-ethylhexyl)-phthalate induces obesity via disruption of host lipid metabolism and gut microbiota in mice", 2022; doi: 10.1016/j.chemosphere.2021.132414