VITAMINA B2-RIBOFLAVINA --VITAMIN B2 - RIBOFLAVIN

- Lu YS, Yao GX, Wang XL, Liu JX, Yu J, Qiu J, Li Y, Qian YZ, Xu YY.

A comprehensive analysis of metabolomics and transcriptomics reveals new biomarkers and mechanistic insights on DEHP exposures in MCF-7 cells. *Chemosphere*. 2020 Sep; 255:126865. doi: 10.1016/j.chemosphere.2020.126865.

Di-(2-ethylhexyl) phthalate (DEHP) is one of the most important environmental pollutants and affects multiple pathways upon human exposure. DEHP could induce MCF-7 cell proliferation at a very low dose; however, the possible linkage between DEHP and the cell proliferation effect is still unclear. Here, we carried out a comprehensive metabolome and transcriptome analysis to depict the possible molecular mechanisms of the effect of DEHP exposure on MCF-7 proliferation. In this paper, MCF-7 cells treated with DEHP at a dose of 1 μM for 48 h were selected for metabolome and transcriptome analysis. Untargeted and targeted metabolomics identified 8 differential metabolites, including amino acids, purine, pyrimidine and nucleotides. The metabolite changes were associated with 9 metabolic pathways. Disorders in riboflavin, histidine, beta-alanine metabolism, and nitrogen metabolism caused by DEHP exposure are important concerns for MCF-7 proliferation. Moreover, a transcriptomics study of the MCF-7 cells found a total of 500 differentially expressed genes (DEGs). KEGG enrichment analyses showed that pathways in cancer had stronger responses. The results of integrated analysis of the interactions between the DEGs and metabolites revealed significant changes in the purine metabolism pathway, which will shed light on the mechanism of MCF-7 cell proliferation after DEHP exposure. Overall, this study depicts the possible contribution of DEHP exposure to MCF-7 cell proliferation and highlights the power of omics platforms to deepen the mechanistic understanding of toxicity caused by endocrine disrupting chemicals.

- Wei Z, Xi J, Gao S, You X, Li N, Cao Y, Wang L, Luan Y, Dong X.

Metabolomics coupled with pathway analysis characterizes metabolic changes in response to BDE-3 induced reproductive toxicity in mice. *Sci Rep*. 2018 Apr 3;8(1):5423. doi: 10.1038/s41598-018-23484-2.

Polybrominated diphenyl ethers (PBDEs) may affect male reproductive function. 4-bromodiphenyl ether (BDE-3), the photodegradation products of higher brominated PBDEs, is the most fundamental mono-BDE in environment but is less studied. The purpose of this study was to investigate the reproductive toxicity induced by BDE-3 and explore the mechanism by metabolomics approach. In this study, mice were treated intragastrically with BDE-3 for consecutive six weeks at the dosages of 0.0015, 1.5, 10 and 30 mg/kg. The reproductive toxicity was evaluated by sperm analysis and histopathology examinations. UPLC-Q-TOF/MS was applied to profile the metabolites of testis tissue, urine and serum samples in the control and BDE-3 treated mice. Results showed the sperm count was dose-dependently decreased and percentage of abnormal sperms increased by the treatment of BDE-3. Histopathology examination also revealed changes in seminiferous tubules and epididymides in BDE-3 treated mice. Metabolomics analysis revealed that different BDE-3 groups showed metabolic disturbances to varying degrees. We identified 76, 38 and 31 differential metabolites in testis tissue, urine and serum respectively. Pathway analysis revealed several pathways including Tyrosine metabolism, Purine metabolism and Riboflavin metabolism, which may give a

possible explanation for the toxic mechanism of BDE-3. This study indicates that UHPLC-Q-TOFMS-based metabolomics approach provided a better understanding of PBDEs-induced toxicity dynamically.

- Chen M, Zhou K, Chen X, Qiao S, Hu Y, Xu B, Xu B, Han X, Tang R, Mao Z, Dong C, Wu D, Wang Y, Wang S, Zhou Z, Xia Y, Wang X.

Metabolomic analysis reveals metabolic changes caused by bisphenol A in rats. *Toxicol Sci.* 2014 Apr;138(2):256-67

Bisphenol A (BPA) is a widely used material known to cause adverse effects in humans and other mammals. To date, little is known about the global metabolomic alterations caused by BPA using urinalysis. Sprague-Dawley rats were orally administrated BPA at the levels of 0, 0.5 μg/kg/day and 50 mg/kg/day covering a low dose and a reference dose for 8 weeks. We conducted a capillary electrophoresis in tandem with electrospray ionization time-of-flight mass spectrometry based nontargeted metabolomic analysis using rat urine. To verify the metabolic alteration at both low and high doses, reverse transcription-polymerase chain reaction (RT-PCR) and western blotting were further conducted to analyze hepatic expression of methionine adenosyltransferase Iα (Mat1a) and methionine adenosyltransferase IIα (Mat2a). Hepatic S-adenosylmethionine (SAMe) was also analyzed. A total of 199 metabolites were profiled. Statistical analysis and pathway mapping indicated that the most significant metabolic perturbations induced by BPA were the increased biotin and riboflavin excretion, increased synthesis of methylated products, elevated purine nucleotide catabolism, and increased flux through the choline metabolism pathway. We found significantly higher mRNA and protein levels of Mat1a and Mat2a, and significantly higher SAMe levels in rat liver at both low and high doses. These two genes encode critical isoenzymes that catalyze the formation of SAMe, the principal biological methyl donor involved in the choline metabolism. In conclusion, an elevated choline metabolism is underlying the mechanism of highly methylated environment and related metabolic alterations caused by BPA. The data of BPA-elevated accepted biomarkers of injury indicate that BPA induces DNA methylation damage and broad protein degradation, and the increased deleterious metabolites in choline pathway may also be involved in the toxicity of BPA.