# UNTARGETED METABOLOMICS ANALYSIS REVEALS THE METABOLIC IMPACT OF BISPHENOL EXPOSURE ON PANCREATIC B-CELLS

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## ABSTRACT

Bisphenols are chemical compounds used in many consumer products like toys and food containers. They have been linked with various endocrine and metabolic diseases such as Type 2 diabetes. The pancreas plays a critical role in energy metabolism and homeostasis through the secretion of hormones, such as insulin. In this study, EndoC-βh1 cells were used to investigate the metabolic effects of BPA, BPF, and BPS in parallel, to assess the impact that these chemicals have on insulin secretion functions in the presence of high and low glucose levels, and to investigate the gaps in current knowledge about metabolic diseases. Untargeted metabolomics analysis was performed using an Agilent 6540 Ultra High Definition Accurate-Mass QTOF instrument in positive and negative ionization modes. Moreover, the samples were analyzed using Reversed Phase (RP) and HILIC analytical columns to increase the coverage of the detected metabolites. Data pre-processing and processing steps (data cleaning, log transformation, normalization, and batch effect correction) were performed through the Bioconductor R-based package XCMS. The xMSannotator R package was used for Network-Based annotation, retrieving information from HMDB, Metlin, and Lipid Maps. Statistical and fold change analysis determined the significantly differential metabolites, which were mapped to metabolic pathways. After statistical analysis, 29 significantly differentially detected metabolites were identified across all chemical treatments and glucose conditions. These features were mostly metabolites from the sterol lipids, glycerophospholipids, and fatty acyl categories. Additionally, based on the fold change analysis, 814 features were annotated. Most of the annotated metabolites from both analyses were lipids, specifically glycerophospholipids, fatty acyls, and sphingolipids. Pathway analysis revealed that bisphenols exposure significantly affected Sphingolipids and Glycerophospholipids metabolism. Both BPA and BPF significantly influenced

Amino acid metabolism, Glycolysis, Gluconeogenesis, and the TCA cycle under decreased glucose levels. Increased glucose levels revealed alterations in amino acids, glucose, and sphingolipid metabolism, as well as gluconeogenesis. BPF and BPS induced changes in sterol lipid levels, disrupting steroidogenesis. To conclude, the results of the present study provide important information about the potential biomarkers and the relevant toxicity of three ubiquitous bisphenols in pancreatic β-cells.

**KEYWORDS:** Untargeted metabolomics, Pancreatic b-cells, Bisphenols, Metabolic disorders