

# Differential effects of the combination of bisphenol A and its emergent substitute molecules on the vascular endothelium.

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## Abstract

Plastic production, disposal, and recycling system represent one of the higher challenges for the planet's health. Its direct consequence is the release of endocrine disruptors, such as bisphenol A (BPA), and its emerging substitute molecules, bisphenol F and S (BPF and BPS), to the environment. Therefore, bisphenols are usually present in human biological fluids. Since BPA, BPS, and BPF have structural analogies and similar hormonal activity, their combined study is urgently needed. The present manuscript studied the effect of the mixture of bisphenols (BPmix) in one of the world's largest human cohorts (NHANES cohort). Descriptive and comparative statistics and binomial and multinomial logistic regression analyses determined a significant association between BPmix and heart disease, independent of the covariates age, gender, BMI, smoking, diabetes, and dyslipidemia. Endothelial dysfunction is a hallmark of cardiovascular disease; thus, the average ratio of bisphenols found in humans was used to develop studies in murine aortic endothelial cells. The first results showed that BPmix had a higher effect on cell viability than BPA, enhancing its deleterious biological action. However, the flow cytometry, western blot, and immunofluorescence assays demonstrated that BPmix induces a differential effect on cell death. While BPA exposure induces necroptosis, its combination with the proportion determined in the NHANES cohort induces apoptosis. In conclusion, the evidence suggests the need to reassess research methodologies to study endocrine disruptors in a more realistic way.

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