

## **BISPHENOLS AND THE FEMALE REPRODUCTIVE SYSTEM**

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### **ABSTRACT**

BPA-free products made with substitute chemicals were made in response to the growing concern about the negative impacts of Bisphenol A (BPA) on human health. Bisphenol S (BPS) is one of the most widely used replacements for BPA. However, BPS may not be safer than BPA. Studies now show that BPS also exhibits endocrine-disrupting activities similar to BPA. BPS is obesogenic, cardiotoxic, neurotoxic, and immunotoxic. However, there is little understanding if this chemical is reprotoxic or can promote protumorigenic effects. This study addressed these concerns. It aims to determine whether BPS is involved in disease development and progression using the endometrial adenocarcinoma (Ishikawa) cell line and mouse reproductive tissues. Further, cetaceans, known as sentinel species of the marine environment, were also utilized to explore reproductive diseases associated with endocrine-disrupting chemicals such as BPA and BPS. Results of this study showed that BPS could increase cell proliferation and stimulate migration in Ishikawa cells in association with the upregulation of estrogen receptor beta (ESR2) and vimentin (VIM). Proliferation and migration in neoplastic cells, such as the endometrial adenocarcinoma cell line, are hallmarks of disease progression. In mice, BPS is reprotoxic as it stimulates ovarian atrophy and the appearance of proliferative and migratory lesions in their reproductive tissues. These proliferative and migratory lesions in the reproductive tissues signify the onset of disease development. The collected reproductive tissues of cetacean species also showed phenotypes that can be associated with the effects of bisphenols, as observed in the laboratory setting using a mouse model. Overall, *in vitro* and *in vivo* results obtained in this study showed that BPS is protumorigenic and reprotoxic, a phenotype also observed with BPA exposure. Moreover, proliferative, and migratory lesions in the reproductive organs of various cetacean species may indicate that aside from genetic and physiological factors, pollution may play a role in forming these lesions, as oceans where cetacean lives are known as one of the major sinks for pollutants.