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**Bisphenol A at Low Nanomolar Doses Confers Chemoresistance in  
Estrogen Receptor Alpha Positive and Negative Breast Cancer Cells**

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**Running Title:** Chemoresistance by Bisphenol A

**Key Words:** bisphenol A, breast cancer cells, chemotherapeutic agents, cytotoxicity, estrogen receptors

**Abbreviations:**

BPA- bisphenol A

CSS - charcoal-stripped serum

DES- diethylstilbestrol

E2- estradiol

ER $\alpha/\beta$ - estrogen receptor  $\alpha$  or  $\beta$

ERR- estrogen-related receptor

GPR30 - G protein-coupled receptor 30

MTT- 4-[2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo [1,5-a]pyrimidin-3-yl]phenol

PHTPP - 4-[2-Phenyl-5,7-bis(trifluoromethyl)pyrazolo [1,5-a] pyrimidin-3-yl]phenol

**Article Descriptor:** Breast Cancer

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## Outline

Abstract

Introduction

Materials and Methods

Drugs and inhibitors

Cell lines and culture conditions

Cytotoxicity assay

Western blotting

Real-time PCR

Data analysis

Results

BPA protects T47D cells from chemotherapeutic-induced cytotoxicity

BPA antagonizes chemotherapeutic agents in MDA-MB-468 cells

BPA, at low nM concentrations, protects cells from doxorubicin-induced cytotoxicity

The protective effects of BPA are not mediated via classical estrogen receptors

Relative receptor expression in T47D and MDA-MB-468 cells

BPA may promote chemoresistance by altering anti-apoptotic proteins

Discussion

References

Table

Figure legends

Figures

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

## **Abstract**

*Background.* Resistance to chemotherapy is a major problem facing breast cancer patients, and identifying potential contributors to chemoresistance is a critical area of research. Bisphenol A (BPA) has long been suspected to promote carcinogenesis, but the high doses of BPA used in many studies generated conflicting results. In addition, the mechanism by which BPA exerts its biological actions is unclear. While estrogen has been shown to antagonize anti-cancer drugs, the role of BPA in chemoresistance has not been examined.

*Objective.* The objective was to determine whether BPA at low nanomolar concentrations opposes the action of doxorubicin, cisplatin and vinblastine in the ER $\alpha$  positive T47D and the ER $\alpha$  negative MDA-MB-468 breast cancer cells.

*Methods.* The responsiveness of cells to anti-cancer drugs and BPA was determined by the MTT cytotoxicity assay. Specific ER $\alpha$  and ER $\beta$  inhibitors and real-time PCR were used to identify potential receptor(s) that mediate the actions of BPA. Expression of anti-apoptotic proteins was assessed by Western blotting.

*Results.* BPA antagonizes the cytotoxicity of multiple chemotherapeutic agents in both ER $\alpha$  positive and negative breast cancer cells independent of the classical ERs. Both cell types express alternative ER receptors, including GRP30 and members of the estrogen related receptor (ERR) family. Increased expression of anti-apoptotic proteins is a potential mechanism by which BPA exerts its anti-cytotoxic effects.

*Conclusions.* BPA at environmentally relevant doses reduces the efficacy of chemotherapeutic agents. These data provide considerable support to the accumulating evidence that BPA is hazardous to human health.