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Bisphenol A and Hormone-Associated Cancers:Current Progress and Perspectives

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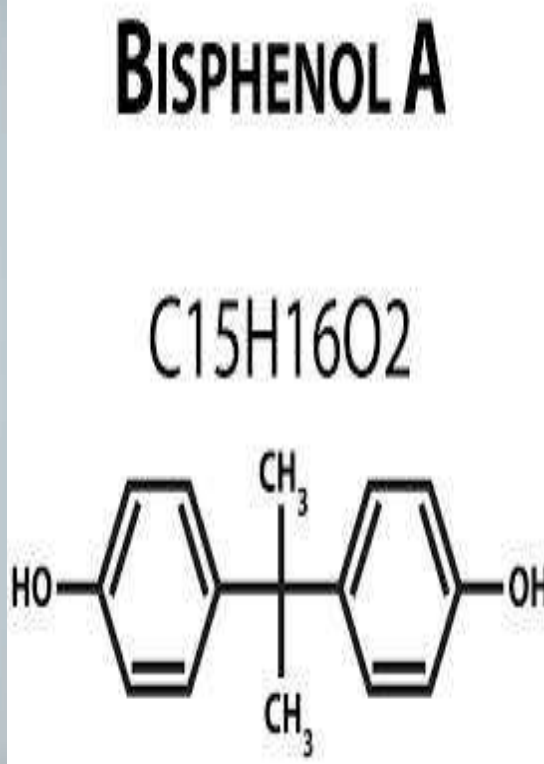
Definition of Bisphenol A (BPA)

Bisphenol A (BPA) is an industrial chemical used primarily in the production of polycarbonate plastics and epoxy resins and has been commercially available since 1957. Currently, BPA is one of the highest volume chemicals produced worldwide.

It is composed of two phenol groups that is produced by condensing acetone with carbolic acid.



Sources of Exposure

BPA is widely present in many hard plastic containers, water bottles, baby bottles feeding, some dental sealants and metal-based food and beverage cans.

human exposure does occur when BPA leaches from plastic and epoxy resin-containing bottles and cans due to heating or repeatedly wash or exposed to pH changes (either acidic or basic) because hydrolysis of the ester bond linking BPA monomers.

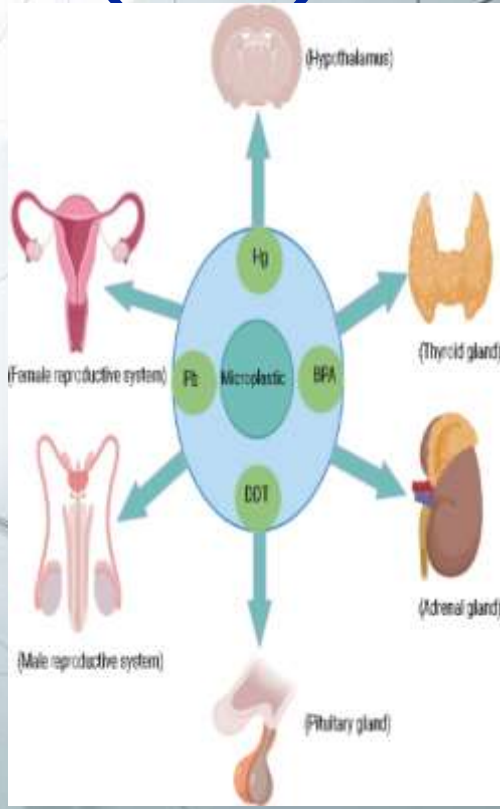
Are exposure to BPA high?

human exposure to BPA is widely spread and by using different measurement techniques, BPA has been found to be present in human serum, urine, amniotic fluid, and breast milk in the populations of industrialized countries worldwide.

In a reference population of 394 adults in the United States, BPA was detected in 95% of urine samples with a median concentration of 1.28mg/L

What are the fears of Bisphenol A (BPA)

Bisphenol A (BPA) exhibits hormone-like properties so consider as (endocrine disruptor) and due to its widespread use so the risk of biological accumulation, toxicity in the reproductive organs, inhibitory effects on testosterone synthesis increased ,also thyroid hormone imbalances and metabolic disorders.



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Hormonal Impact

The estrogenic activity of BPA represents the major endocrine-disrupting effect of BPA ,it can mimic estrogen to interact with estrogen receptors α, and β, leading to changes in cell proliferation, apoptosis, or migration and there by contributing to cancer development and progression like breast cancer , ovarian cancer and endometrial carcinoma, even in low dose.

Brest cancer

Estrogen and estrogen signaling pathways play pivotal roles in the development of the mammary gland and breast carcinogenesis.

Specifically, both ER- ά and ER- β are first expressed at embryo stage.

BPA is able to induce expression of WNT-4 gene and receptor activator of nuclear factor kappa-B ligand (RANKL), the two key molecules of hormone function in the regulation of mammary stem cell proliferation and carcinogenesis by regulation of mullerian duct development and ovarian androgen biosynthesis also contribute to human follicle development and/or maintenance.

Breast cancer

BPA also effected on adult normal mammary gland and transformed mammary gland cells. It is promote cell proliferation and increase cell size in mammary gland sphere cultures, but inhibiting apoptosis .

By multiple oncogenic signaling pathways, including:

1)vascular endothelial growth factor (VEGF) signaling, which is associated with breast tumor angiogenesis

2) the DNA repair pathway

3) ERK1/2 cascade activation

4) STAT3 signaling.

5)stimulated the GPER/EGFR/ERK pathway

Ovarian cancer

many studies revealed that Approximately 50% of human ovarian epithelial cancer cells express higher levels of ER than do cell of benign tumors and normal ovary, Both ER- ά and ER- $_{\beta}$ are expressed in normal and transformed ovarian cells.

Also postmenopausal women have suggested that estrogen-only replacement therapy increases the incidence and mortality of ovarian cancer,

BPA interrupts ovarian steroidogenesis by altering the steroidogenic enzymes, contribute tumor progression and/or may regulate proliferation and apoptosis of ovarian cells.

Ovarian cancer

Also BPA exposure increases the incidence or exacerbates the clinical course of polycystic ovary syndrome. In rodent models, it is well documented that neonatal exposure to BPA is associated with altered ovarian morphology, an increased number of cystic ovaries, cystic endometrial hyperplasia, and reduction in the pool of primordial follicles in the rat ovary, which is associated with an increased proliferation rate likely mediated by an estrogenic pathway.

Prenatal exposition to BPA also causes a variety of development abnormities of the ovary (eg, endometriosis, altered number of primordial developing follicles, ovarian lesions, and inhibition of meiotic progression of oocytes

Ovarian cancer

Also BPA was shown to regulate the expression of a battery of genes in ovarian tissues, some of which are associated with oncogenic signaling or ovarian cancer development.

Studies revealed BPA treatment is able to up-regulate Cdk4, Ccne1, cyclin D1, IGF-1R, and Bcl2 but down regulate p21 and Aryl-hydrocarbon receptor nuclear translocator 2 (ARNT2), resulting in cell proliferation and inhibition of apoptosis.

BPA has also been shown to regulate the transforming growth factor beta (TGF-b), JAK/STAT3, MAPK/ERK, and PI3K/Akt signaling pathways and BPA also stimulates granulosa-lutein cells to express matrix metalloproteinase-9 (MMP-9), an extracellular matrix protein that is associated with progression of ovarian cancer

Prostate cancer

The role of BPA in prostate tissue is relatively complicated compared to that in the mammary gland or ovary. Both steroid receptors (ERs and AR) play crucial roles in the development and progression of prostate cancer.

A number of studies have shown that BPA can regulate the proliferation and migration of prostate cancer cells by inducing nuclear translocation of the tumor-derived receptor (AR-T877A) and DNA methylation patterns of multiple cell signaling genes in prostate cancer cells and AR mutation. also the major action of BPA was to down- regulate ER- β.

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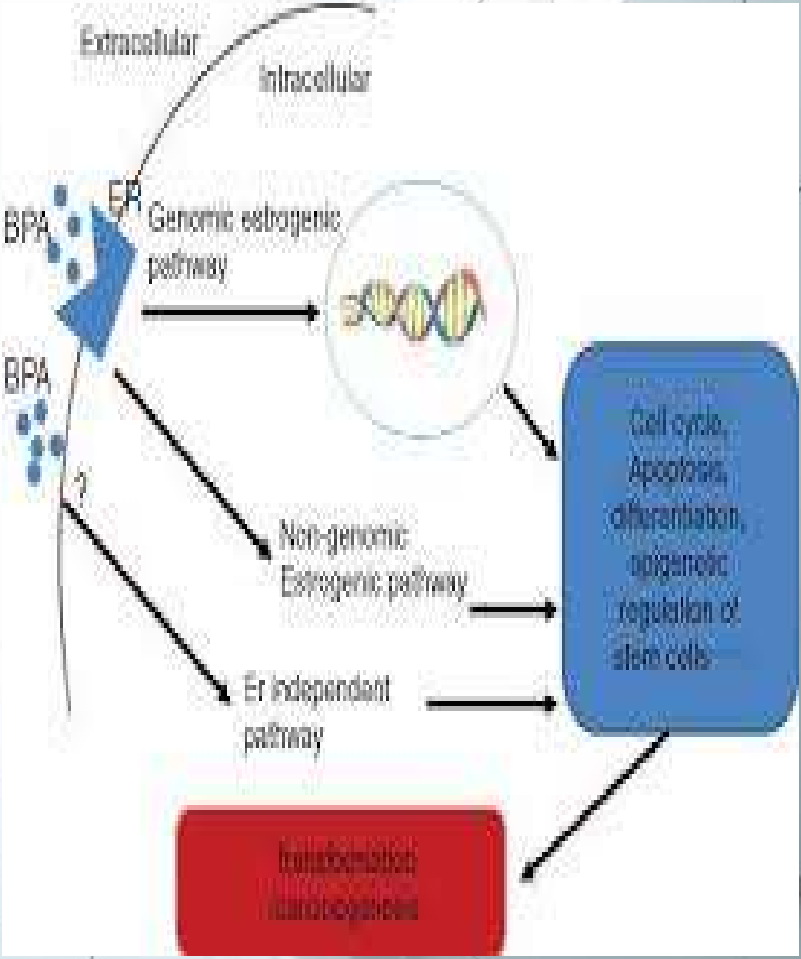
The role of BPA in hormone-associated cancers conclusions by:

1) BPA is a typical xenoestrogen and its estrogenic activity and estrogen-independent activity are likely responsible for its roles in promoting carcinogenesis of multiple cancers
(like in figure).

2) BPA interacts with other steroid receptor such as AR to promote proliferation of prostate cancer cells

3) fetal exposure to BPA could lead to ‘‘long-lasting’’ effects on the carcinogenesis of certain organs



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How can reducing the BPA exposure

-Avoid the use of plastic bottles.
- use of “BPA-free” labeled bottles or bottles made of plastics with a cloudy or frozen look, as they do not contain BPA.
-Liquid or food packed in metal containers should be avoided.
-should not reuse old or damaged containers.
- Don't put plastic containers in the microwave or dishwasher.
-Alcohol-based hand cleaners increase BPA absorption through the skin therefore, it is wise to wash one’s hands with soap and water before handling food
-Eliminate the impact of high temperatures.
-Consumption of coffee prepared in automatic coffeemakers should be avoided.
-Dental patients are advised to ask their dentists for BPA-free sealants or fillings
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Thank you