## LAY ABSTRACT

TITLE: Effects of Benzophenone-3 and Propylparaben Induce Estrogen Receptor-Dependent R-Loops and DNA Damage in Breast Epithelial Cells and Mice

JOURNAL: Environmental Health Perspectives, 2020

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This is attributed to the BCERP grant ES026140

Estrogens play a pivotal role in breast development in women but can also contribute to risk of breast cancer. A variety of environmental chemicals have been shown to act like estrogens, referred to as xenoestrogens, and may interfere with or amplify the normal actions of estrogens and increase the risk of breast cancer. These chemicals are most often identified using cancer cells that activate specific genes and grow more rapidly when exposed to these chemicals.

In this study, we examined the actions of 2 chemicals (propylparaben, PP; benzophenone-3, BP3, also known as oxybenzone) that are common ingredients in sunscreens, cosmetics and other personal care products. The effects of these chemicals were compared with the natural estrogen (17beta-estradiol or E2) in cells grown in the laboratory and breast tissue (mammary glands) of mice.

Both BP3 and PP had estrogen-like activities triggering activation of genes and growth of breast cancer cells in laboratory experiments. But these effects required levels of chemicals that exceed the levels that most women are normally exposed to. In contrast, BP3 and PP caused breaks in DNA of cells at levels that are 1/10th that required to stimulate growth or gene activation. This damage to DNA required interactions with the estrogen receptors in the cells, and therefore, this DNA-damaging activity is limited to cells such as those found in the breast. BP3 and PP also caused damage to DNA of the cells in the mammary glands of mice, but without causing other effects of estrogen.

The results show that exposure to low doses of the chemicals BP3 and PP can damage DNA specifically in breast cells, and possibly other cells with estrogen receptors. This DNA damage mediated by estrogen receptors is a new mechanism by which estrogens

and xenoestrogens can promote breast cancer. The methods offer a more sensitive tool to screen for the potential harmful effects of xenoestrogens which would otherwise be overlooked by methods currently used.