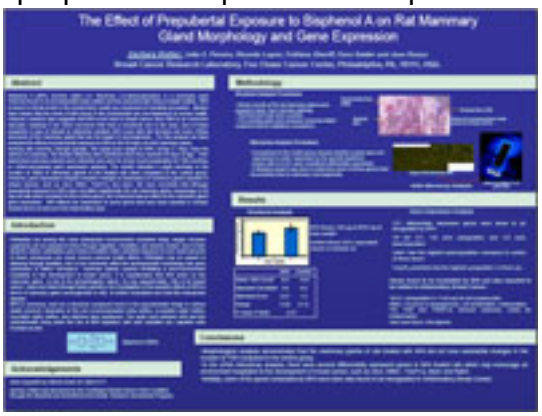
The effect of prepubertal exposure to Bispenol A on rat mammary gland morphology and gene expression.



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Bisphenol A (BPA), formerly called 4,4'- dihydroxy- 2,2-diphenylpropane, is a commonly used chemical found in re-microwaveable baby bottles and the polycarbonate lining of plastic bottles. BPA is found in normal levels in the environment, mostly as a byproduct of industrial processes. Studies have shown that the levels of BPA found in the environment are non-hazardous to human health. However, research also suggests that BPA could lead to breast cancer since BPA is an endocrine disruptor, meaning it can mimic the hormones that have a functional role in the body.

Due to these properties it was of interest to determine if BPA could alter the terminal end buds (TEBs) structures of the mammary gland, which are the target of carcinogenesis.. For this purpose we have analyzed the effects of prepubertal exposure to BPA on the 50 days old rat's mammary gland. Nursing rats received, through gavage, 250 µg/kg body weight of BPA, during 21 days from the delivery to weaning. The female offspring were sacrificed when they reached 50 days of age. Their abdominal mammary glands were extracted and used for whole mount preparation for TEB counting, or gene expression analysis through cDNA-microarrays. The results indicated a slight decrease in the number of TEBs in mammary glands of the treated rats when compared to the control group. However, the gene expression analysis revealed changes in expression of numerous genes reported in breast cancers, such as Vav2, Nfkb1, Tnsrf11a, and Mycn. We have concluded that although prepubertal exposure to BPA does not affect significantly the rat mammary gland morphology of 50 day old rats when compared to the control group, the compound has an effect on the rat's gene expression. BPA altered the expression of some genes that have been reported in primary breast cancer as well as in the inflammatory type.. (Zachary Rotter was supported by Huntington Breast Cancer Action Coalition fellowship, Huntington, NY, and this work was supported by NCI and NIEHS Grant UO1 ES012The Effect of Pre-pubertal 2,3,7,8-tetrachlorodibenzo-p-dioxin Exposure on

Terminal End Bud Differentiation and Genetic Expression in Rat Mammary Glands

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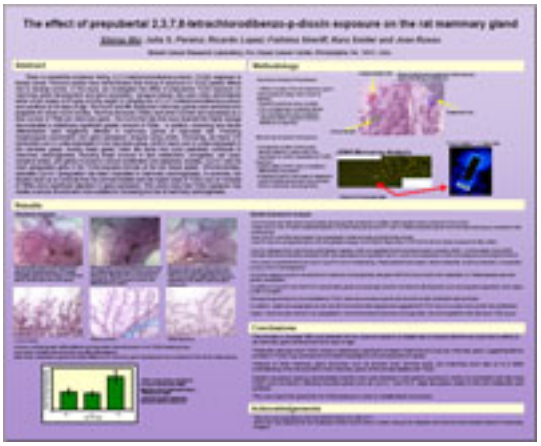

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Substantive evidence linking 2,3,7,8-tetracholorodibenzo-p-dioxin (TCDD) exposure to breast cancer risk has predominantly been on the cellular and histological level, due to conflicting and variable-prone epidemiological data. Previous studies have also demonstrated that timing of exposure to TCDD greatly affects risk tumorigenesis. In this study, we investigated the effect of prepubertal TCDD exposure on mammary gland development and genetic expression. Sprague-Dawley rats were orally administered either of two doses (6.67ng/kg of body weight or 20ng/kg bw) of 2,3,7,8-tetracholorodibenzo-p-dioxin and sacrificed at 50 days of age. 4,5 abdominal mammary glands were extracted and prepared with the whole mount technique. Terminal end buds (TEBs) were then counted per tissue sample. We found that rats administered the higher dosage demonstrated a statistically significant greater amount of TEBs. Observations showed that in addition to the TEB count, branching and differentiation were negatively affected in mammary glands of high-dose rats, although no quantitative analysis was conducted. Following morphological examination, gene expression analysis via a microarray found 472 probes over or under-expressed in the high-dose cohort while 8, were over or under-expressed in the low-dose cohort. Among these genes, there are numerous genes that could potentially contribute to mammary carcinogenesis, including ones involving lipid metabolism, known oncogenes, genes involved in the reproductive cycle, genes that could potentially create an environment ill-suited to react to oxidative stress, and genes involved in cellular proliferation and apoptosis. Of these genes, Cyp1b1 was the most upregulated gene in both groups. Environmentally activated Cyp1b1 upregulation has been implicated in mammary carcinogenesis. We observed that the rats treated with the higher dose of TCDD had an increase of TEBs and greatly affected gene expression in the mammary gland. This could imply that TCDD exposure may create environments more suitable for the development of cancer,

increasing the risk for mammary carcinogenesis. (Shirou Wu was supported by Huntington Breast Cancer Action Coalition fellowship and this work was supported by NCI and NIEHS Grant UO1 ES012771)

The effect of prepubertal 2,3,7,8-tetrachlorodibenzo-p-dioxin exposure on the rat mammary gland.

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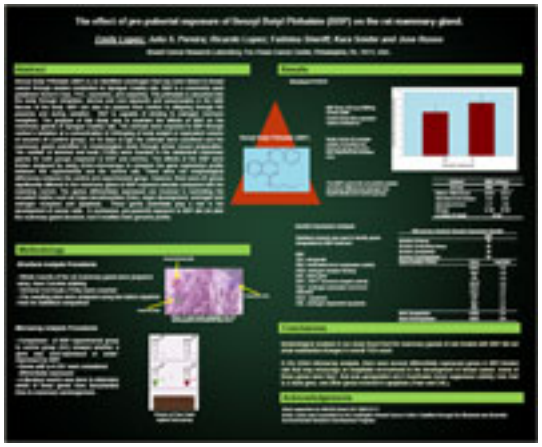

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Benzyl Butyl Phthalate (BBP) is an identified carcinogen that has been linked to breast cancer through studies conducted on Sprague Dawley rats. BBP is a commonly used plasticizer found in toys, PVC, cosmetics, and carpeting. This phthalate is absorbed into the body through inhalation, dermal and oral exposure and accumulates in the fatty tissues of the body. BBP can also be passed from mother to offspring through the placenta and during lactation. BBP is capable of binding to estrogen hormone receptors. The purpose of this study was to examine the effects of BBP on the mammary glands of Sprague Dawley rats. The animals were exposed to BBP through mother's lactation at a concentration of 500µg/kg of body weight or equivalent volume of sesame oil (control group). At 50 days of age the animals were sacrificed and the mammary gland submitted to morphological study through whole mount preparation. The number of terminal end buds (TEBs) was counted in the abdominal mammary glands for both groups (exposed to BBP and control). The effects of the BBP were further analyzed by using cDNA-microarrays to compare the gene expression profile between the experimental and the

control rats. There were not morphological differences between the control and experimental group. However, there were 80 genes significantly different in the mammary gland of BBP exposed animals compared with the matching control. The genes differentially expressed are involved in controlling the circadian rhythm such as Dopa decarboxylase (Ddc), organ development, androgen and estrogen receptors and apoptosis. These genes potentially play a role in the development of cancer cells. In conclusion, pre-pubertal exposure to BBP did not alter the mammary gland structure, but it modifies their genomic profile (*Emily Lopes was supported by the Huntington Breast Cancer Action Coalition through the Students and Scientist Environmental Research Scholarship Program. This work was supported by NCI and NIEHS Grant UO1 ES012771)

The effect of pre-pubertal exposure of Benzyl Butyl Phthalate (BBP) on the rat mammary gland.

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