

Changes in Tumor Suppressor and Oncogene Expression Induced in the Mammary Gland of Animals Exposed to BPA, BBP, and TCDD at different developmental stages.

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Xenobiotics, such as Bisphenol A (BPA), n-benzyl butyl phthalate (BBP) and 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD), are endocrine disruptors that can affect the susceptibility of the mammary gland to carcinogenesis. This study investigates whether exposure to these compounds at different stages (prenatal, prepubertal) and dose levels (low, high), affects the gene expression profile of oncogenes and tumor suppressor genes in the rat mammary gland at different ages. To examine the significance of biological functions represented by the genes differentially expressed between exposed and non-exposed rat mammary glands at 21, 35, 50 and 100 days we used GO annotations, that describe groups of genes in terms of their associated biological processes. Through GOSTATS tool provided by Bioconductor, conditional hypergeometric test statistics were performed to evaluate the overrepresentation of GO terms among differentially expressed genes. No significant overlap of enriched GOs among these xenoestrogenic compounds was found. For further analyses, GO terms were combined according to their commonality of biological functions in a variety of groups related to oncogenes and tumor suppressor genes. A list of 327 known and novel oncogenes was annotated using GeneRIF information from Gene Database of NCBI. A similar list of over 550 tumor suppressor genes was annotated. Rat homologues were taken and viewed as heat maps with TCDD having the largest effect on the expression of tumor suppressor genes.

Prenatal exposure to TCDD induced the highest amount of down-regulated and up-regulated genes at 100 days of age; whereas there were no changes in gene expression at 21 days of age. Neither BPA nor BBP treatments resulted in changes in gene expression at 100 days. However, both BBP and BPA showed the highest change in gene expression at 35 and 50 days for both oncogenes and tumor suppressor genes.

Conclusions: The effects observed are not only compound-dependent but also specific to the stage of life when the animal received the treatment, the dose administered, and the age when the animals were studied. Little overlap of GOs was observed for the three compounds, emphasizing that each compound induces a specific genomic signature.

Our data strongly indicate that each xenobiotic agent induces a set of specific changes in the mammary gland that may lead to different biological responses.

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