



## ENDOCRINE DISRUPTING EFFECTS OF BUTYLPARABEN: A REVIEW

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### ABSTRACT

In recent years, there has been an increasing concern in the field of endocrine disruption over the presence of various endocrine disrupting chemicals in Pharmaceuticals and Personal care products (PPCPs). This concern has also been as PPCPs are most widely used and had led to introduction of thousands of new and complex chemicals that enter the environment in large quantities. The effect of the chemicals has not only been restricted to human who are exposed directly to the chemicals or the animals which gets exposed to the chemicals through wide variety of veterinary drugs, but also the aquatic organisms and other form of Wildlife which are non target and indirectly gets exposed to the chemicals through individual human activity. Parabens includes a group of compound of which methylparaben, butylparaben, ethylparaben, propylparaben are most widely used as preservatives in various PPCPs. Recent concern over the use of parabens has been drawn by the scientific community as these chemicals are reported to exert a weak estrogenic activity, with butylparaben showing the most potent activity among methyl-, ethyl- and propyl esters in *in vitro* recombinant yeast assay and in *in vivo* uterotrophic assay. Human exposure to butylparaben which occur mainly through inhalation, ingestion, or eye or skin contact, from intake of foods or drugs or use of cosmetics and personal care products where butylparaben is mainly used as a preservative. Effects of butylparaben are studied in various animal model systems like rodents to determine the possible effects in human which showed various effects which include defects in male reproductive system like increase in weight of epididymis, also change in serum testosterone level and a significant increase in uterine weight in ovariectomized and immature rats. Other effects include irritation to the respiratory tract, allergic skin reactions, atrophy of lymphoid tissue in the spleen, thymus, and lymph nodes and multifocal degeneration and necrosis in the liver parenchyma were also observed. The aquatic effects of butylparaben include the feminization of male fish and alteration of the behaviors of either sex at part-per-trillion concentrations. A multitude of other aquatic effects are possible because hormone systems are central to the development, functioning, and reproduction of most organisms.

**Keywords:** Butylparaben, PPCP, endocrine disruption.

### INTRODUCTION

Alkyl esters of p- hydroxy benzoic acid are commonly used as antimicrobial preservatives in cosmetics, pharmaceuticals, and food <sup>1,5</sup>. Parabens include a group of synthetic chemicals that are considered safe and have led to their extensive use in many PPCPs due to their heat stability and antimicrobial activity. It is found that repeated contact with products or foods containing parabens leads to widespread human exposure through ingestion, inhalation, or dermal contact. Methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), and butyl paraben (BP) are the most widely used parabens of which butylparaben is of growing concern as recent studies have revealed in *in vitro* and *in vivo* models that BP mimics estrogen activity, thereby acting as a potential xenoestrogen. Studies showed that BP exerts reproductive, developmental as well as teratogenic toxicity in experimental animals <sup>2</sup>.

Butylparaben is widely used by manufacturing companies for its low cost and efficiency as a microbial agent. Butylparaben is a very popular preservative because of its ability to inhibit DNA and RNA synthesis like ATPase and phosphotransferase in some bacterial species and disrupt their membrane transport proteins. It is used in various cosmetics as a preservative like eye care make up products, sunscreen, facial products and skin anti aging products. Butylparaben have been of recent concern because of its existence in low concentration in breast tumors <sup>5</sup>.

#### Endocrine disruption by butylparaben:

Butylparaben acts as potential endocrine disruptors which are chemicals present in the environment and is of great scientific concern because of their possible health threats to human by interfering with the endocrine system of human either by interfering with the functions of natural hormones of the body and thereby elicit a wide range of disorder including reproductive disorder, cardiovascular disorders and

mutagenicity. Butylparaben not only affect human but escape to the environment affecting non target organisms which includes various wildlife species and aquatic organisms <sup>3,6</sup>.

Butylparaben binds with low affinity to estrogen receptors and regulate estrogen responsive reporter gene expression in experimental cell system. Parabens were found to possess weak estrogen receptor activity *Saccharomyces cerevisiae* based Lac-Z reporter assay. In a yeast two-hybrid assay using the ER  $\alpha$ -TIF system, methylparaben, ethylparaben, propylparaben and butylparaben were positive for estrogen activity.

#### Effect of butylparaben in male reproductive system in mammal:

Various studies of different doses of butylparaben in different mammalian model system including rat and mice have revealed adverse effects of butylparaben on male reproductive system which includes degeneration of increase in relative weight of epididymis, decrease in sperm count and quality of sperm and decrease in level of male hormone testosterone <sup>1</sup>.

a) Oishi (2001) in his study in 3-weekold Wistar rats, butylparaben was administered at doses of 0.00%, 0.01%, 0.10% and 1.00% with the animal's diet which revealed decrease in absolute and relative weights of epididymides in a dose-dependent manner, decrease in cauda epididymal sperm reserve of all treated groups was significantly decreased. The daily sperm production (DSP) in the testis was also significantly lower in all treated groups and serum testosterone concentration was lowered dose-dependently and was significant at 0.1% or more.

b) Oishi, 2002a and Oishi, 2002b reported a decline in sperm counts of male CD-mice as a result of 0.01% n-butyl- or n-propyl-paraben in the diet.

c) Reproductive studies in mice and rats have shown that maternal exposure to butylparaben in diet results in adverse effects on male reproductive system of F<sub>1</sub> offspring. Effects of butylparaben on male reproductive system of rats and mice have shown increasing concern in the scientific community over the human exposure of butylparaben.

**Effect of butylparaben in female reproductive system and in mammary gland in mammal:**

a) Lemini et al. reported substantially increased uterine mass in ovariectomized adult CD-1 mice at doses of 21, 70, and 210 mg/kg butylparaben.

b) Butylparaben is found to show increase proliferation of estrogen dependent

MCF-7 human breast cancer cells (Darbre, 2001). Parabens induce proliferation of MCF-7 cell; a human breast cancer derived cell line although potency 5 to 6 orders of magnitude below that of 17  $\beta$  Estradiol. (Van Meeument et al, 2008)

**Effect of butylparaben on thyroid gland:**

Butylparaben is considered a potential weak thyroid receptor agonist based upon increased cell proliferation at 3  $\mu$ M. The effect was slightly more pronounced in the presence of triiodothyronine (T<sub>3</sub>).

**Developmental defects caused by exposure of butylparaben:**

Subcutaneous administration of butylparaben (100 – 200 mg/kg body weight) in pregnant rats from gestation day 6 to postnatal day 20 is found to decrease the proportion of pups born alive and the proportion of pups that survived upto the weaning period. (Kang et al., 2002)

**Endocrine disruption of butylparaben in fish:**

In juvenile rainbow trout (*Oncorhynchus mykiss*) butylparaben was found to induce yolk protein, vitellogenin thus testing positive for estrogenic activity.

Other study on butylparaben in mice after chronic oral feeding is found to exhibit high incidence of amyloidosis affecting spleen, liver, kidney and adrenal gland. Butylparaben strongly inhibited thromboxane (TXB<sub>2</sub>) synthesis irreversibly in vitro and inhibited platelets function.

**CONCLUSION:**

Many people are unaware of health and environmental concern has emerged among scientists around the world because of the wide use of butylparaben in the environment. Understanding these topics is essential for educating the public and medical professionals about potential risks associated with exposure of endocrine disruptors.

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