doi: <https://doi.org/10.20546/ijcrar.2024.1212.009>

Parabens' Impact on Human Health: Endocrine Disruption, Reproductive Effects, and Carcinogenic Potential

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Abstract

Parabens, esters of p-hydroxybenzoic acid, are widely used as preservatives in cosmetics, pharmaceuticals, and food products. Their extensive use has led to the detection of parabens in various environmental and biological samples, with concentrations in human urine as high as 227 ng/mL, particularly in regions like South Korea. Evidence suggests that parabens exhibit estrogenic activity, contributing to endocrine disruption, with adverse effects on reproductive health, early puberty onset, and increased breast cancer risk. Research has found that parabens, particularly propyl- and butylparaben, can interfere with hormone regulation, reduce sperm production, and decrease testosterone levels in animal models. Furthermore, parabens have been detected in breast tissue and are associated with tumor progression in breast cancer cells. Although regulatory bodies, such as the European Union, have established limits (0.4% for a single paraben and 0.8% for combined parabens in cosmetics), there is no globally accepted exposure threshold. The potential cumulative exposure due to their widespread presence highlights the need for clearer safety guidelines and further research on the long-term health impacts of parabens, particularly in vulnerable populations.

Article Info

Received: 20 October 2024

Accepted: 24 November 2024

Available Online: 20 December 2024

Keywords

Parabens, Endocrine Disrupters, Breast Cancer, Reproductive impact of Paraben.

Introduction

In recent years, the safety of parabens has been a subject of concern. Denmark has raised alarms about the potential endocrine-disrupting effects of parabens at high exposure levels. Studies on young male rats have shown that oral exposure to propyl- and butylparaben can lead to adverse effects on sperm production and testosterone levels, prompting the formation of a committee under the List of Undesirable Substances (LOUS, 2003). Currently, parabens are classified as endocrine disruptors, which have been shown to have genotoxic and cytotoxic effects, (Güzel and Tüylü, 2019; Roszak *et al.*, 2020), impacting various internal organs and systems, including

the reproductive, immune, and endocrine systems (Chiara *et al.*, 1994; Jordan and deCatanzaro, 2009; Karolina, 2019). Some studies have also linked parabens to obesity, neurological disorders, developmental disorders, and neoplastic processes (Lucie *et al.*, 2018; Jiang *et al.*, 2018; Amelia *et al.*, 2013; Roje *et al.*, 2013). Due to these adverse effects, many countries have implemented legislation to limit the use of parabens. In the EU, for example, the permitted content of parabens in cosmetics is capped at 0.4% for a single paraben and 0.8% for all parabens combined (P82, 2010)

Parabens, esters of p-hydroxybenzoic acid, are widely used as preservatives in various industries, including

cosmetics, food packaging, and pharmaceuticals (Tahir and Saad, 2021). Propylparaben, a member of the paraben family, is valued for its effective antimicrobial properties and ability to extend product shelf life. In the cosmetics and personal care sector, propylparaben is a common ingredient in moisturizers, shampoos, conditioners, makeup, and skincare products, preventing microbial growth and maintaining product integrity. Similarly, in pharmaceuticals, propylparaben is used as a preservative in topical creams, ointments, solutions, and oral medications. In some regions, propylparaben is also approved as a food additive, used to preserve processed foods, baked goods, beverages, and condiments. The most commonly used parabens in cosmetics are methylparaben, ethylparaben, propylparaben, and butylparaben. Parabens are ubiquitous in our environment, found in water, soil, animals, and humans. (Lincho *et al.*, 2021) Research has shown that increasing the length of the alkyl chain in parabens enhances their antimicrobial activity, although this comes at the cost of reduced water solubility (Piao *et al.*, 2014).

Presence Reported

Parabens have been detected in various environmental and biological samples, with significant concentrations reported in different regions. In Asian ecological water samples, high levels of parabens have been found, ranging from 55.9 ng/mL for methylparaben to 69.9 ng/mL for propylparaben (Unuabonah *et al.*, 2021). Similarly, in the United States, the Centers for Disease Control and Prevention (CDC) reported urinary paraben concentrations in the general population, with geometric mean values of 48.1 µg/L for methylparaben and 5.74 µg/L for propylparaben in 2013-2014. Processed products have also been found to contain parabens at concentrations between 450 and 2000 mg/kg (Honda *et al.*, 2018; Ocaña-González *et al.*, 2015)

A recent study in China by Mao *et al.*, (2024) detected methylparaben and propylparaben in human serum and whole blood, with mean concentrations of 2.3 and 2.1 ng/mL in serum, and 1.9 and 1.3 ng/mL in whole blood, respectively. The study also found significant correlations between serum and whole-blood paraben concentrations (Mao *et al.*, 2024). The widespread presence of parabens in various matrices has raised concerns about their potential impact on human health and the environment.

The global paraben market size was valued at \$91.1 million in 2021 and is expected to reach \$164 million by

2031, growing at a CAGR of 5.5%. The demand for propylparaben alone is substantial, with a consumption of 110k tonnes in 2021, projected to grow at a CAGR of 3.2% (A17414, 2022).

The increasing use of parabens in various industries has led to their ubiquitous presence in the environment, highlighting the need for ongoing monitoring and assessment of their potential risks. (ACHEMANALYST, 2024)

Physiological Fate of Parabens

The distribution of parabens and 4-HB in human blood has been investigated, revealing a pattern of partitioning between human serum and whole blood (Kp). The mean Kp values of parabens, except benzylparaben (BzP), increase with the alkyl chain length, ranging from 0.83 to 1.6. BzP and propylparaben (PrP) have comparable mean Kp values of 1.4, while 4-HB has the lowest mean Kp value of 0.75 (Mi-Yeon *et al.*, 2019). These findings are crucial for selecting the appropriate blood matrix for assessing human exposure and conducting epidemiological studies on parabens.

Previous studies have shown that oral administration of parabens leads to their excretion in urine, primarily as hydroxybenzoic acid, glycine conjugates, and glucuronide conjugates. However, the extent of excretion varies inversely with the length of the alkyl chain. For instance, after 24 hours, 25-39% of methylparaben is excreted as p-hydroxybenzoic acid, while 25-29% is excreted as the glycine conjugate (Tsukamoto and Terada, 1960; Tsukamoto and Terada, 1962). In contrast, the excretion of butylparaben is significantly lower, ranging from 40-48% (Hu *et al.*, 2015)

Animal studies have also investigated the fate of parabens following intravenous injection. These studies have shown that parabens are rapidly metabolized, with low levels detected in blood, while p-hydroxybenzoic acid is detected in various tissues, including the brain, spleen, pancreas, liver, and kidney. The recovery of parabens from these tissues varies between 58% and 94%, except for butylparaben, which is recovered at a lower rate of 40-48% (Soni *et al.*, 2005; Lincho *et al.*, 2021; Thigpen *et al.*, 1956).

Overall, these findings suggest that parabens are extensively metabolized and excreted in urine, with the extent of excretion dependent on the length of the alkyl chain. The results also imply that skin care products may

lead to higher levels of parabens in the body compared to oral administration, highlighting the need for further investigation into the safety of paraben use in personal care products.

Regulatory Status of Parabens

There is no uniform global regulation regarding parabens in products, with different countries having varying guidelines and restrictions. The European Union bans 8 types of parabens in cosmetic products, while the United States allows parabens in limited amounts in cosmetics, with the FDA regulating their concentrations. Canada bans 3 types of parabens but allows others with restrictions. Asian countries like Japan have placed restrictions on certain parabens in cosmetics. Germany has stricter guidelines, prohibiting the combination of parabens from exceeding 0.2% per item. However, France requires labeling and warnings for products containing parabens (Fransway *et al.*, 2019; Błędzka *et al.*, 2014)

Parabens have received approval from various regulatory bodies, including the FDA, JECFA, and FEMA, for use in food, cosmetics, and pharmaceuticals. JECFA has established an acceptable daily intake (ADI) of 0-10 mg/kg body weight (bw) for parabens. The average daily intake of methylparaben, a commonly used paraben, is reported to be 0.22 mg (Seetaramaiah *et al.*, 2011). In cosmetics, parabens are permitted up to a concentration of 0.8% by the Danish and European Economic Community (EEC) regulations (EU regulations: Parabens, 2023).

However, some parabens have faced regulatory restrictions in recent years. In 2015, the European Union banned the use of isopropyl paraben and isobutyl paraben in personal care products, pending further research. The Association of Southeast Asian Nations (ASEAN) has also implemented similar restrictions (Table-1).

According to a study published by Gálvez-Ontiveros *et al.*, (2021), a significant proportion of parabens were detected in various food categories, with surprisingly high levels found in Non/minimally processed foods, Processed foods, and Ultra-processed foods. The research suggests that parabens are more widespread in the food supply than previously thought, with significant amounts present in foods that are not typically considered processed (Ontiveros *et al.*, 2021).

Parabens' Impact on Human Health: A Growing Concern

Since the turn of the century, parabens have faced scrutiny due to their potential health impacts. Despite their widespread use, research has detected parabens in various environments, including drinking water and soil, raising concerns about cumulative exposure. As the market for parabens continues to grow, it is essential to separate fact from fiction and understand the potential health risks associated with their use. Research has linked excessive paraben exposure to various health issues, particularly through skincare products. Various side effects reported so far include endocrine disruption, neurological developmental disorders, carcinogenicity, reproductive disorders, and increased oxidative stress.

These findings highlight the need for a comprehensive understanding of paraben's health impacts, beyond the controversy surrounding their use. With their ubiquitous presence in the environment and consumer products, it is crucial to address the potential long-term consequences of paraben exposure on human health.

Endocrine Disruption

The potential for parabens to interfere with endocrine function has been a debatable topic. However, a thorough examination of the available literature suggests that the claims of endocrine disruption are substantiated. Parabens are classified as endocrine-disrupting chemicals (EDCs), capable of influencing the hypothalamic-pituitary-thyroid (HPT) axis, which regulates thyroid hormone (TH) biosynthesis (Azeredo *et al.*, 2023; Boberg *et al.*, 2016; Biro *et al.*, 2012).

A recent review comprehensively analyzed the existing data and found that all commonly used parabens exhibit estrogenic activity to varying degrees in both *in vitro* and *in vivo* assays (Boberg *et al.*, 2010). Notably, only one out of 25 *in vitro* studies reported negative findings in estrogenicity assays, suggesting a significant body of evidence supporting the estrogenic properties of parabens (Darbre and Harvey, 2008; Parker *et al.*, 1998). Furthermore, the estrogenic activity of parabens has been shown to increase with the length and branching of the alkyl chain (Darbre *et al.*, 2002; Pugazhendhi *et al.*, 2005; Hager *et al.*, 2022). Additionally, p-hydroxybenzoic acid (PHBA) has been found to possess estrogenic activity in both *in vitro* and *in vivo* assays (Okubo *et al.*, 2001; Routledge *et al.*, 2002).

Recent studies have investigated the potential endocrine-disrupting effects of parabens, with findings suggesting that they can mimic endogenous hormones and interact with signal transduction pathways, including HER2, to modulate local estrogen metabolism (Hager *et al.*, 2022; Vo *et al.*, 2010). *In vitro* protein assays have demonstrated that propylparaben (PrP) and butylparaben (BuP) can bind to estrogen receptors (ERs), potentially disrupting steroid hormone synthesis and secretion (Liang *et al.*, 2023). This raises concerns about the environmental and human health impacts of parabens, particularly in childhood, where the estrogenic burden of parabens and their metabolites may exceed that of endogenous estradiol.

Moreover, exposure to parabens has been linked to shorter menstrual cycle length in females ($p < 0.05$), suggesting a potential impact on reproductive health (Zhang *et al.*, 2023; Nishihama *et al.*, 2016). The endocrine-disrupting abilities of parabens may also affect humans during vulnerable developmental periods (Jensen *et al.*, 2021). However, conflicting findings have also been reported, highlighting the need for further research to understand the effects of parabens on human health fully. Interestingly, long-chain parabens appear to be more toxic than short-chain esters and p-hydroxybenzoic acid (PBHA), which may be related to differences in metabolism (Jensen *et al.*, 2021).

Research suggests that exposure to parabens, may contribute to the trend of earlier thelarche (breast development) and potentially impact fertility and reproductive health (Nishihama *et al.*, 2016; Gore *et al.*, 2015). Studies have consistently shown a decline in the age of thelarche over the past several decades, with a mean decrease of almost 3 months per decade from 1977 to 2013 and 1940 to 1994 (Biro *et al.*, 2005; Eckert-Lind *et al.*, 2020).

While the exact causes of this trend are not fully understood, evidence suggests that exposure to EDCs, including parabens, may play a role in altering puberty timing (Harley *et al.*, 2019; Lee *et al.*, 2019; Jensen *et al.*, 2021; Petca *et al.*, 2019). An evaluation of human and animal studies indicates that EDCs and body fat are significant factors associated with changes in puberty timing (Braun *et al.*, 2017; Teitelbaum *et al.*, 2012). Furthermore, research has linked urinary parabens to poor sperm quality, including reduced motility, morphology, and volume (Okonofua *et al.*, 2019). Additionally, studies have consistently shown that parabens and their metabolites can induce uterotrophic

effects, indicating estrogenic activity (Christiansen and Taxvig, 2010; Engeli *et al.*, 2017; Lemini *et al.*, 1997; Mitra *et al.*, 2021; Lemini *et al.*, 2004).

Obesity

Research suggests a potential correlation between paraben exposure and an increased risk of obesity, mediated by their estrogen-mimicking properties and subsequent endocrine-disrupting effects. Studies have consistently shown associations between paraben exposure and various anthropometric and physiological markers of obesity, including elevated body mass index (BMI) (Deierlein *et al.*, 2017; Quirós-Alcalá *et al.*, 2019), increased waist circumference (Xu *et al.*, 2022), higher leptin levels, a hormone regulating energy balance, and body weight (Kolatorova *et al.*, 2018; Kim and Chevrier, 2020). Furthermore, maternal paraben exposure has been linked to an increased risk of childhood overweight development, potentially via altered neuronal appetite regulation mediated by Pro-opiomelanocortin (POMC) (Leppert *et al.*, 2020). This effect is accompanied by epigenetic modifications in the neuronal POMC enhancer-1, leading to reduced hypothalamic POMC expression. While the current evidence base comprises animal studies and observational human research, these findings suggest a plausible link between paraben exposure and obesity.

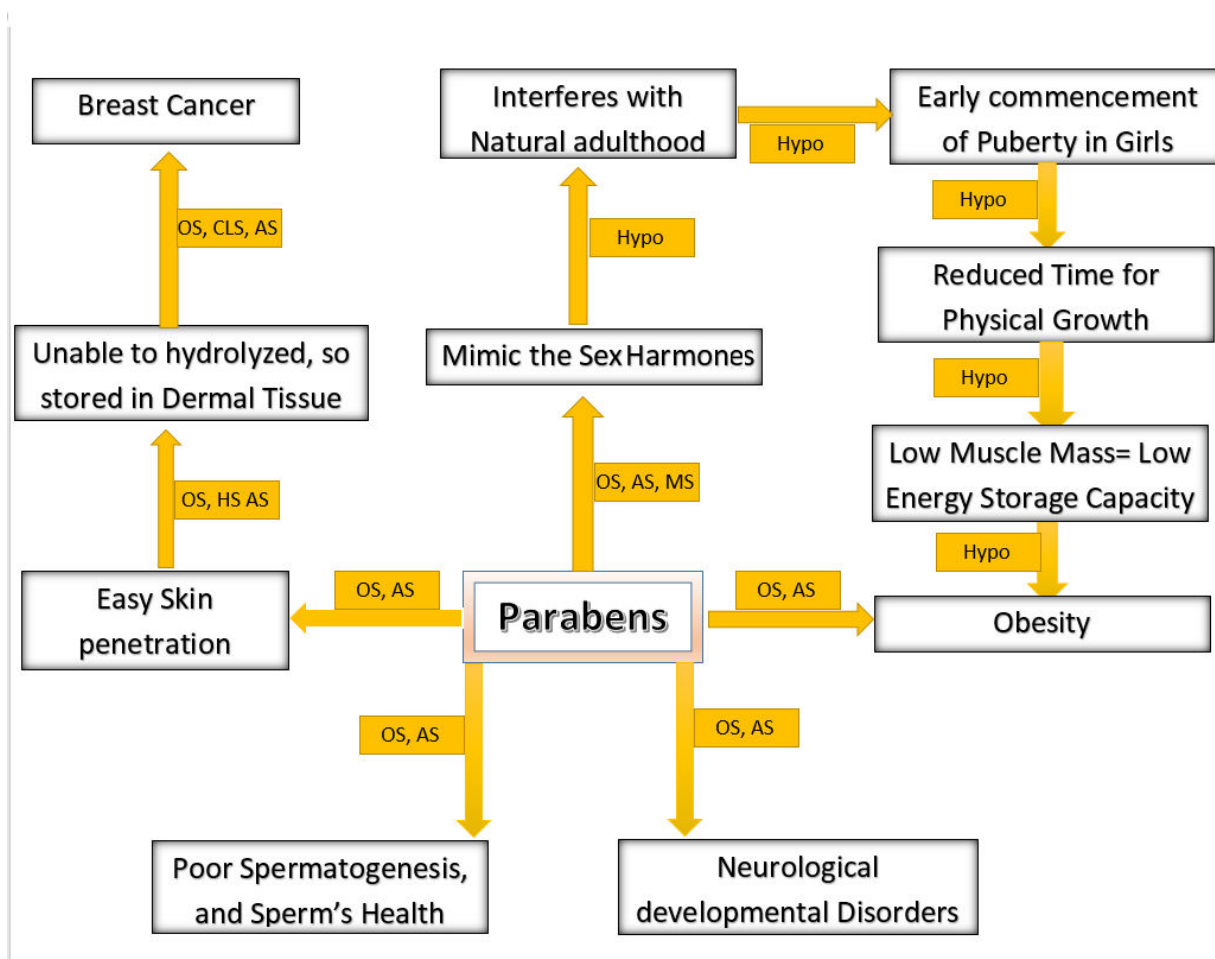
Carcinogenicity

Accumulating evidence suggests a potential link between paraben exposure and breast cancer development. The high presence of parabens in breast tissues and their estrogen-mimicking properties raise concerns about their impact on breast tissue development during puberty. Parabens may influence breast tissue development through two primary mechanisms: (1) promoting the proliferation of breast stromal cells and (2) epigenetic modifications (Pugazhendhi *et al.*, 2020; Tapia *et al.*, 2023). Research has shown that parabens can induce hallmarks of cancer in human breast epithelial cells, even at regulatory exposure levels (Drabre and Harvey, 2014; Zhang *et al.*, 2019). Moreover, combinations of parabens at concentrations measured in human breast tissue can increase the proliferation of MCF-7 human breast cancer cells (Amelia *et al.*, 2013; Peinado *et al.*, 2013; Wróbel and Gregoraszcuk, 2014). *In vitro* studies have also demonstrated that parabens can enhance migratory and invasive properties of human breast cancer cells, suggesting a potential role in cancer progression (Zhang *et al.*, 2019).

Table.1 Frequencies (%) and mean (ng g⁻¹) of parabens vs FEMA use levels for parabens in Food category Usual use level [O,O]

		Reported					Recommended					
							Usual Level			Maximum Level		
		MetPB	EthPB	ButPB	PropPB	∑PBs	MetPB	PropPB	∑PBs	MetPB	PropPB	∑PBs
Unprocessed or Minimally Processed Foods (n = 32)	Frequency (%)	70	23.3	3.3	10	73.3						
	Mean (ng g ⁻¹)	106.90 (95.37)	29.54 (40.06)	2.5 (1.0)	34.95 (48.0)	80.7 (81.56)	-	-	-	-	-	-
Processed Foods (n = 21)	Frequency (%)	42.86	23.81	9.52	4.76	52						
	Mean (ng g ⁻¹)	142.05 (120.2)	60.28 (56.2)	55.35 (42.2)	65.5 (26.2)	130.7 (87.3)	0-0.99	0.06-0.97	0.06-1.96	0.01-0.99	0.02-0.97	0.01-1.96
Ultra-Processed Foods (n = 47)	Frequency (%)	38.3	6.38	10.64	12.77	49						
	Mean (ng g ⁻¹)	41.75 (47.18)	28.6 (12.0)	39.87 (60.07)	3.15 (2.0)	40.31 (48.46)	0.0-0.5	0.0-0.25	0.0-0.5	0.0-0.5	0.025-0.02	0.00-0.045
All (n = 100)	Frequency (%)	49	15	8.1	10.2	57.14						
	Mean (ng g ⁻¹)	84.6 (88.5)	42.19 (44.71)	39.07 (50.83)	21.1 (31.5)	73.86 (76.76)						

Figure.1



Furthermore, parabens have been shown to exhibit estrogenic activity in human breast cancer cell lines, with p-hydroxybenzoic acid (PHBA) displacing estradiol from the cytosolic estrogen receptor in MCF7 cells (Wróbel and Gregoraszczyk, 2015). Exposure to EDCs like parabens during puberty has been linked to an increased risk of developing breast cancer later in life (Braun *et al.*, 2017; Lucaccioni *et al.*, 2020).

Conclusion

Looking at prescribed guidelines and overall amounts observed in the products, animal tissue, water bodies, and soil, clearly explains the various side effects reported in the recent past.

The findings collectively suggest that parabens can potentially disrupt normal endocrine function, particularly in the context of thyroid hormone regulation and estrogenic activity. As such, it is essential to

consider the potential endocrine-disrupting effects of parabens in evaluating their overall safety and health impacts. The evidence suggests that paraben exposure may contribute to changes in puberty timing and potentially impact reproductive health, highlighting the need for further research and consideration of the potential health impacts of these ubiquitous chemicals. A few studies have suggested the link between parabens exposure and obesity in kids.

Further investigation is warranted to elucidate the underlying mechanisms and establish a definitive causal relationship between paraben exposure and obesity. Reports also suggest that paraben exposure may contribute to breast cancer development and progression, highlighting the need for further research into the potential health impacts of these ubiquitous chemicals. Nonetheless, the available pieces of evidence are enough to advocate a need for revised guidelines, especially for the products, which are used by kids.

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How to cite this article:

Alok Tripathi. 2024. Parabens' Impact on Human Health: Endocrine Disruption, Reproductive Effects, and Carcinogenic Potential. *Int.J.Curr.Res.Aca.Rev.* 12(12), 70-79. doi: <https://doi.org/10.20546/ijcrar.2024.1212.09>