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Toxic Effects of Paraben and its Relevance in Cosmetics: A Review

Pierce Adrianne A. Alaba, Edjay D. Cañete, Bin Salih S. Pantalan, Joanna Marie C. Taguba, Lovely Dianne I. Yu, Erwin M. Faller

Pharmacy Department, San Pedro College, Davao City, Philippines

ABSTRACT

Parabens can be found in a wide variety of products, depending on the range, including cosmetics. Because of its extensive application as a preservative in skin care and beauty products. Parabens' odorless, colorless, tasteless, and hygroscopic tiny crystals/powders quality make them freely soluble in propylene glycol, alcohol, glycerin, and ether, whereas in water, it is almost insoluble or very slightly soluble in nature. Integrating the use of paraben as a preservative fosters an implication of its antimicrobial property, delivering the needed optimal and maximum effect in the production setting. However, the benefit of paraben also undermines its side effects and toxic effects in the human body. This article provides insight on paraben's relevance in the cosmetic and beauty industry, highlights how paraben works as a preservative, explains its side effects and its toxic effects in the human body.

Keywords: Parabens, toxicology, cosmetics, preservatives

INTRODUCTION

Synthetic preservatives known as parabens are widely utilized in beauty products, pharmaceuticals, and food sectors (US FDA, 2022). Parabens have been extensively employed as a go-to preservative in a variety of items since the 1950s. These have been employed by the skincare and cosmetics industries because they are affordable and effective. By the 1990s, parabens had been labeled as xenoestrogens. These are substances that act like hormones in the body, causing estrogen disruption. When you use cosmetics that include these ingredients, they will surely absorb into your skin, sending estrogen into your body unintentionally. This might expose people to specific health concerns over time (Aker, et.al, 2016). Their primary goal is to preserve the microbiological purity of chosen items, such as cosmetics, medications, and food, in order to extend their shelf life.

Parabens prevent items against degradation and microbes, increasing their shelf life by many months without affecting their composition or functionality. Parabens have little effect on the scent, taste, density, or other properties of cosmetics or food. However, parabens, which are included in most creamy or liquid cosmetics (facial creams, moisturizers, foundation, tinctures, balms, antiperspirants, and fragrances), are becoming more problematic due to a lengthy list of potential negative effects (US FDA, 2022). Parabens are made from para-hydroxybenzoic acid (PHBA), which may be found in a variety of natural plants (Cherian, et.al, 2020). In reality, parabens are a group of several compounds that have a common molecular structure. Ethylparaben, butylparaben, isobutylparaben, isopropylparaben, methylparaben, and propylparaben are all often found in cosmetics and personal care products (Reeder & Atwater, 2019). Parabens have been a controversial issue after they were discovered in the cells of breast cancer patients, their usage became very contentious. Parabens were discovered to have an effect on hormone function in early studies. Cholesterol, blood sugar, thyroid, and immunological function may all be affected. The usage of parabens has also been linked to allergies, obesity, and infertility (Barabasz, et.al, 2019). The FDA declared that the use of methyl- and propyl parabens in foods and beverages up to 0.1 % was safe (Becker & Heldreth, 2018). Parabens are found in cosmetics in amounts ranging from 0.01 to 0.3%. These chemicals are safe in levels up to 25%, according to the CIR (Becker, 2022).

METHODS

The review about parabens was from data gathered from journal databases and from publicly available sources like PubMed, Google Scholar, Research Gate, Sciencedirect, Elsevier, FDA news sites, MDPI and Open access journals. Articles that were deemed relevant to the topic and are timely published were included in this review. There were no requirements for article format. As a result, any relevant literature was evaluated, including research on clinical trials, thorough reviews, editorial articles, and news coinciding with the central theme of the study.

Physical and Chemical Properties

Parabens are odorless, colorless, tasteless, and hygroscopic tiny crystals/powders. These compounds are freely soluble in propylene glycol, alcohol, glycerin, and ether, whereas in water, it is almost insoluble or very slightly soluble. Water solubility diminishes as the length of the alkyl chain lengthens. Parabens also have high oil in water partition coefficient. They are relatively resistant to saponification and are stable in hydrolysis when autoclaving (Cherian,*et.al,* 2020).

The kind of alkyl group distinguishes the parabens, affecting their water solubility and antibacterial effectiveness. The antibacterial efficacy of parabens increases as the alkyl chain length increases, but in turn diminishes its water solubility (Lincho, et.al, 2021). They are chemically stable lipophilic compounds with poor to extremely weak water solubility depending on chain length (Wzorek & Nowak, 2019). Moreover, parabens are intriguing substances because they are inert, possess low frequency of sensitization, stability and capacity to not change product consistency or color, no odor or taste, and their water solubility, which is adequate enough to create solutions (Lincho, *et.al*, 2021). Because they do not change product consistency, the characteristics of foods and cosmetics including its smell and density remains unchanged too.

Table 1. General Physicochemical Properties of Parabens (Wzorek & Nowak, 2019)

Property	Methyl	Ethyl	Propyl	Butyl
1	2	3	4	5
Molecular weight	152.16	166.18	180.21	194.23
Melting point (T)	131 125–128	116–18 115–118	96.2–98 95–98	8–69 68–72
Boiling point (“C)	270–280	297–298	–	–
Density	–	–	1.0630	–
Refractive index	1.5250	1.5050	1.5050	–
*max”’ in H_20	–	256 (1.5 x $1O^{-2}$)	256 (1.5 x 10^{-2})	256 (1.55 x 10^{-2})
PKa	8.17	8.22	8.35	8.37
Inorganic impurities**				
As	1 ppm	–	1 ppm	1 ppm
Pb	10 ppm	–	10 ppm	10 ppm
Ash	0.1%	0.1%	0.1%	0.1%
Residue on ignition* (%)	0.05	0.05	0.05	0.05
Loss on drying* (%)	0.5	0.5	0.5	0.5
Acidity* (mEq/750 mg)	0.02	0.02	0.02	0.02
Solubility				
Alcohol	vs	vs	s	s
Water	sl	sl	i	i
Ether	vs	vs	s	s
Acetone	vs	s	s	s
Benzene	sl	–	–	–
Carbon tetrachloride	sl	–	–	–
Glycerin	sl	sl	–	sl

Parabens and its applications

Parabens can be found in a wide range of products such as cosmetics, foods and pharmaceuticals. In the food industry, parabens are mainly used as preservatives because of their good antimicrobial properties, low production costs, and chemical stability (Lincho, *et.al*, 2021). Hair care products, makeup, shaving products, and moisturizers are among the cosmetics that may contain parabens. Many major deodorant brands do not include parabens at this time, while others do (US FDA, 2022). In addition, these are also used in leave-on, rinse-off, and bath formulations. Many kinds of parabens were found in products that can be accidentally ingested like lipstick. These are also seen in mascara, creams, lotions, and cosmetic sprays and face powders which can be possibly inhaled (Becker, 2022).

Parabens: How does it work as preservative?

Parabens are commonly used as preservatives in cosmetics to avoid growth of bacteria and mold in items prone to microbial growth. They are used as most of these compounds are effective over a widespread pH range. According to a previous study by Nguyen, et.al (2005), parabens work as antimicrobial agents by disrupting osmotic gradients in bacteria by interacting with mechanosensitive channels.

Recent information on its mechanism of action was from a Cosmetic Chemist Article published in 2016, where it stated that parabens work by inhibiting the synthesis of DNA, RNA, and enzymes in bacterial cells and by cellular membrane transfer process interference

The usability of products is prolonged by up to months through the use of parabens as the products do not develop molds and are protected against other potentially harmful fungus and bacteria (Wzorek & Nowak, 2019)

On the other hand, its cytotoxic activity may be connected to mitochondrial failure caused by stimulation of membrane permeability transition (Cosmetic Chemist, 2016). This stimulation is followed by the depolarization of the mitochondria and cellular ATP depletion due to disentanglement of oxidative phosphorylation.

In the presence of particular surfactants, creation of hydrogen bonds or the integration of molecules into micelles can impair the antibacterial action of parabens. It is very vital that the surfactants to be combined with the parabens to be used in a product are suitable with each other. Also, because these

preservatives are only active in the aqueous phase, solubilizing aids such as ethanol, glycerol, or propylene glycol must be added to the formulation (Wzorek & Nowak, 2019).

Examples and Comparison of various parabens used in cosmetic

Some of the known parabens used in cosmetics are methylparaben, propylparaben, butylparaben, ethylparaben, potassium methylparaben, isopropylparaben, potassium ethylparaben, isobutylparaben, potassium propylparaben, potassium butylparaben, sodium ethylparaben, sodium methylparaben, sodium butylparaben, sodium isopropylparaben, sodium propylparaben, and sodium isobutylparaben (Wzorek & Nowak, 2019). Out of these, the most commonly used are methylparaben, propylparaben, butylparaben, and ethylparaben. (US FDA, nd.)

Table 2. Previous Panel Safety Assessments of Parabens (Cherian,*et.al*, 2020)

Parabens	Conclusion	Reference
Methylparaben, Ethylparaben, Propylparaben, and Butylparaben	Safe as cosmetic ingredients in the present practices of use	1984
Benzylparaben	Available data are insufficient to support the safety	1986
Isobutylparaben and Isopropylparaben	Safe as cosmetic ingredients in the present practices of use	1995
Methylparaben, Ethylparaben, Propylparaben, Butylparaben, Benzylparaben, Isopropylparaben, and Isobutylparaben	Safe in the present practices and concentrations	2008

Scientific Committee on Consumer Safety (SCCS), a scientific committee of the European Commission evaluated various parabens. For Methyl paraben and ethyl parabens, its usage is restricted to a limited amount with a maximum of 0.4% for single esters (as acid) and a maximum of 0.8% for the total of esters (as acid). Propylparaben and Butylparaben are also restricted at maximum of 0.14% for the total of propylparaben and butylparaben (as acid). In other words, the use of these parabens at concentrations that are still effective is still considered safe and legal. However, Isopropyl paraben, Isobutyl, Pentyl, Phenyl, and Benzyl parabens are banned for use by the SCCS guidelines (Lebreux, 2017).

Shorter-chain, such as methyl and ethyl parabens, are frequently combined, whereas butylparaben is commonly used alone. Propyl- and butyl-parabens have longer chains and are associated with higher estrogenic effects. It's been proven that the branching structure boosts sensitization potency and estrogenic effect (Stoiber, 2019).

Usual Dosage amount in products

According to the European Scientific Committee on Consumer Safety (2011), the overall concentration of parabens with smaller molecules (methyl and ethyl) allowable in consumer products is 8 g per kilogram at maximum with none exceeding 4 g/kg. This assessment coincides with the up-to-date scientific data. The committee suggests lowering the limit to a maximal concentration of 1.9 g/kg parabens for the longer paraben molecules (propyl- and butyl parabens). As for other parabens, there is still little data so possible risks can't be assessed (ESCCS, 2011).

Side Effects of Parabens

Parabens are a collection of synthetic chemicals that have been employed as preservatives in a variety of health, beauty, and personal care products since the 1950s. Parabens are found in products that include methylparaben, ethylparaben, propylparaben, butylparaben, and isobutylparaben. To suppress the growth of fungus, bacteria, and other potentially harmful germs, these substances are added to deodorants, toothpaste, shampoos, conditioners, body lotions, and makeups, among other items. Researchers have also shown that over 90% of everyday food items have quantifiable quantities of parabens, which explains why even people who avoid potentially toxic personal care products have parabens.

What concerns public health activists is that while individual goods may contain trim levels of parabens that are within the permissible limits established by the US Food and Drug Administration, According to the Food and Drug Administration (FDA), cumulative exposure to chemicals from a variety of items may be overwhelming our systems and contributing to a variety of health issues (Scientificamerican, 2014). If you're attempting to avoid particular chemicals or compounds, reading cosmetics labels may be stressful. Half of the components are unintelligible to non-chemists, and even parabens might be challenging to identify. Parabens are preservatives that extend the shelf life of products and assist prevent the formation of dangerous germs and mold (Monna, 2022). Fungistatic and bacteriostatic preservatives hinder the growth and development of microorganisms, whereas chemicals that kill living bacteria through cell damage are classified as preservatives (bactericidal and fungicidal preservatives) (Barabasz *et al*, 2022).

Paraben as Endocrine Disruptors

Paraben is deemed to be Endocrine Disruptors, which are chemicals that fool the body into thinking they're hormones. The body may suffer if this results in a hormonal imbalance. The parabens propyl-, isopropyl-, and isobutyl parabens were discovered to imitate the hormone estrogen in animal experiments. As a result, hormone signals were disturbed, and female rat reproductive development was damaged (Monna, 2022). The non-profit Campaign for Safe Cosmetics claims that parabens are known to alter hormone function, linked to an increased risk of breast cancer and reproductive damage (CSC). "Parabens imitate estrogen by connecting to estrogen receptors on cells," according to research. According to a study, excess estrogen can cause responses, including increased breast cell division and tumor growth in some situations (Scientificamerican, 2014). Parabens have a similar chemical structure to the hormone estrogen. According to research, parabens have lately been linked to occurrences of early puberty in females due to their estrogen-mimicking properties. Endocrine disturbance can cause several issues over time, including adult acne, male breast growth, developmental and neurological diseases, and cancer. Other research has found that parabens can change thyroid hormone levels, potentially creating health problems (Kim et al., 2019).

Paraben and Breast Cancer

While some study has shown that parabens can imitate the estrogenic activity in the body's cells, this estrogenic activity has been linked to some types of breast cancer. Estrogen is a female hormone that has been linked to the growth and division of both normal and malignant breast cells. Breast cancers have also been shown to contain parabens. In 2004, British scientist Philippa Darbre released a study that claimed to have discovered paraben levels in breast cancer tissue samples. This investigation identified evidence of five distinct parabens in 19 out of 20 human breast cancer tumors. Darbre discovered that parabens not only enter the body through the skin but also accelerate the proliferation of cancer cells already there (Mufudza et al., 2012).

Also, according to CSC, a 2004 British research found residues of five parabens in 19 out of 20 women's breast cancers. "This recent study doesn't demonstrate a causal link between parabens and breast cancer, but it is substantial since it detected the presence of intact parabens—that is, parabens that have not been altered by the body's metabolism—which is an indication of the chemical's ability to penetrate the skin and remain in breast tissue," the group says. According to the CSC, parabens

have also been related to reproductive, immunological, neurological, and skin irritation issues (Scientificamerican, 2014).

Paraben and Reproductive Problems

Parabens have been related to an increased risk of reproductive issues in studies. These alterations may have negative health consequences for both women and their children, including reproductive disorders, an increased risk of cancer in adults, and developmental problems in children (Aker et al., 2016).

Parabens have been proven to bind to and change endocrine receptors in the body, and the larger and more complex the paraben's structure, the greater the receptor's influence. Both female and male endocrine functions have been affected by these substances. Anti-androgenic effects and changes in testosterone transcription have been seen in laboratory investigations of estrogen receptors and function and androgen (male hormone) receptors. Male and female reproductive development and fertility difficulties have been linked to high levels of parabens. In animal experiments, rats born to mothers exposed to high levels of parabens had their reproductive development disrupted: female rodents developed defective ovaries (Lora, n.d).

In contrast, in animal research, male rodents had decreased testosterone and sperm production in maturity. Many endocrine disruptors have been demonstrated to affect reproductive tract development, including parabens. DES (diethylstilbestrol) is a synthetic estrogen molecule used to prevent miscarriage and premature birth in the 1940s and 1960s but was taken off the market in 1971 due to an increased risk of uterine abnormalities and vaginal cancer in daughters born to mothers who used DES during pregnancy (Lora, n.d).

Male fertility. The evidence on the effects of parabens on male reproductive health is mixed. According to an essential scientific study, parabens bind to and modify androgen (male hormone) receptors, resulting in anti-androgenic effects and changes in testosterone transcription. Some clinical trials demonstrate an impact on testosterone production, sperm parameters, and male fertility. The study's exposure to parabens in male rats has been demonstrated to be linked to altered testicular development and poor, poor sperm production in offspring. In one study, men with high levels of five different parabens in their urine had low morphology of sperm, higher DNA fragmentation, lower sperm motility, and low level of testosterone. Low sperm counts and low testosterone levels

have been linked to high levels of parabens. Other research has shown a weak link between paraben levels in men's urine and semen analytical parameters. Butylparaben caused more DNA damage in sperm in one study of 190 males, although there was no substantial difference in other sperm parameters with methylparaben or propylparaben. There is research on fertility treatment effectiveness in men with high levels of methylparaben. However, one study of 218 infertile couples found that males with high levels of methylparaben who had IUI for fertility therapy had reduced live birth rates (Lora, n.d).

Female fertility. Studies on the effects of paraben exposure on fertility therapy have yielded varied findings. The EARTH study found no effect of methyl-, propyl-, or butylparaben levels on total mature oocytes, the proportion of high-quality embryos, fertilization rates, or treatment outcomes in 245 women who had 356 in vitro fertilization treatment cycles. In one investigation of male patient paraben levels and IVF results in 211 treatment cycles, inferior embryo quality was found, yet couples with high paraben levels had equivalent live birth rates. The same study looked at the results of IUI (intrauterine insemination) and found that teams with high levels of urinary parabens had fewer live babies (Lora, n.d).

Paraben and Obesity

Parabens, among other endocrine disruptors, have been linked to an increased risk of obesity. Endocrine disruptors are linked to an increase in fat cell number and size and changes in appetite, satiety (feeling full), dietary choices, metabolism, insulin sensitivity, and energy balance. Although there is more excellent evidence for the impact of endocrine disruptors like bisphenols and diethylstilbestrol in obesity, laboratory studies demonstrate that parabens increase adipocyte differentiation (fat cell formation) and affect gene expression in fat cells (Lora, n.d).

Paraben and Skin Allergic Reaction

Parabens can cause skin irritation and allergies, particularly in delicate, damaged, or cracked skin. Parabens have been shown in studies to be particularly inflammatory in those who have psoriasis, eczema, or a pattern of contact dermatitis. This is why topical hydrocortisone creams and antibiotic ointments seldom include parabens (Lora, n.d).

Although parabens have been well tested and only permeate the skin to a bit of level, a rising number of people – medical professionals, members of environmental and pro-consumer groups – are raising

concerns about their safety. It is postulated that the most common parabens present in cosmetics are associated with the following issues.

Thus, the most frequent parabens used in cosmetics are thought to be linked to the following problems (Barabasz, 2022):

- Parabens disrupt the bacterial flora, may impair the epidermis' water management, and contribute to weakening the lipid layer, causing skin irritation and allergies. Skin that has lost its natural protection against the elements is vulnerable to allergic severe responses. This is why some people believe they are allergic to parabens. Parabens can also cause skin irritation such as redness, itching, and urticaria. The more paraben-containing cosmetics you use, the more likely you will have skin issues. Individuals with fragile and sensitive skin prone to irritation should pay special attention to this issue.
- Because of the adverse effects of parabens on skin health, cosmetics manufacturers are employing fewer quantities of these preservatives.
- They interfere with hormone function; one theory claims that parabens interfere with sex hormones, reducing male fertility.
- They can have carcinogenic effects. The paraben that has the most substantial impact is butylparaben. It is blamed for triggering breast cancer.
- Pregnant women should not use them since they may harm fetal development.

Advantage of Paraben-free cosmetics

Parabens, among other excipients, were employed as preservatives and antimicrobials in cosmetics, cosmeceuticals, and various healthcare goods. Paraben derivatives have unique physicochemical characteristics that allow them to be used to develop cosmetic products across multiple dosage forms. Parabens are economically efficient because of their cheap production costs, in addition to their potency and efficacy. Despite their beneficial properties, parabens' safety has been questioned following the detection of these compounds in several biological tissues following repeated and long-term usage of products containing them. After scientific publications connected skin exposure to parabens with health risks, including breast cancer, the use of parabens garnered public attention. As a result, international authorities established guidelines for the proper amounts of paraben in various cosmetic items (Al-Halaseh *et al*, 2022).

Earlier in the 1920s, parabens were utilized in beauty products as a type of chemical preservative. However, in the last decade, the long-term consequences of paraben exposure have been a source of worry. While virtually all beauty products contain preservatives to help them last longer, paraben-

free cosmetics may be a better choice. If a product is paraben-free, the label will often declare "free from parabens" or "0 percent parabens." In order to check if the product is paraben-free, check the ingredients list on the back of the container. Three of the most prevalent paraben components are methylparaben, propylparaben, and butylparaben. Isopropylparaben and isobutylparaben also show the presence of parabens. Parabens are referred to as "parahydroxybenzoate." (Watson, 2022)

Paraben free products are healthier

As we all know, the skin is an integral part of the human body. Your skin will be healthier if your body is healthy, and vice versa. According to studies, using any product, including skincare products containing parabens, is connected to cancer. Using different preservatives on your skin is generally not recommended. Your body is designed to cleanse itself and eliminate pollutants via your skin, its biggest organ. As a result, when you use cosmetics containing strange preservatives, chemicals, and perfumes like parabens, they tend to build up in skin tissues, causing significant harm (Valdino, n.d).

Promotes younger skin

Unfortunately, most over-the-counter anti-aging treatments include a paraben that, sadly, makes you seem older. Yes, some parabens do the exact reverse of what they promise. Methylparaben, a frequently used paraben, is a misleading chemical that ages your skin rather than making it look younger. Methylparaben inhibits the development of collagen, a protein that makes up the majority of your connective tissue and keeps your skin tight. Therefore, the loss of collagen can affect our skin, making our skin sag and loose (Valdino, n.d).

Prevent skin allergic reaction

When using skin care products, the majority of people may develop allergies. Most of the time, they cannot determine which component is causing their allergies. Without your knowledge, parabens might be causing redness, extreme itching, pimples, or blotchy spots on your skin. Investing in organic skincare products, paraben-free and entirely natural, is the most outstanding alternative for you (Valdino, n.d).

Paraben-free cosmetic products are environment friendly

Because parabens are chemicals, it's no surprise that they harm the environment. When you rinse off your face cleanser, the residue (containing parabens) is carried into an ample water supply and ends up in the ocean. Parabens impact not just humans but also aquatic species and terrestrial mammals,

causing hormonal abnormalities. You are helping the environment by choosing paraben-free skincare products (Valdino, n.d).

RESULTS AND DISCUSSION

The existence of parabens on personal care products have been analyzed by Guo et al. (2014) which was stated in their study that in 52 various personal care products samples and measured the most commonly found parabens and the results were as follows MeP (77%), PrP (73%), EtP (46%), and BuP (25%). This provides us with the information of which is more common among the different types of parabens being used in cosmetics. Multiple studies compiled are results of experiments on mostly animals and a few human studies showed that of paraben in regard to the endocrine system and relating to it (Nowak et al.,2018)

EtP=Ethylparaben
Prp=Propylparaben
BuP=Butylparaben
BzP=Benzylparaben
iso-PrP=iso-Propylparaben
iso-BuP=iso-Butylparaben
↑ - increase, ↓ - decrease, ↔ - no effect

Table 3. Endocrine disrupting effects results on parabens

Parabens	Endocrine Disrupting effects	Subjects of study	References
MeP, EtP, PrP, BuP	↔ concentration of cortisol	Human infants and their mothers	Kang et al. 2013
MeP, EtP, PrP	↔ obesity development in adolescence	Children	Deierlein et al. 2017
BuP	↓ concentration of estradiol; ↓ ratio of estradiol/progesterone	Pregnant female	Aker et al. 2016
MeP	↑ concentration of sex hormone-binding globulin	Pregnant female	Aker et al. 2016
BuP	↑ concentration of free thyroxine	Pregnant female	Aker et al. 2016
EtP, PrP	↓ concentration of free thyroxine	Female	Koeppe et al. 2013
EtP, PrP, BuP	↓ concentration of free triiodothyronine	Female	Koeppe et al. 2013
EtP, PrP, BuP	↓ concentration of free triiodothyronine	Male	Koeppe et al. 2013
BuP	↑ sperm's DNA damage	Human	Meeker et al. 2011
MeP, PrP	↔ quality of the sperm	Human	Meeker et al. 2011, Scinicariello and Buser 2016

Legend:
MeP=Methylparaben

MeP, EtP, PrP, BuP	↓ activity of estrogen sulfotransferases	Human epidermal keratinocytes	Prusakiewicz et al. 2007
MeP, PrP, BuP	↓ testosterone-induced transcriptional activity	Human embryonic kidney cells HEK 293	Pop et al. 2016
BuP	dose-dependent weak antiandrogenic activity	Human breast cancer cells MDA-kb2	Chen et al. 2007
EtP, BuP	↔ concentration of progesterone; ↔ concentration of estradiol	Rats' fetuses	Taxvig et al. 2008
BuP	↔ concentration of testosterone	Rats' fetuses	Taxvig et al. 2008
BuP	↓ mRNA expression of benzodiazepine receptor (Bzrp) and steroidogenic acute regulatory protein (StAR)	Rats' female fetuses	Taxvig et al. 2008
BuP	↔ weight and histopathology of adrenal glands	Rats' fetuses and dams	Taxvig et al. 2008
BuP	↑ concentration of 17β-estradiol; ↑ concentration of progesterone; ↓ weight of testicles and ovaries	Rats' offsprings	Zhang et al. 2014
BuP	↓ quality of sperm	Rats' offsprings	Boberg et al. 2016, Guerra et al. 2017.
EtP, BuP	↔ concentration of thyroid hormone	Rats' dams and offspring	Taxvig et al. 2008
BuP	↓ mass of rats' reproductive organs	Mice	Oishi 2001, 2002a, 2004
MeP, EtP, PrP	↔ mass of rats' reproductive organs	Mice	Oishi 2001, 2002a, 2004
PrP, BuP	↑ concentration of estradiol	Mice	Pollock et al. 2017

MeP	↑ concentration of serum leptin	Female mice	Hu et al. 2016
MeP, BuP	↓ concentration of procollagen type 1 N-terminal propeptide; ↔ concentration of C-terminal telopeptide of type I collagen	Female mice	Hu et al. 2016
BuP	↓ concentration of cortisol	Female rats	Taxvig et al. 2008
iso-PrP, BuP, isoBuP	↑ weight of the uterus	Female rats	Vo and Jeung 2009
PrP, BuP	↓ sperm reserve in the epididymis	Male rats	Oishi 2001, Zielińska et al. 2016
EtP, BuP	↔ concentration of cortisol	Male rats	Taxvig et al. 2008
MeP, EtP	↔ concentration of testosterone; ↔ concentration of luteinizing hormone; ↔ concentration of follicle stimulating hormone	Rats	Oishi 2004
MeP, EtP, PrP, isoPrP, BuP	↓ concentration of thyroxine ↓ weight of the thyroid gland; ↑ weight of the ovaries ↑ weight of the adrenal glands;	Rats	Vo et al. 2010
BuP	↓ concentration of testosterone	Rats	Zhang et al. 2014
MeP, PrP	↑ expression of genes of integral membrane-associated protein-1, intestinal calcium-binding protein, progesterone receptor	Rats	Sun et al. 2016
BuP	↓ expression of gene CYP19a1	Rats	Boberg et al. 2016
BuP	↑ number of the Leydig's cells; ↑ concentration of testosterone; ↓ concentration of luteinizing hormone; ↓ concentration of follicle	Rats	Guerra et al. 2017

	stimulating hormone		
PrP, isoPrP, BuP, iso-BuP	↑ expression of Calbindin-D9k mRNA and protein; ↑ expression of mRNA progesterone receptor	Rat pituitary cancer cell line	Vo and Jeung 2009
BuP	agonist of peroxisome proliferator-activated receptor γ; ↑ lipid accumulation	Murine 3T3-L1 preadipocytes	Taxvig et al. 2012
MeP, EtP, PrP, BuP, BzP	↑ intracellular lipid accumulation; ↑ activation of peroxisome proliferator-activated receptor α and γ; ↑ activation of glucocorticoid receptor	Murine 3T3-L1 preadipocytes	Hu et al. 2013
MeP, PrP, BuP, BzP	↓ activity of fatty amide acid hydrolase; ↑ activation of peroxisome proliferator-activated receptor γ	Murine 3T3-L1 preadipocytes	Kodani et al. 2016
MeP, BuP	↓ osteogenic and chondrogenic differentiation	Multipotent stem cell line C3H10T1/2	Hu et al. 2017

Source:Nowak, K., Ratajczak–Wrona, W., Górska, M., & Jabłońska, E. (2018). Parabens and their effects on the endocrine system. doi:10.1016/j.mce.2018.03.014

Results hint that pregnant women exposed to parabens, most specifically Butylparaben, have a tendency for disrupting endocrine effects on the thyroid and hormones like estradiol and the like.(Aker et al., 2016) Adults have shown to have higher concentrations of parabens in the body compared to adolescents, this may explain the longer exposure or use of paraben related products and it was found out that women had higher concentrations compared to men.(Koeppe et al., 2013) Male participants were engaged in the study for the possible reproductive effects of paraben and it was found to have been conclusive to sperm damage but no such claims on changes of sperm quality. (Meeker et al., 2011)

According to one of the studies it was stated that parabens have an effect in estrogen sulfation. It could be the possible binding of parabens on the active site or within the site in which inhibits leads to possible inhibition of estrogen homeostasis.(Prusakiewicz et al., 2007) Sperm count on male rats were negatively affected when exposed to parabens and having different results of concentrations in each type. For female rats the growth of their mammary glands have been shown to be the result

when exposed to butyl paraben.(Boberg et al., 2016) Impaired sperm motility was found on male rodents along with the changes in spermatogenesis kinetics and sperm head deformations was relatively common with exposure to parabens. (Guerra et al., 2016)

Despite such results on studies FDA has treated parabens and other preservatives similar to other cosmetic components under the law, but should still be within the guidelines of safety stated by the FDA. To take action against a cosmetic for safety concerns, however, we must have credible scientific evidence that the product is dangerous when customers follow the guidelines on the label or when they use it incorrectly.(US FDA, 2022) Government entities all across the world, including the United States, the European Union, Japan, Australia, and Canada, are allowed to use parabens. In all of these countries, safe levels of paraben preservatives have been recognized. Consumers should not be concerned about the use of paraben-containing cosmetics, according to the FDA. Medical and toxicological specialists have classified methyl and propylparaben as "Generally Regarded As Safe" for use in food preservation by the FDA. (US FDA, 2022)

Despite widespread use, the ability of paraben esters to sensitize the skin and cause allergic contact dermatitis has been remarkably rare, especially when compared to other commonly used topical antimicrobial agents and preservative ingredients. When compared to other commonly used preservatives, prevalence rates are reported to be low, ranging between 0.6 and 1.7 percent in North America and 0.5 to 1.3 percent in Europe. Paraben mixture is considered a rare allergen, with an average prevalence of about 1%.(Fransway *et al*., 2019). The total amount of parabens permitted is 8 g per kilogram of cosmetic product, with no single paraben exceeding 4 g/kg. The SCCS determined that this limit is safe for the smaller paraben molecules (methyl- and ethyl paraben). The Scientific Committee on Consumer Safety recommends lowering the limit to 1.9 g/kg parabens for the longer paraben molecules (propyl- and butyl parabens). Parabens including isopropyl, isobutyl, and phenylparaben have insufficient data and their risks are unknown.(Int J Toxicol., 2011) Unintentional paraben exposure. Face powders, for example, contain up to 0.5 percent ethylparaben, resulting in accidental inhalation. Aerosol products, like hair sprays, contain non-respirable droplets/particles. While particle/droplet size is crucial, so are the physicochemical properties of the spray components and actual exposure conditions in real-world settings. Furthermore, nasopharyngeal or bronchial droplets/particles are not toxicologically hazardous. Assuming the results are accurate, unintentional inhalation is unlikely to constitute a significant route of exposure with local respiratory or systemic repercussions. (Priya & Jinqui, 2020) Parabens have a weak estrogenic activity in vitro, which increases with alkyl side chain length and branching. Their potency is 1,000–1,000,000 times less potent than 17-estradiol. In some studies, parabens exhibit

weak estrogenic activity in vivo, but with extremely low potency (approximately 10-5 to 10-6 that of estradiol). In vitro and in vivo, P-hydroxybenzoic acid, a common metabolite, has no estrogenic activity. Although a report purportedly linking parabens in underarm cosmetics to breast cancer sparked widespread interest, a closer examination revealed "no evidence of demonstrable risk."(Krowka & Loretz, 2017)

Emerging toxicological concerns concerning parabens are significant. In addition to endocrine action, spermatogenesis and adipogenesis are non-allergologic effects. Parabens are safe for cosmetic, food, and pharmaceutical use if all toxicological endpoints are considered. This article's objective is to reassure consumers regarding paraben safety and enable educated choices. Parabens are not responsible for these major health concerns. Because parabens have no major skin toxicity, removing them from consumer items may result in less proven and potentially dangerous replacements.(Fransway *et al.*, 2019) Parabens are not toxic in the concentrations found in cosmetics. They are not genotoxic, carcinogenic, or teratogenic. Less than 1% of parabens are in food. As the ester linkage appears to be easily hydrolyzed, p-hydroxybenzoic acid is formed. After dermal exposure, skin esterases metabolize parabens, while after oral exposure, esterases hydrolyze parabens during first-pass metabolism. (Krowka & Loretz, 2017) Ingredients for wound treatment must be safe. Particularly criticized are paraben preservatives. Parabens have been connected to allergic contact dermatitis as well as oestrogen-like action. Parabens are extremely infrequent allergens compared to other antimicrobials and preservatives. Surprisingly, parabens have not been connected to breast cancer in humans. According to scientific and regulatory study, the present safety restrictions governing their use are adequate. Despite repeated worries, typical paraben levels are unlikely to cause harm.(Eveline & Brackman, 2021)

CONCLUSION

A lot of confusion throughout the years about the safeness of the use of parabens which is also a delicate thing to talk about. Majority of results point to negativity about parabens and results show that they do interfere with receptors in our body mostly related to our endocrine system. Some effects that occurred in animal studies do not conform with human studies but compared to concentrations found in cosmetic products and of sorts is different compared in the studies which leads us to say that the obtained results may be unreliable for comparison on humans. Despite the efforts and studies performed on human testing of parabens there are still plenty of unclear issues that still require further study into uncovering and understanding of the previous findings.

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References:

1. Aker, A.M., Watkins, D.J., Johns, L.E., Ferguson, K.K., Soldin, O.P., Anzalota Del Toro, L.V., Alshawabkeh, A.N., Cordero, J.F., Meeker, J.D., 2016. Phenols and parabens in relation to reproductive and thyroid hormones in pregnant women. Environ. Res. 151, 30–37. doi:10.1016/j.envres.2016.07.002.
2. Amended safety assessment of parabens as used in cosmetics. (n.d.). Available at: https://journals.sagepub.com/doi/full/10.1177/1091581820925001
3. Reeder, M & Atwater,A.R. (2019). Parabens: The 2019 nonallergen of the year. Cutis. Available at: https://pubmed.ncbi.nlm.nih.gov/31116813/
4. Barabasz, W., Pikulicka, A., Wzorek, Z., & Nowak, A. K. (2019, December 1). Ecotoxicological aspects of the use of parabens in the production of cosmetics. Technical Transactions. Available at: https://sciendo.com/es/article/10.4467/2353737XCT.19.126.11451
5. Becker, L. C., & Heldreth, B. H. (2018, February 23). *Safety assessment of parabens as used in cosmetics*. parabens.pdf. Available at: https://www.cir-safety.org/sites/default/files/parabens.pdf
6. Becker, L, (2022). Safety Assessment of Parabens as Used in Cosmetics. [online] Cir-safety.org. Available at: https://www.cir-safety.org/sites/default/files/parabens.pdf?fbclid=IwAR1E3qFY-2veUB8FMPmj-3tPdatLhJiBk3NmrpxuPsKTjkFxFnI7kG9aLuI.
7. Boberg, J., Axelstad, M., Svingen, T., Mandrup, K., Christiansen, S., Vinggaard, A.M., Hass, U., 2016. Multiple endocrine disrupting effects in rats perinatally exposed to butylparaben. Toxicol. Sci. 152, 244–256. doi:10.1093/toxsci/kfw079.
8. ChemicalSafetyFacts.org. (2022, April 12). *What are parabens?: Uses, benefits, and Chemical Safety Facts*. Available at: https://www.chemicalsafetyfacts.org/parabens/
9. Cherian, P., Zhu, J., Bergfeld, W., Belsito, D., Hill, R., Klaassen, C., Liebler, D., Marks, J., Shank, R., Slaga, T., Snyder, P. and Heldreth, B., (2020). Amended Safety Assessment of Parabens as Used in Cosmetics. International Journal of Toxicology, [online] 39(1_suppl), pp.5S-97S. Available at: https://journals.sagepub.com/doi/pdf/10.1177/1091581820925001.

10. Cosmetic Chemist. (2016). Methylparaben. Available at: http://www.thecosmeticchemist.com/molecule_of_the_week/methylparaben.html#:~:text=Interestingly%2C%20it%20is%20believed%20that,and%20enzymes%20in%20bacterial%20cells.
11. Cosmetics & Toiletries. (2020, November 12). Preserving the facts on Parabens: An overview of these important tools of the Trade. Available at: https://www.cosmeticsandtoiletries.com/research/literature-data/article/21836796/preserving-the-facts-on-parabens-an-overview-of-these-important-tools-of-the-trade
12. Dermatology, F. the *A. in. (n.d.). Paraben toxicology : Dermatitis®. LWW. Available at:https://journals.lww.com/dermatitis/Abstract/2019/01000/Paraben_Toxicology.3.aspx
13. Scientific Committee on consumer safety (SCCS) [Internet]. Public Health. [cited 2022May18]. Available from: https://ec.europa.eu/health/scientific-committees/scientific-committee-consumer-safety-sccs_en
14. Guerra, M.T., Sanabria, M., Leite, G.A., Borges, C.S., Cucielo, M.S., Anselmo-Franci, J.A., Foster, W.G., Kempinas, W.G., 2016. Maternal exposure to butyl paraben impairs testicular structure and sperm quality on male rats. Environ Toxicol. doi:10.1002/tox.22323.
15. Guo, Y., Wang, L., Kannan, K., 2014. Phthalates and parabens in personal care products from China: Concentrations and human exposure. Arch. Environ. Contam. Toxicol. 66, 113–119. doi:10.1007/s00244-013-9937-x.
16. Int J Toxicol. Final amended report on the safety assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in cosmetic products. 2008;27 Suppl 4:1-82. doi: 10.1080/10915810802548359. PMID: 19101832.
17. Jeanette Kimszal, R. D. N. (2021, October 11). *What's the deal with parabens?* Verywell Health. Available at: https://www.verywellhealth.com/are-parabens-bad-for-you-5204132
18. Kang, S., Kim, S., Park, J., Kim, H.J., Lee, J., Choi, G., Choi, S., Kim, S., Kim, S.Y., Moon, H.B., Kim, S., Kho, Y.L., Choi, K., 2013. Urinary paraben concentrations among pregnant women and their matching newborn infants of Korea, and the association with oxidative stress biomarkers. Sci. Total Environ. 461–462, 214–221. doi:10.1016/j.scitotenv.2013.04.097.
19. Kim G Harley, Kimberly P Berger, Katherine Kogut, Kimberly Parra, Robert H Lustig, Louise C Greenspan, Antonia M Calafat, Xiaoyun Ye, Brenda Eskenazi, Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys, Human Reproduction, Volume 34, Issue 1, January 2019, Pages 109–117, https://doi.org/10.1093/humrep/dey337
20. Koeppe, E. S., Ferguson, K. K., Colacino, J. A., & Meeker, J. D. (2013). Relationship between urinary triclosan and paraben concentrations and serum thyroid measures in NHANES 2007-

2008. The Science of the total environment, 445-446, 299–305. https://doi.org/10.1016/j.scitotenv.2012.12.052

21. Laura, MD, S. (n.d.). The Paraben Paradox: Safe Preservative or Fertility and Health Toxin? Lorashine.Com. Available at: https://www.lorashahine.com/blog/2020/6/20/the-paraben-paradox-a-safe-preservative-or-fertility-and-health-toxin
22. Lebreux, F. (2017, July). Preservative Deep Dive: Parabens and their Alternatives. Prospector.com. Available at: https://knowledge.ulprospector.com/6776/pcc-preservative-deep-dive-parabens-alternatives/
23. Lidia K. Al-Halaseh PhD,Sujood Al-Adaileh Bpharm,Alsafa Mbaideen Bpharm,Maha N. Abu Hajleh PhD,Ali Al-Samydai PhD,Zainab Zaki Zakaraya PhD,Wael Abu Dayyih PhD. (2022, January 15). Implication of parabens in cosmetics and cosmeceuticals: Advantages and limitations. Wiley Online Library. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/jocd.14775
24. Lincho, J., Martins, R. and Gomes, J., (2021). Paraben Compounds—Part I: An Overview of Their Characteristics, Detection, and Impacts. Applied Sciences, [online] 11(5), p.2307. Available at: https://www.mdpi.com/2076-3417/11/5/2307/htm?fbclid=IwAR3hz9ENZ_LI2kpZTA28X4faUxy9XW09_F8wFv0rdxGGJ_RegvEAYNIKBO.
25. Lora, MD, S. (n.d.). The Paraben Paradox: Safe Preservative or Fertility and Health Toxin? Lorashine.Com. Available at: https://www.lorashahine.com/blog/2020/6/20/the-paraben-paradox-a-safe-preservative-or-fertility-and-health-toxin
26. Meeker, J.D., Yang, T., Ye, X., Calafat, A.M., Hauser, R., 2011. Urinary concentrations of parabens and serum hormone levels, semen quality parameters, and sperm DNA damage. Environ Health Perspect. 119, 252–257. doi:10.1289/ehp.1002238.
27. Monna, B. (2022, February 6). Cleaning Up Your Beauty Routine? Here's the Deal with Parabens. Greatist.Com. Available at: https://greatist.com/health/parabens
28. Mufudza, C., Sorofa, W., & Chiyaka, E. T. (2012). Assessing the effects of estrogen on the dynamics of breast cancer. Computational and mathematical methods in medicine, 2012, 473572. https://doi.org/10.1155/2012/473572
29. Nguyen, T., Clare, B., Guo, W. & Martinac, B. (2005, March). European Biophysics Journal. Available at: 34(5), 389–395. doi:10.1007/s00249-005-0468-x
30. Nowak, K., Ratajczak–Wrona, W., Górska, M., & Jabłońska, E. (2018). Parabens and their effects on the endocrine system. Molecular and Cellular Endocrinology, 474, 238–251. doi:10.1016/j.mce.2018.03.014

31. Parabens inhibit fatty acid amide hydrolase: A potential role in paraben-enhanced 3T3-L1 adipocyte differentiation. Toxicol. Lett. 262, 92–99. doi:10.1016/j.toxlet.2016.09.011.
32. Parabens. Safe Cosmetics. (n.d.). Available at: https://www.safecosmetics.org/get-the-facts/chemicals-of-concern/parabens/#:~:text=In%20cell%20studies%2C%20parabens%20have%20been%20found%20to,used%20as%20a%20sensitive%20measure%20of%20estrogenic%20activity.
33. Prusakiewicz, J.J., Harville, H.M., Zhang, Y., Ackermann, C., Voorman, R.L., 2007. Parabens inhibit human skin estrogen sulfotransferase activity: Possible link to paraben estrogenic effects. Toxicology. 232, 248–256. doi:10.1016/j.tox.2007.01.010.
34. Scientificamerican.Com. (2014, October 6). Should People Be Concerned about Parabens in Beauty Products? . Available at: https://www.scientificamerican.com/article/should-people-be-concerned-about-parabens-in-beauty-products/#:~:text=%E2%80%9COf%20greatest%20concern%20is%20that,for%20Safe%20Cosmetics%20(CSC)
35. Scientific Facts on Parabens used in cosmetics. (n.d.). Parabens used in cosmetics. Available at: http://www.greenfacts.org/en/parabens-cosmetics/index.html
36. Soni, M. G., Carabin, I. G., & Burdock, G. A. (2005, March 13). *Safety assessment of esters of P-hydroxybenzoic acid (parabens)*. Food and Chemical Toxicology. Available at: https://www.sciencedirect.com/science/article/abs/pii/S0278691505000530?via%3Dihub
37. Stoiber, T. (2019, April). What Are Parabens, and Why Don't They Belong in Cosmetics? Environmental Working Group. Available at: https://www.ewg.org/what-are-parabens
38. Torfs, E., & Brackman, G. (2021, April). A perspective on the safety of parabens as preservatives in Wound Care Products. International wound journal. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8243994/
39. US FDA, (2022). Parabens in Cosmetics. [online] U.S. Food and Drug Administration. Available at: https://www.fda.gov/cosmetics/cosmetic-ingredients/parabens-cosmetics
40. US FDA, (2022, April). What are parabens?: Uses, benefits, and Chemical Safety Facts. ChemicalSafetyFacts.org. Available at: https://www.chemicalsafetyfacts.org/parabens
41. Valdino, J. (n.d.). 6 REASONS FOR YOU TO CHOOSE PARABEN-FREE SKINCARE. Mldelicatebeauty. Available at: https://mldelicatebeauty.com/blogs/my-blogs/paraben-free-skincare-product
42. Watson, K. (2022, June 16). What Does Paraben-Free Mean in Beauty Products? Healthline. Available at: https://www.healthline.com/health/paraben-free#on-the-label

43. W.Ł.B.A.P.Z.W.A.K.N. (2022, May 15). Ecotoxicological aspects of the use of parabens in the production of cosmetics. Sciendo.Com. Available at: https://sciendo.com/es/article/10.4467/2353737XCT.19.126.11451
44. Wild Naturals. (2017, December 11). *The history behind Parabens and why they are prominent in most Skincare*. Wild Naturals. Available at: https://wildnaturals.com/blogs/blog/the-history-behind-parabens-and-why-they-are-prominent-in-most-skincare-products
45. Wzorek, Z. & Nowak, A.K. (2019, December). Ecotoxicological aspects of the use of parabens in the production of cosmetics. Research Gate. Available at: DOI: 10.4467/2353737XCT.19.126.11451
46. Zielińska, K.A., Van Moortel, L., Opdenakker, G., De Bosscher, K., Van den Steen, P.E.,2016. Endothelial Response to Glucocorticoids in Inflammatory Diseases. Front.Immunol. 7, doi:10.3389/fimmu.2016.00592.