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Assessment of Health Impacts of Parabens in Pharmaceutical and Food Products

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ABSTRACT

Many peoples are exposed daily to cosmetics, pharmaceutical and packaged food products. These products contain Para-hydroxybenzoic acid esters (Parabens). Parabens are synthetically produced preservatives used in personal care products, food and drink, medicines and pharmaceutical preparations. Parabens are readily absorbed through the skin and the gut and excreted in urine. However, some of these compounds may be retained in the body. Parabens have been measured in blood and urine including that of pregnant women, amniotic fluid, placental tissue, cord blood and breast tissue. Parabens are also widespread in our environment. There are many forthcoming types of research evidences that Parabens and Para-hydroxybenzoic acid may act as estrogenic endocrine disruptors. Parabens may increase breast cancer risk, particularly if exposure occurs during critical periods of development. Parabens have been implicated in the proliferation of breast cancer and marine toxicity. This review has been focused on the vital role and research findings of the published literature regarding the deleterious effects of the Parabens.

INTRODUCTION:

Parabens are a category of extensively used preservatives in cosmetic and pharmaceutical preparations subsequently from the 1930s. Chemically, they are a series of parahydroxybenzoates or esters of para-hydroxybenzoic acid also known as 4-hydroxybenzoic acid (1). Their effectiveness as preservatives, in combination with their low-cost analogs, is the secrete of the long history of their use, and the inefficaciousness of some natural alternatives as compared to its which explains why Parabens are so usual. (2, 3) Fascinatingly, Parabens are also present in nature (e.g. blueberries, cloudberry, yellow passion fruit) (4), but at very low concentrations. For example, the concentration of methylparaben in *Andrographis paniculata* is much lower is only 0.0008% of its weight (5). Thus, paraben intake from plant sources is negligible (6). The concentration of Parabens in cosmetic formulations can reach up to 0.8% that is nearly 1000 times more than natural sources. Due to the low level of accumulation in plants, all industrially used Parabens are produced synthetically (7). Chunyang Liao has been evaluated on the existence of Parabens in foodstuffs and dietary supplements of humans. In this study, food samples collected from Albany, New York, United States, were collected into eight categories namely, beverages, dairy products, fats and oils, fish and shellfish, grains, meat, fruits, and vegetables, and analyzed for five Parabens by using high-performance liquid chromatography-tandem mass spectrometry. The >90% of food products had measurable concentrations of Parabens, and the total concentrations (sum of five Parabens) extended from below the limit of quantitation to 409 ng/g fresh weight (mean: 9.67 ng/g; median: 0.92 ng/g). From that Methyl-, ethyl-, and propyl-Parabens were the major compounds. Ying Gao and Kurunthachalam Kannan have been reported a survey on Phthalates and Parabens in Personal Care Products (PCPs) from the United States and Its Implications for Human Exposure. Despite the extensive usage of phthalates and Parabens in personal care products, in this study, they found nine phthalates and six Parabens were determined in 170 PCPs (41 rinse-off and 109 leave-on formulations), plus 20 baby care products collected from Albany, New York. (8, 9)

❖ **Parabens are also widely used in cosmetics in different product categories:**

A. Cosmetics and Personal Care Products:

1. Shampoos and conditioners

2. Body lotions

3. Shower gels

4. Scrubs

5. Sunscreen cosmetics

6. Deodorants and antiperspirants

7. Moisturizers

B. Edible products:

1. Beverages; i.e. beer, soft drinks, frozen dairy products

2. Jams, Jellies, and pickles

3. sauces, desserts,

4. Processed fish, processed vegetables, and flavoring syrups.

❖ **Chemistry, Mode of Action and Antimicrobial Efficacy:** Parabens are active against a wide range of microorganisms. However, their antibacterial mode of action has not been well understood. They are thought to act by disrupting membrane transport processes (10) or by inhibiting synthesis of DNA and RNA (11) or of some key enzymes, such as *ATPase's* and phosphotransferases, in some bacterial species.(12) Propylparaben had been considered more active against most bacteria than methylparaben. The stronger antibacterial action of propylparaben may be due to its higher solubility and high permeability bacterial membrane, which may allow it to reach cytoplasmic targets in greater concentrations. However, since a majority of the studies on the mechanism of action of Parabens propose that their antibacterial action is linked to the membrane, it is likely that its greater lipid solubility disrupts the lipid bilayer, thus interfering with bacterial membrane transport processes and perhaps triggering the leakage of intracellular constituents.(13)

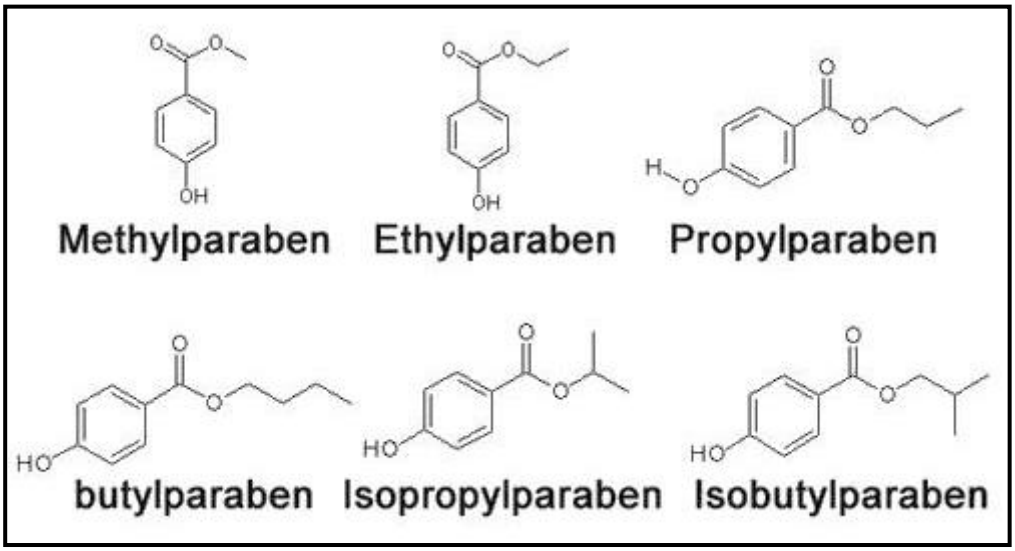

Figure 1: Chemical Structure of alkyl esters of para-hydroxybenzoic acid

Parabens have very low toxicity. Singhal et al. most likely make this assumption based on the large LD_{50} value in mice. Methyl and propylparaben, two of the most commonly used Parabens in products today, have an LD_{50} value greater than 8000 mg/kg in propylene glycol.(14) Upon entering the body, Parabens are supposed to first be absorbed in the intestines, followed by the hydrolysis into Para-hydroxybenzoic acid (PHBA) in the liver, which is then excreted in urine (15, 16). They were generally recognized as safe (GRAS),(6) because PHBA is less toxic than the parent compounds and the excretion process usually takes place within 24 hours. Furthermore, Aubert et al; demonstrated that Parabens are quickly excreted in the urine and do not produce significant systemic exposure. Along with intestinal absorption, Parabens may be absorbed through the skin and mucosa. Some investigation also proposes that there is esterase's present in the skin that aid in partially translating Parabens into PHBA upon topical application.(17, 18)

Table No. 1 Material Safety Data Sheet of four Parabens

Parabens Types	Hazardous Identifications	Toxicological Information	CAS
Ethyl Paraben	Hazardous in case of ingestion, skin contact (irritant, permeator), of eye contact (irritant), of Inhalation (Repeated or prolonged exposure causes target organs damage)	Oral, mouse: LD_{50} = 3000 mg/kg	120-47-8
Methyl Paraben		Oral, mouse: LD_{50} > 8gm/kg	99-76-3
Butyl Paraben		Oral, mouse: LD_{50} = 13200 mg/kg	94-26-8
Propyl Paraben		Oral, mouse: LD_{50} = 500 mg/kg	94-13-3

Chen Yiqun et al; had been investigated the oxidation efficacies of methyl- and Ethylparaben by the heat-activated persulfate process. Their deprivations were found to be strongly affected by the heating temperature, persulfate dosage, and solution pH. Methylparaben and Ethylparaben degradations followed pseudo-first-order kinetics. The formed reactive species, including SO4 and HO-, concurrently contributed to the degradation of Parabens. The removals of Methylparaben and Ethylparaben showed positive relationships between heating temperature and persulfate dose. However, the pseudo-first-order rate constants decreased by 26.5% and 40.7% for Methylparaben and Ethylparaben degradations, respectively. (19)

❖ **Parabens in our Body:** Parabens consumed with food are fully metabolized: enzymes of our digestive system break these chemicals into smaller compounds that are further excreted with urine, (20) Parabens from personal care products are absorbed through the skin. Skin enzymes cannot process all topically applied Parabens (21), and some amount of them is retained in the body tissues. (15, 22) The occurrence of intact Parabens in urine after application of paraben-containing cosmetics confirms that our body cannot fully metabolize these chemicals. Moreover, women using personal care products more extensively than men have 4-times higher levels of Parabens in urine. (21, 23, 24)

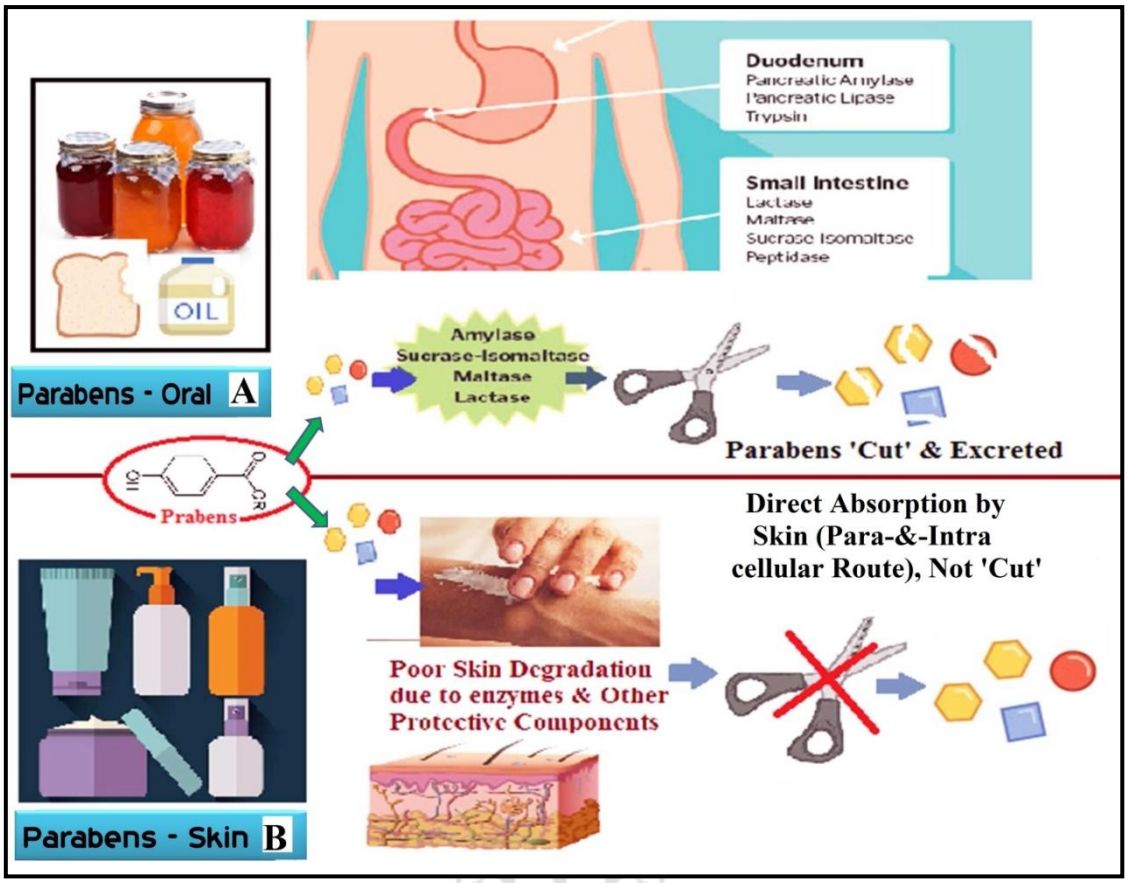

Figure 2: Possible Mechanism of Paraben Absorption, Metabolism, and Excretion and Accumulation A) Oral B) Skin

Because of their low toxicity and effective antimicrobial activity, Parabens, comprising methylparaben, have been used in food for more than 60 years. Under FDA regulation, methylparaben is generally recognized as safe (GRAS) when used as a chemical preservative in foods, with a use limit not exceeding 0.1%. (25, 26)

❖ **Major Health Concerns Regarding Parabens:**

1. Cancer:

In former studies, researchers have concluded that Parabens are practically non-irritating and non-sensitizing in human with normal skin. Paraben sensitization has been reported when Paraben-containing medicaments have been applied to the damaged or broken skin. Photo-contact sensitization and Phototoxicity tests on product formations of Methylparaben, Propylparaben, and Butylparaben gave no evidence of significant photoreactivity. Earlier, it

was concluded that Methylparaben, Ethylparaben, Propylparaben, and Butylparaben are safe as cosmetic ingredients in the present practices of use. (27)

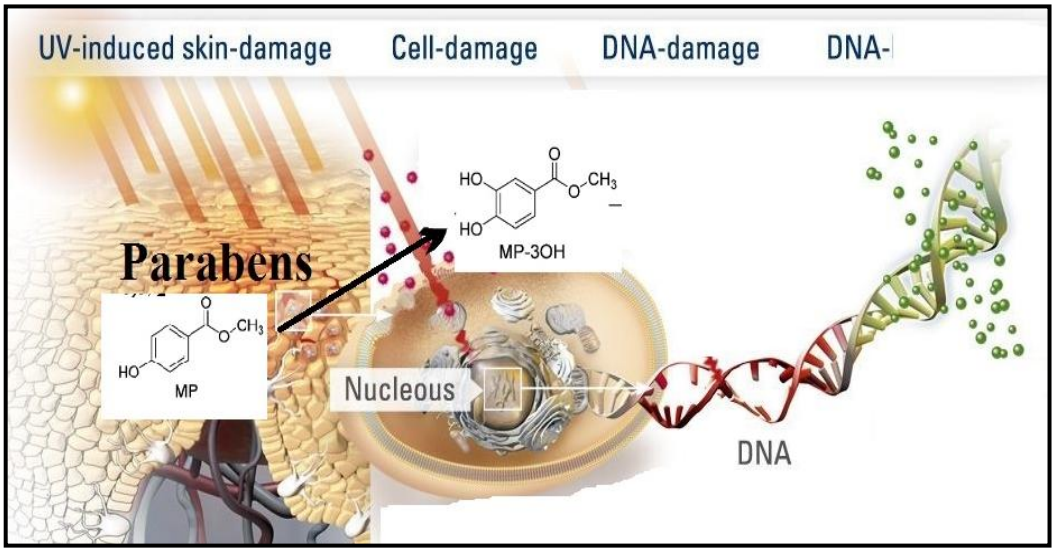

Figure 2: Combined activation of Methylparaben by sunlight irradiation and skin esterases lead toward oxidative DNA damage

The Cosmetic Ingredient Review (CIR) Expert Panel concludes that the available data are insufficient to support the safety of Benzyl paraben as used in cosmetics. (6) However, Parabens were implicated in numerous cases of contact sensitivity associated with cutaneous exposure; reported to cause contact dermatitis reactions in some individuals on cutaneous exposure but the mechanism of this sensitivity is unknown. The mechanism of cytotoxic action of Parabens may possibly be linked to mitochondrial failure dependent on initiation of membrane permeability transition accompanied by the mitochondrial depolarization and exhaustion of cellular ATP through uncoupling of oxidative phosphorylation, which is depicted in the Figure 2. (25, 28)

Parabens in cosmetics and sunscreens undergo photochemical decomposition which one is one of the important clearance routes along with dermal tissue metabolism (29). In a recent study, Methylparaben (MP) photoproducts and metabolites were characterized, and their DNA-damaging actions were evaluated based on the formation of 8-Oxo-2'-deoxyguanosine (8-oxodG) in calf thymus DNA. The present study has demonstrated that MP is converted to DNA damaging compounds by the combined activation with sunlight irradiation and skin esterase metabolism. This activation occurs with the use of MP-containing products such as cosmetics and sunscreens, because the source of light used in the experiment is natural

sunlight, and the concentration of cosmetic MP (<0.3%) is more than two times that used in this study. A predictive result by Yoshinori Okamoto et al; (30) Represented that PHBA was also generated as a methylparaben photoproduct. Although PHBA was not activated via metabolism by skin enzymes, the other photoproduct, 3-Hydroxy Methylparaben (MP-3OH), produces an active metabolite(31). This active metabolite hydroxylated p-hydroxybenzoic acid (h-PHBA), produced by hydrolysis of 3-Hydroxy Methylparaben (MP-3OH) methyl ester. This indicates that the responsible enzyme(s) for the activation contained in the S9 is a certain *esterase*(s), as supported by a previous report was detected that PC might be produced as a minor MP photoproduct by sunlight irradiation; therefore, a major contributor to the h-PHBA formation and subsequent DNA damage would be esterase(s) in this study. (32, 33) Human exposure doses to Parabens cannot be accurately estimated based only on paraben concentrations in urine because Parabens do get metabolized to p-hydroxybenzoate at different rates.(34, 35)

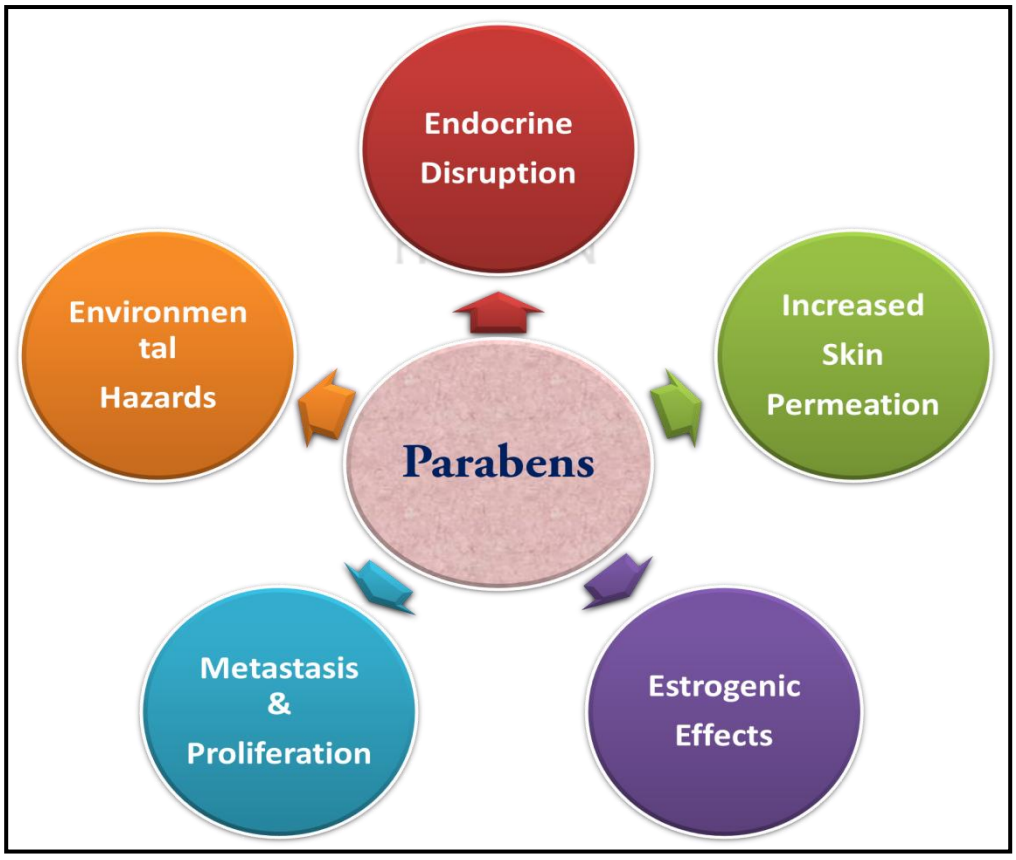

Figure 3 Various Effects of Parabens

2. Endocrine System Related Issues: Endocrine disruptors are chemicals that can interfere with endocrine (or hormone) systems at certain doses (36). Even though potential

EDCs may be present in the environment at only very low levels, they may still cause destructive effects, specifically when several different compounds act on one target. EDCs include persistent pollutants, agrochemicals, and widespread industrial compounds. Not all EDCs are synthetic compounds; many plants produce substances (phytoestrogens) that can have different endocrine effects either adverse or beneficial in certain circumstances (37, 38). These disruptions can cause cancerous tumors, birth defects, and other developmental disorders. Recently the Endocrine Society released a statement on endocrine-disrupting chemicals (EDCs) specifically listing obesity, diabetes, female reproduction, male reproduction, hormone-sensitive cancers in females, prostate cancer in males, thyroid, and neurodevelopment and neuroendocrine systems as being affected biological aspects of being exposed to EDCs (39, 40). An increasing body of evidence reveals relations between various therapeutic environmental compounds that act as endocrine disrupting substances (EDS) and many sex hormone-sensitive diseases/disorders (41-43). Given the recognized extensive human exposure to antimicrobial EDS, both the mechanism(s) of endocrine action and the structure-activity relationships (SARs) of these compounds should be fully investigated. It is also important that exposure levels be determined by direct measurements in the near future. Further examination with adequate screening systems and in vivo confirmation is immediately needed to fully appreciate the spectrum of these endocrine disrupting properties (44). The most extensive disrupting activity to be described has been that resulting from the property of Parabens to bind to human ER (estrogenic receptors) and then to act via ER-mediated mechanisms to control gene expression and cell growth in estrogen-responsive cells. Moreover, endocrine disrupting activity demonstrated in the ability of Parabens to antagonize AR-mediated events in androgen-responsive cells and to act as SULT (sulfotransferase enzymes) inhibitors. Other reports were suggested Parabens can influence the secretion of lysosomal enzymes in lymphocytes (45), can impair mitochondrial function in rat hepatocytes (46) can cause DNA damage in CHO cells (47) and can potentiate UV-induced impairment including reactive oxygen species and nitric oxide production in keratinocytes (48). Darbre et al 2009 proposed a link between breast malignancy and the application of cosmetic preparations with estrogenic and/or genotoxic properties provide an evidence-based assumption capable of further testing. Although individual chemicals will have been tested by current safety guidelines, the effects of long-term use of combinations of these chemicals over a whole epoch by people of all ages across the whole world warrant retrospective investigation. If the use of underarm cosmetics is an issue in the growth of

breast cancer, then options for prevention could be individual decisions to stop using or through alterations to product formulations.(49).

3. Estrogenic Activity Related Issues: Pugazhendhi pope et al; addresses the question of whether p-hydroxybenzoic acid, the common metabolite of Parabens, possess estrogenic activity in human breast cancer cell lines. Following on from previous studies showing a reduction in estrogenic activity of Parabens with shortening of the linear alkyl chain length; this study was compared with the estrogenic activity of p-hydroxybenzoic acid where the alkyl grouping is no longer present with methylparaben, which has the shortest alkyl group. (50) Various in vitro assays were showed that Parabens can bind to estrogen receptor (51) and that individual paraben may have a weak estrogenic activity. A correlation between the length of the Paraben ester chain and the estrogen city has been established (52). On the other hand, Parabens have been reported to stimulate the proliferation of MCF-7 breast cancer cells. (53, 54) The estrogenic effects of three classes of substances included in cosmetic formulations, ultraviolet (UV) screens, and musk fragrances were studied. Their estrogenic activity was measured with the use of three reporter cell lines: HELN, HELN ER-alpha, and HELN ER-beta. These three cell lines used for the measurement of estrogenic activity toward estrogen receptors alpha and beta (ER-alpha and ER-beta, while considering nonspecific interactions. (54)

4. Skin Toxicity Related Issues: In 1974 Marzulli and Maibach Suggested a commentary on the status of topical Parabens in relation to Skin Hypersensitivity that is, In 1972, the North American Contact Dermatitis group tried to define the relative incidence of positive paraben patch test in dermatitis patients. The test was conducted on 1,200 subjects in 10 geographic areas of the U.S. and Canada; a uniform patch test practice was used. About 3% were found to be sensitized (55). Seventy years of use have confirmed the excellent safety of Parabens as stable, effective, and nonirritant preservatives.(27, 56, 57) In 1940, Bonnevie in Denmark described the first case of allergic contact dermatitis from Parabens. (58, 59) Allergic dermatitis, eczema is, therefore, often difficult to diagnose, presenting as recalcitrant dermatitis that fails to improve or worsens under seemingly adequate treatment (60, 61). By contrast, cosmetics appear to be a relatively uncommon source of sensitization. Often, paraben sensitive individuals are able to tolerate paraben-containing cosmetics if they were applied to normal skin. Fisher called this phenomenon the “paraben paradox” and

emphasized the fact that traumatized or eczematized skin is more readily sensitized by Parabens or other contact allergens than normal skin (62).

Contact with foods preserved with Parabens may rarely cause hand dermatitis in cooks and food handlers (63). However, there seems to be no need for restrictive diets in paraben-sensitive subjects since ingestion does not induce relapse or exacerbation of preexisting contact dermatitis (64). Parenteral administration of paraben-containing products has occasionally resulted in systemic contact dermatitis, a more or less widespread eczematous eruption in individuals previously sensitized to Parabens from topical exposure (65, 66). One case of the generalized delayed eruption with an urticarial morphology was caused by methylparaben. (67, 68)

5. Ecological Hazard Related to Parabens:

Parabens are now concerning part of human and ecosystems mainly aquatic. There is still less available evidence about the adverse effects of these compounds on aquatic organisms. Moreover, information regarding their levels and impending environmental long-term effects are now absent. (69) In earlier studies, three Parabens and common metabolite *p*-hydroxybenzoic acid tested for their ability to evoke an estrogenic response *in vivo*. Yolk protein introduction in sexually immature rainbow trout was used as an estrogen-specific endpoint after periodic injections of the compounds. All tested Parabens were estrogenic in doses between 100 and 300 mg/kg, while the metabolite showed no activity. Ethylparaben was found to be about sixty times weaker than propyl- and butylparaben which had estrogenic potencies comparable to those previously found for bisphenol A. (70) The acute toxicity of 21 Parabens and their chlorinated derivatives was explored by means of two toxicity bioassays using *Daphnia magna* immobilization test and the inhibition of bioluminescence of *Vibrio fischeri*. The average effective concentration (EC50) values of the tested Parabens ranged from 2.2 to 62 mg L-1in the D. *magna* test and from 0.0038 to 5.9 mg L-1 in the *V. fischeri* test at 15 min after exposure. (71) In the same case, chronic toxicity also found in 12 compounds of Parabens and their chlorinated by-products were investigated using 7-day *Ceriodaphnia dubia* test under stationary renewal condition in order to produce evidence on how to disinfect by-products of preservatives that are discharged in marine systems. The mortality and inhibition of reproduction inclined to increase with growing hydrophobicity and decreased with the degree of chlorination of Parabens. The EC50 values for mortality, offspring number, and first brood production ranged between 0.30–3.1, 0.047–

12, and 1.3–6.3 mg L−1, respectively.(72) Aquatic concentrations of seven parabens were determined in urban streams highly affected by treated or untreated domestic sewage in Tokushima and Osaka, Japan. The observed highest concentrations were 670, 207, and 163 ng L-1 for methylparaben, *n*-propylparaben, and *n*-butylparaben, respectively in specimen sites with a watershed area of no sewer system in Tokushima. Conventional acute/chronic toxicity tests were conducted using medaka (*Oryzias latipes*), *Daphnia magna*, and *Pseudokirchneriella subcapitata* for four Parabens, which was consistent with our earlier study on three Parabens, *n*-butylparaben, *i*-butylparaben, and Benzylparaben. The aquatic toxicity on fish, daphnia, and algae were weaker for the Parabens with a shorter alkyl chain than those with a longer alkyl chain as predicted by their hydrophobicity. (73)

CONCLUSION:

Parabens is a series of compounds used as a classic antimicrobial preservative in foods, drugs, and cosmetics for over 60 years. Parabens absorbed through the skin and from the gastrointestinal tract, further hydrolyzed to p-hydroxybenzoic acid, conjugated, and then rapidly excreted in the urine. While no evidence of accumulation and toxicity, studies in animals indicate that methylparaben is practically non-toxic by both oral and parenteral routes. In contrast, some recent literature suggested that the mechanism of cytotoxic action of Parabens might be linked to mitochondrial failure dependent on induction of membrane permeability transition accompanied by the mitochondrial depolarization and depletion of cellular ATP through uncoupling of oxidative phosphorylation. Parabens were reported to cause contact dermatitis reactions in some individuals on cutaneous exposure. Parabens have been implicated in numerous cases of contact sensitivity related to cutaneous exposure; endocrine disruption and marine animal toxicity (i.e. Daphnia Magna etc.) however, the mechanism of this sensitivity is unknown. It has been estimated that women are exposed to 50 mg per day of Parabens from cosmetics. However, more research is needed concerning the resulting levels of Parabens in people. (6, 74) from all of above, it was concluded that current ongoing researches and formerly published work have been directed us toward the safety and possible hazardous effects of Parabens.

❖ **Conflict of Interest:** Authors Declare No Conflict of Interest.

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