Safety and Toxicity Assessment of Parabens in Pharmaceutical and Food Products

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Safety and Toxicity Assessment 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 researches evidenced 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 parahydroxybenzoic acid also known as 4-hydroxybenzoic acid. [1] Their effectiveness as preservatives, in combination with their low-costanalogs, 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]

OCCURRENCE AND EXPOSURE

Chunyang Liao has been evaluated the 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 [8, 9] has 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.

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

1. **Cosmetics and Personal Care Products**
   a. Shampoos and conditioners
   b. Body lotions
   c. Shower gels
   d. Scrubs
   e. Sunscreen cosmetics
   f. Deodorants and antiperspirants
   g. Moisturizers.

2. **Edible Products**
   a. Beverages; i.e. beer, soft drinks, frozen dairy products
   b. Jams, Jellies and pickles
   c. sauces, desserts,
   d. 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 is not 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

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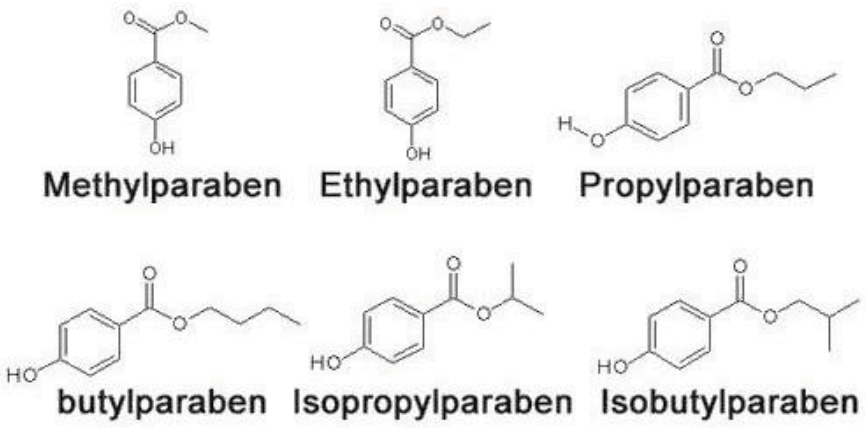

Figure 1: Chemical structure of alkyl esters of parahydroxybenzoicacid

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]

Parabens have very low toxicity. Singhal *et al*., [14] most likely make this assumption based on the large LD50 value in mice. Methyl and propylparaben, two of the most commonly used Parabens in products today, have an LD50 value greater than 8000 mg/kg in propylene glycol. 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*., [17, 18] research demonstrates that Parabens are quickly excreted through 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.

In another study, Chen Yiqun *et al*., [19] 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 SO_4 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. As a health concern, M G Soni *et al*., [20] add focus on the Parabens on the basis of published researches. In early 2005 It is the opinion of the SCCP that, viewing the current knowledge, there is no evidence of demonstrable risk for the development of breast cancer caused by the use of underarm cosmetics.[21]

Methyl and ethylparaben can be safely used up to the maximum authorized concentration as actually established (0.4%). The available data do not enable a decisive response to the question of whether propyl, butyl and isobutyl paraben can be safely used in cosmetic products at individual concentrations up to 0.4%. More information is needed in order to formulate a final statement on the maximum concentration of propyl, isopropyl, butyl and isobutyl paraben allowed in cosmetic products. Further, in 2008 as already concluded in earlier opinions, methyl paraben and ethyl parabens were not subject of concern. The SCCP is of the opinion that, based upon the available data, the safety assessment of propyl and butyl paraben cannot be finalized yet. In 2011 The use of butylparaben and propylparaben as preservatives in finished cosmetic products as safe to the consumer, as long as the sum of their individual concentrations does not exceed 0.19%. With regard to methylparaben and ethylparaben, the previous opinion, stating that the use of the maximum authorized concentrations can be considered safe, remains unchanged. Limited to no information was submitted for the safety evaluation of isopropyl- and isobutyl-paraben. Therefore, for these compounds, the human risk cannot be evaluated. The same is true for benzylparaben. For general cosmetic products containing parabens, excluding specific products for the nappy area, the SCCS considers that there is no safety concern in children (any age group) as the MOS was based on very conservative assumptions, both concerning toxicity and concerning exposure. In the case of children below the age of 6 months and with respect to Parabens present in leave-on cosmetic products designed for application on the nappy area, a risk cannot be excluded in the light of both the immature metabolism and the possibly damaged skin in this area. Based on a worst case assumption of exposure, safety concerns might be raised. Given the presently available data, it is not possible to perform a realistic quantitative risk assessment for children in the pertinent age group as information on internal exposure in children is lacking. With regard to pregnant women, the unborn fetus will be better protected than the neonate/newborn or early infant exposed dermally to parabens by the more efficient systemic

Parabens inactivation by the mother. Up to 2013, the concerns related to parabens expressed previously and repeated in new views remain unaffected and reinforced after the evaluation of both the reproductive toxicity and the toxicokinetic studies on propylparaben recently submitted to the SCCS. The same data were extrapolated for the evaluation of the risk by butylparaben exposure. The additional submitted data does not remove the concern expressed in the previous opinions on the relevance of the rat model for the risk assessment of Parabens. [1, 14, 18, 21, 22]

INTERNATIONAL CRISES RELATED TO PARABENS

The Scientific Committee on Consumer Safety (SCCS) finally concluded that, for overall cosmetic products containing Parabens SCCS considers that there is no safety concern in children (any age group), both concerning toxicity and exposure. The view of the SCCS was additionally found to be supported by recent human biomonitoring data from Europe and the United States (for adults and children above 6 years) suggesting that systemic exposure doses are considerably lower than 30 estimated in the paraben opinion. The current proof of evidence supports the view that the known metabolites of Parabens, PHBA and conjugated Parabens can considered not possessing estrogenic potential, based on the outcome of experimental studies and Structure activity relationship (SAR) considerations. The conclusions continued: "In the case of children below the age of 6 months and with respect to Parabens present in leave-on cosmetic products intended for application on the nappy area, a risk cannot be excluded in the light of both the immature metabolism and the possibly damaged skin in this area. Based on a worst-case assumption of exposure, safety concerns might be raised. [23-28] Given the presently available data, it is not possible to perform a realistic quantitative risk assessment for children in the pertinent age group as information on internal exposure in 40 children is lacking. Scientifically comprehensive data on the pivotal link between dermal absorption in rats and humans, in particular with regard to the metabolism of the parent parabens in the skin and specific exposure information for cosmetic products used for children would allow a modification of the above valuation. With regard to pregnant women, the unborn fetus will be better protected than the neonate/newborn or early infant exposed dermally to Parabens by the more efficient systemic Parabens inactivation by the mother". [29, 30] Scientific Committee on Consumer Safety commission improves the safety of cosmetics with the adopted actions the Commission limits the maximum concentration of two preservatives, propylparaben and butylparaben, from currently allowed a limit of 0.4% when used individually and 0.8% when mixed with other esters, to 0.14%, when used individually or together. They were banned from leave-on products designed for the nappy area of young children below the age of three since prevailing skin irritation and occlusion may allow increased penetration than intact skin. The new rules will apply for products put on shelves after 16 April 2015 Earlier this year, the Commission banned the use of five other Parabens in cosmetic products - Isopropylparaben, Isobutylparaben, Phenylparaben, Benzylparaben and Pentylparaben due to the lack of data necessary for reassessment. Products placed on the market after 30 October 2014 will have to be free from these substances.

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, [31] Parabens from personal care products are absorbed through the skin. Skin enzymes cannot process all topically applied Parabens, [32] and some amount of them is retained in the body tissues. [15, 33] 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.[32, 34, 35] 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%. [20, 36]

A general hypothetical way of metabolism of Parabens in the body shown in Figure 2, in earlier literature, it was reported that the saturated aqueous solutions of propylparaben are moderately irritating to the eye. Ingestion of a 0.03% propylparaben solution causes irritation to the intestinal mucosa. Acute toxicity studies in animals designate that propylparaben is relatively non-toxic by both oral and parenteral routes, although it is mildly irritating to the skin. Following chronic administration, no observed effect levels (NOEL) as high as 1200-4000 mg/kg have been reported and a no-observed-adverse-effect level (NOAEL) of 5500 mg/kg was reported in the rat. Propylparaben was found to be not carcinogenic; mutagenic also it was not cytogenic *in-vitro* in the absence of carboxylesterase inhibitors. Propylparaben by the oral intake produces cell proliferation in the forestomach of rats. In one in vitro study, sperm was not viable at concentrations as low as 3 mg/ml propylparaben. propylparaben did affect sperm counts in vivo at all levels from 0.01% to 1.0%. A placebo-controlled oral challenge with a mixture of 100 mg of methyl- and 100 mg of propylparaben was performed in 14 patients with a positive patch test to Parabens-mix. Two of the 14 patients had flares of their dermatitis after challenge with oral Parabens, but not the placebo. One patient had a flare at a paraben patch test site on the back. The other 11 patients had no reaction to the oral challenge. [21]

MAJOR HEALTH CONCERNS REGARDING PARABENS

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

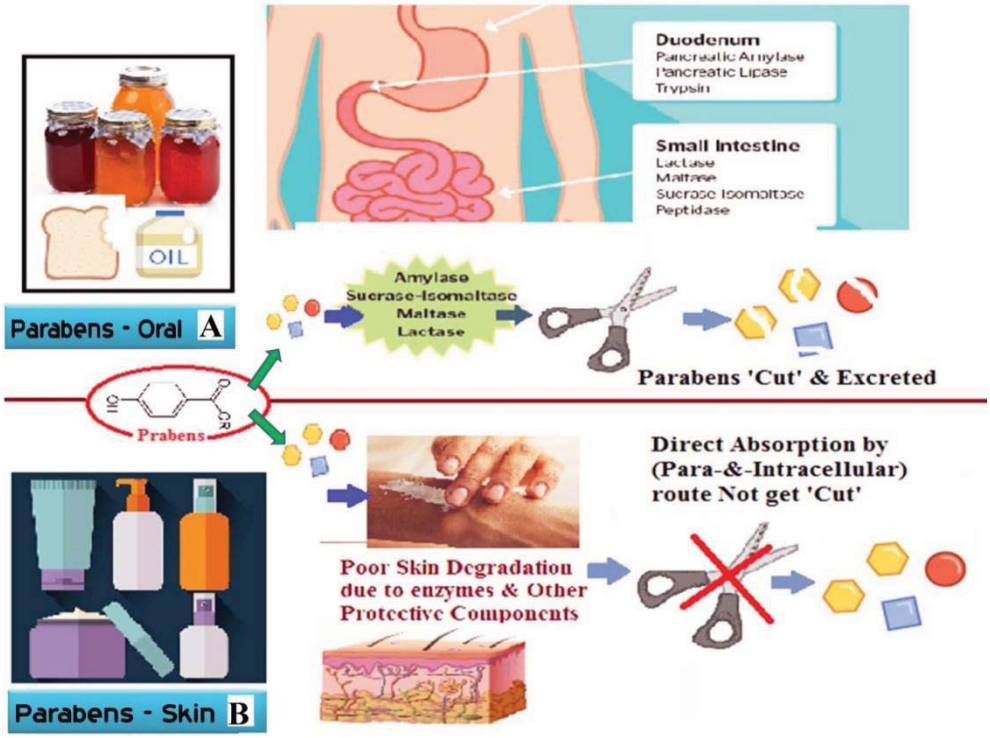

Figure 1: Possible mechanism of paraben absorption, metabolism and excretion A) Oral B) Skin

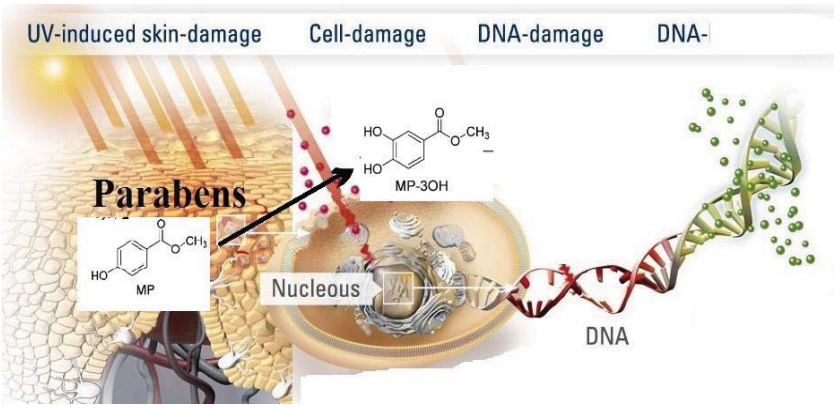

Figure 3: Combined activation of methylparaben by sunlight irradiation and skin esterases lead toward oxidative DNA damage

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. [37] The Cosmetic Ingredient Review (CIR) Expert Panel concludes that the available data are insufficient to support the safety of Benzylparaben 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, [20, 38] which is depicted in the Figure 3.

Parabens in cosmetics and sunscreens undergo photochemical decomposition which one is one of the important clearance routes along with dermal tissue metabolism. [39] In the present 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.*, [40] 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. [41] 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. [42, 43] Human exposure doses to Parabens cannot be accurately estimated based only on paraben concentrations in urine because Parabens do get metabolized to p-HB at different rates. [22, 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 was 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*., [49] 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 a issue in the growth of breast cancer, then options for prevention could be individual decisions to stop usage or through alterations to product formulations.

Endocrine System Related Issues

Endocrine disruptors are chemicals that can interfere with endocrine (or hormone) systems at certain doses. [50] 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. An extensive range of substances, both natural and synthetic, are thought to cause endocrine disruption, comprising pharmaceuticals, dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, plasticizers such as bisphenol A. Endocrine disruptors may be found in many everyday products– including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics and pesticides. [51-54] 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. [55, 56] 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. [57, 58] 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. [59-61] 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. [62]

Direct Toxicity through Lymphatic System

A recent review by Darbre (2003) published in a journal of Applied Toxicology, has attracted public and scientific interest that requires perspective, particularly on the use of esters of *p*-hydroxybenzoic acid (Parabens) as preservatives in underarm cosmetics. The Parabens used as antimicrobial preservatives in underarm deodorants and antiperspirants and in a wide range of other consumer products. The Parabens also have inherent estrogenic and other hormone-related activity (increased progesterone receptor gene expression). As estrogen is a major etiological factor in the growth and development of the majority of human breast cancers, it has been previously suggested.The hypothesis forwarded that underarm cosmetics may be implicated in the incidence of breast cancer (Darbre, 2003) has been discussed also in terms of the potential toxicity of oestrogenic formulation ingredients (Harvey, 2003). Although recent efforts have been made to examine 'antiperspirant use and the risk of breast cancer', [63] who report no association based on the reflective interview.

Estrogenic Activity Related Issues

Pugazhendhi pope *et al*., [64] 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**.** Various

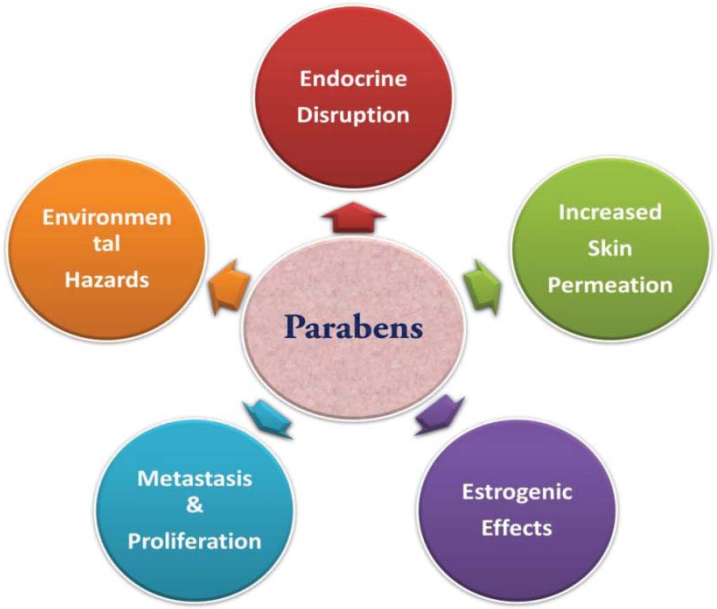

Figure 4: Various hazardous effects of parabens

in-vitro assays were showed that Parabens can bind to estrogen receptor [65] 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. [66] On the other hand, Parabens have been reported to stimulate the proliferation of MCF-7 breast cancer cells. [67, 68] 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. Eight of the 15 substances tested showed specific estrogenic activity with the following degree of potency on ER-alpha butylparaben > propylparaben > homosalate = octyl-dimethyl-PABA = 4-methyl-benzylidene-camphor = octyl-methoxycinnamate > ethylparaben = galaxolide. Among these active substances, Parabens activated ER-alpha and ER-beta similarly, Methylparaben, Ethylparaben, musk moskene, celestolide and cashmeran did not activate estrogenic responses up to 10^{-5} M. [68]

Skin Toxicity Related Issues

In 1974 Marzulli and Maibach Suggested an Commentary on 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. 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. [69] Seventy years of use have confirmed the excellent safety of Parabens asstable, effective and nonirritant preservatives. [21, 37, 70] In 1940, Bonnevie in Denmark described the first case of allergic contact dermatitis from Parabens. [28, 71] Allergic dermatitis, eczema is, therefore, often difficult to diagnose, presenting as recalcitrant dermatitis that fails to improve or worsens under seemingly adequate treatment. [72, 73] 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 are 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. [74] These different effect combined depicted in the Figure 4.

Contact with foods preserved with parabens may rarely cause hand dermatitis in cooks and food handlers. [75] 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. [76] Parenteral administration of paraben containing medicines has occasionally resulted in systemic contact dermatitis, a more or less widespread eczematous eruption in individuals previously sensitized to parabens from topical exposure. [77, 78] One case of generalized delayed eruption with an urticarial morphology was caused by methylparaben. [79] The peak blood content of 0.1% of the administered dose present as free, unhydrolyzed paraben following human dermal contact resembles well to the 0.2% uptake of free, unhydrolyzed paraben estimated from an *in-vitro* study on dermal penetration through human full-thickness skin conducted by Fasano *et al*., [80]

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, 81] 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.

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