Open Access Journal
International Journal of Medical Research and Pharmaceutical Sciences
Volume 3 (Issue 8) : August 2016 ISSN: 2394-9414
DOI: 10.5281/zenodo.61076 Impact Factor- 3.109

PARABENS PARADOXES IN COSMETIC FORMULATIONS: A REVIEW

Francisco Ana[*1] and Fonseca Ana Paula[2]

[*1]Department of Pharmacy, Polytechnic Institute of Coimbra, ESTeSC-Coimbra Health School, Coimbra Portugal
[2]Department of Pharmacy, Polytechnic Institute of Coimbra, ESTeSC-Coimbra Health School, Coimbra Portugal

Corresponding author: Fonseca Ana Paula

Keywords:
Parabens, Cosmetics, Parabens toxicity, Parabens safety.

Abstract

Cosmetics are defined as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body, for cleansing, beautifying, promoting attractiveness, or altering the appearance." Consequently, they include products such as skin moisturizers, perfumes, lipsticks, shampoos, deodorants, as well as any material intended for use as a component of a cosmetic product. In order to enhance cosmetic properties, promote cosmetic efficacy and produce more viable products, many cosmetics contain chemical additives, such as parabens. However, recent studies have cautioned that exposure to parabens may have harmful consequences on human health. Therefore, the safety of parabens for use as preservatives in cosmetics has come into controversy, and as a result, consumer demand for paraben-free products, is widely increasing.

In this paper, is reviewed parabens usage, characteristics and legislation associated, as well as hazards to human health. This study also aims to determine the safety of prolonged exposure to parabens used in cosmetics.

For this literature review without meta-analysis were used as databases PubMed and b-on in order to find reliable information on the subject under study.

Therefore, it was possible to confirm that parabens are safe, when used at the maximum authorized concentrations.

INTRODUCTION

‘‘Paraben’’ is an abbreviation of *para-hydroxybenzoic acid*, which refers to a group of alkyl esters with substitutions at the *para* site of the *hydroxybenzoic acid benzene* ring (Figure 1) [1].

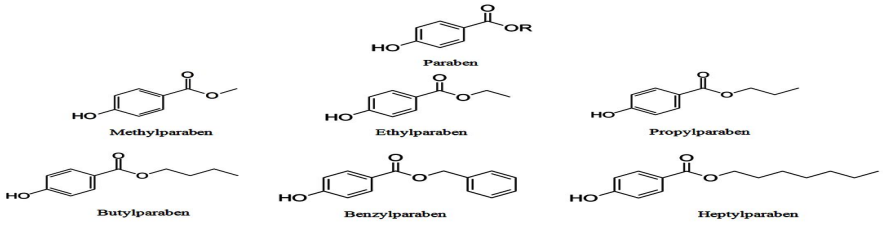


Fig 1. Chemical structure of paraben and alkyl esters of para-hydroxybenzoic acid.

Open Access Journal
International Journal of Medical Research and Pharmaceutical Sciences
Volume 3 (Issue 8) : August 2016 ISSN: 2394-9414
DOI: 10.5281/zenodo.61076 Impact Factor- 3.109

This family of chemicals mainly includes *methyl-paraben, ethylparaben, n-propylparaben, iso-propylparaben, n-butylparaben, iso-butylparaben, benzylparaben,* and *heptylparaben* and their respective sodium salts (Table 1) [2,3].

Table 1. Physical and chemical characteristics of parabens (PB).*[2,3,4]*.

Characteristic	MePB	EtPB	PrPB	BuPB	BePB
Chemical formula	$C_8H_8O_3$	$C_9H_{10}O_3$	$C_{10}H_{12}O_3$	$C_{11}H_{14}O_3$	$C_{14}H_{12}O_3$
Molecular weight (g/mol)	152.16	166.18	180.21	194.23	228.25
pK_a	8.17	8.22	8.35	8.37	-
Log octanol–water partition coefficients (log K_{ow})	1.66	2.19	2.71	3.24	3.56
Solubility in water at 25 °C (g/100 ml)	2.00	0.86	0.30	0.15	0.05

Parabens were first introduced as preservatives in drug products in mid 1920s. Currently, they are widely used preservatives, mainly in cosmetics and pharmaceuticals, but also in food commodities and industrial products [4,5]. Human exposure to parabens occurs mostly through the consumption of personal care products containing parabens [6,7], as cosmetic preparations are frequently used by a great number of people without distinction of age, gender or race and, generally, during a long period of time [8].

Parabens can have multiple biological actions, but it is generally believed that their inhibitory effects on membrane transport and mitochondrial function processes are key for their actions [9]. Their popularity is based on several advantages when compared to other alternatives:

- broad spectrum of activity against yeasts, molds and bacteria;
- chemical stability (for a wide temperature interval and pHs ranging from 4.5 to 7.5);
- inertness;
- low degree of systemic toxicity;
- low frequency of sensitization;
- sufficient water solubility (enabling to obtain effective concentration);
- relatively safe use;
- low costs of production;
- no perceptible odor or taste:
- not causing changes in consistency or coloration of products [2,4,9,10].

Even though parabens have been used for more than 50 years and are generally considered as safe, several studies concerning on the safety of parabens have been published [4,9–13]. Some research results on parabens claimed that they can cause breast cancer or problems in male reproductive system, among other effects [2,14–16].

This review study aims to emphasize the safety of prolonged exposure to parabens used in cosmetics formulations, as an issue of public health.

MATERIAL AND METHODS

A review search of the literature was undertaken between January 1990 to May 2016 using the following combinations of terms: *Parabens*, *Parabens toxicity*, *Parabens safety*, *Parabens review* and *Parabens cosmetics*. Articles in English, Portuguese and Spanish were included. Electronic databases were searched in PubMed, Nature Reviews, ScienceDirect, Elsevier, and b-on. Manual searches of bibliographies were also conducted to identify additional pertinent studies. All of the studies were selected, analyzed and classified according to their quality (Figure 2).

Open Access Journal
International Journal of Medical Research and Pharmaceutical Sciences
Volume 3 (Issue 8) : August 2016 ISSN: 2394-9414
DOI: 10.5281/zenodo.61076 Impact Factor- 3.109

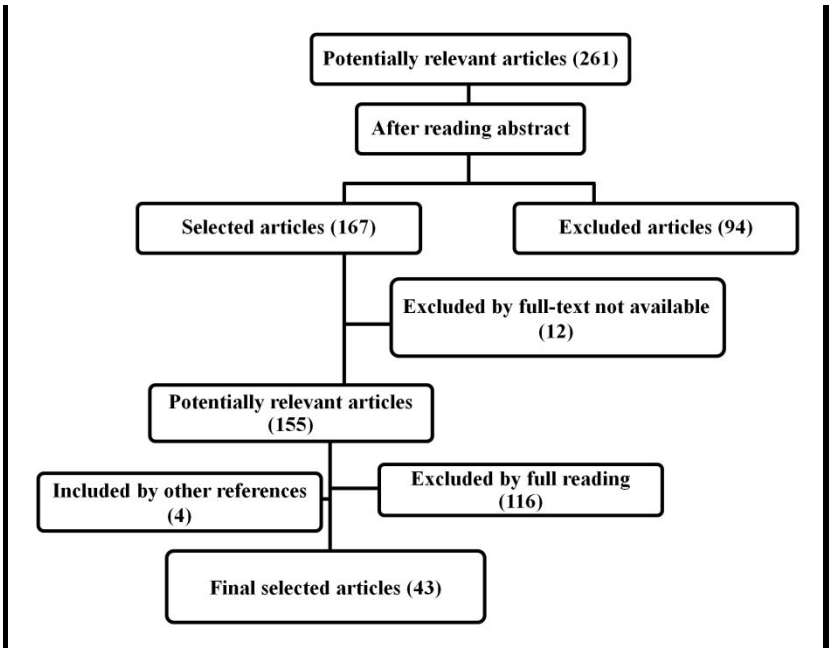


Fig 2. Selection process of the articles (identification, screening, eligibility and inclusion).

RECOMMENDATIONS AND INTERNATIONAL REGULATION

Current regulations on parabens usage differ by country [17]. According to European Union (EU) Council Directive, the allowable content of parabens in cosmetic products is a maximum concentration of 0.4% for each ester and 0.8% for total mixtures of esters [4,10,17].

However, in 2011, the Danish government decided to introduce additional restrictions, banning the use of some parabens (propyl-, isopropyl-, butyl- and isobutyl-parabens) in personal care products intended for children younger than 3 years. This led the EU Scientific Committee on Consumer Safety (SCCS) to reevaluate the subject and suggest that allowed concentrations remain unchanged for methylparaben and ethylparaben but that the sum of individual concentrations of propylparaben and butylparaben in finished products should be limited to 0.19% [4,18]. On the basis of this report, the EU Commission amended the Directive and, in 2014, banned isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben. In 2015, April 16, the Commission limited the maximum concentration of two preservatives, propylparaben and butylparaben, from currently allowed limit of 0.4% when used individually and 0.8% when mixed with other esters, to 0.14%, when used individually or together. They are also banned from leave-on products designed for the nappy area of young children below the age of three since existing skin irritation and occlusion may allow increased penetration than intact skin [18,19].

The governmental units of the United States, Food and Drug Administration (FDA) and Canada (Health Canada), are not authorized to approve cosmetic ingredients under the Federal Food, Drug and Cosmetic Act, but an industry-sponsored organization, the CIR (Cosmetic Ingredient Review) have recommended the same threshold for parabens as that of EU [4,20].

On the other hand, the international certification agencies ECOCERT (France), BDIH (Germany), NaTrue (Belgium), Soil Association (United Kingdom), ICEA (Italy), and BIOCOSC (Switzerland) agreed with the EU and Danish EPA positions, and will no longer certify products containing parabens. The Professional Association for Natural, Ecological and Organic cosmetics, CosmeBio (cosmebio.org), has also banned the use of parabens in cosmetic products since 2002 as “a precautionary principle and out of concern for the health of consumers” [17].

Although no ban on paraben use currently exists in the United States, a number of prominent cosmetic manufacturers are starting to migrate away from parabens and instead focus on alternative preservatives or decrease the amount of parabens in their products due to increasing consumer concerns [17]. Some other commonly used preservatives include formaldehyde, quaternium-15, imidazolidinyl urea, diazolidinyl urea and dimethyloldimethyl hydantoin. Other natural preservatives include thymol, cinnamaldehyde, allyl isothiocyanate, citric acid, ascorbic

Volume 3 (Issue 8) : August 2016 ISSN: 2394-9414
DOI: 10.5281/zenodo.61076 Impact Factor- 3.109

acid and rosemary extract. The use of "natural" preservatives has been advocated, including grapefruit seed extract (GSE).Unfortunately, these preservatives are linked to allergic reactions, among other health problems, and there is a lack of studies to determine their efficacy, safety and toxicology before widespread use [1,20–24]. As a result, fully satisfactory substitutes have yet to be discovered [17].

BIOCHEMICAL AND TOXICOLOGICAL DATA

Pharmacokinetics

Animal studies have shown that parabens are rapidly absorbed, metabolized and excreted [10]. Metabolism of parabens was studied by treating rats with 100mg of methyl- or propylparaben orally. After oral administration in rats, parabens were rapidly absorbed from the gastrointestinal tract and blood [4,10].

Both oral and dermal administrations most likely lead to hydrolysis of parabens by non-specific esterase's, widely distributed in the body and abundant at sites of entry such as skin, subcutaneous fat tissue and digestive system. The main product of the hydrolysis of parabens is p-hydroxybenzoic acid [4].

Because most paraben-containing products are topically applied to the skin, dermal absorption is particularly important. The skin is not an impenetrable barrier, and depending on the specific paraben (i.e., K_{ow}) and the type of formulation (e.g., aqueous or lipid), some fraction of an applied dose may be absorbed and enter the systemic circulation [4].

In an *in vitro* study using human epidermal membranes, the ability of different vehicles (acetone, ethanol or ointment) to affect the permeability of four parabens (methyl, ethyl, propyl, and butyl) with or without occlusion was determined. While the skin permeability of the parabens alone was not measured, the results demonstrated that different vehicles, particularly in conjunction with occlusion, enhanced skin permeability. For example, the percentages of butylparaben in ointment, acetone, or ethanol penetrating the skin over a period of 10 h were 39%, 44%, and 57%. These results suggest that parabens formulated into certain skin-care products can penetrate the skin. The determinants of actual dermal permeability are likely to be a complex interaction of individual parabens, partition coefficient (i.e., log K_{ow}), and the presence of other ingredients in a particular product. It was also demonstrated that permeability increased as a function of *n*-octanol/water partition coefficients (K_{ow}) in the order butyl > propyl > ethyl > methyl [4,25].

Efficiency and pattern of hydrolysis of parabens in the organism vary considerably depending on alkyl chain length and tissue. Though human skin contains carboxylesterase isoforms, which are able to metabolize parabens to pHBA, esterase's levels and activities could be insufficient for a complete hydrolysis of dermally applied parabens. Laboratory tests on rats revealed that over 50% of the paraben dose was unabsorbed following dermal application. Interestingly, *in vitro* studies revealed that parabens undergo much slower hydrolysis in human skin than in human liver, rat liver and rat skin [4].

Following dermal administration, part of MePB does not undergo hydrolysis and therefore a certain amount of unmetabolized compound may remain systemically available. Additionally, skin damage can result in an increase of MePB absorption rate. It is estimated that up to 923 µg/kg bw/day of unhydrolized MePB can become systemically available, following application of leave-on emulsion containing PB to damaged skin [4].

In relation to excretion of parabens and their metabolites, orally or subcutaneously administered parabens were predominantly excreted in the urine, mainly during the first 24 h. However, 2% of applied doses were retained in the tissues and carcasses, while less than 4% were removed with the feces. Parabens and their hydrolysates are excreted in urine as free form or glycine, glucuronide and sulfate conjugates [4].

TOXICITY AND ADVERSE EFFECTS OF PARABENS

Dermal absorption

An extensive number of cosmetic products are applied topically, often multiple times a day. These products are not rinsed off but left on the skin, allowing for continuous dermal exposure, and therefore over a long period may result in absorption and accumulation into underlying tissues [26,27].

Previous reviews have suggested that dermal rather than oral exposure is more likely to have resulted in the parabens entering human tissue, and *Janjua et al in 2007* demonstrated that parabens can be rapidly absorbed through the skin into the human body even from a single dose of a body care product and long-term exposure results in the accumulation of these chemicals [27–29].

Volume 3 (Issue 8) : August 2016 ISSN: 2394-9414
DOI: 10.5281/zenodo.61076 Impact Factor- 3.109

Compared with oral ingestion, uptake of parabens through the skin may thus result in higher serum and urine concentrations of the parent compounds because they bypass hepatic degradation [18].
Others studies have shown parabens to be readily absorbed through animal skin but absorption kinetics combined with lower rates of metabolism in human skin suggests that absorption through human skin is higher than through animal skin. Several studies have now reported a positive correlation between the amount of one or more personal care products used and levels of parabens measured in human blood or urine [8,9,14,18,27,29,34,35,38].
Higher levels of parabens in urine from women over men has been interpreted as related to a higher use of cosmetic products in women. Likewise, higher levels of parabens in African Americans over Caucasians may also relate to patterns of personal care product usage [27].

Parabens and contact allergy
Parabens are practically non-irritating and non-sensitizing in the human population with normal skin. The first case of paraben contact allergy was reported in 1940 by Bonnevie [30].
Allergic contact dermatitis from paraben is low, ranging from 0 to 4.2% [10]. Their capacity to act as sensitizers when used in cosmetics (applied to healthy skin) is low, at around 1%, and in fact they have one of the lowest rates of sensitization of all preservatives [22]. However, the percentage can be significantly increased in patients with previously damaged or broken skin (for instance leg ulcers) [10,30]. A recent multicenter study in patients suffering from chronic leg ulcers showed a percentage of sensitized patients to parabens of 3.1% [30].

Cancer and the use of paraben-containing cosmetics
In 2004, *Darbre et al.* published an article mentioning a possible link between the use of cosmetic products containing parabens and the presence of such preservatives in breast cancer tissues [30]. They suggested that cream or lotion-based cosmetics, containing preservatives such as parabens, used on the underarm, chest, or breast area may be increasing breast cancer incidence in women [17].
A number of *in vitro* and *in vivo* studies demonstrated that skin might absorb parabens, which are then readily detected in tissue, blood, and urine samples. For example, in a related study, butylparaben was applied via a topical cream and was shortly thereafter detected in the blood of the human subjects. On the other hand, urine concentrations of methyl- and propylparaben were higher in adolescent and young women compared to males, which again correlated with increased use of personal care products and cosmetics by women [17].
In a comparative animal study, human skin was observed to retain parabens longer than skin of rats, suggesting a potential for prolonged estrogenic influence on human skin [17]. For that reason, the measurement of intact esters in human breast cancer tissue sparked an international debate in 2004 due to estrogenic properties of parabens. Furthermore, the incidence of about 60% of breast cancers in the upper outer quadrant of the breast suggested that there was a relationship between the chemicals applied underarm and the development of breast cancer [28].
Later, another study has actually shown that this MCF7 human breast cancer cell line is stimulated by ethylparabens and butylparabens at concentrations respectively 1,000 and 10,000 times higher than the 17 ß-oestradiol concentration but that the gene expression was different with parabens and oestrogens and that consequences to the cell lines are therefore not identical [30].
The more recent and larger set of measurements of paraben esters in 160 samples of human breast tissue taken from four serial locations across the breast from axilla to sternum from 40 patients undergoing mastectomy for breast cancer has confirmed widespread distribution of parabens both across individual breasts and between women. One or more paraben ester was detected in 158 of 160 of the tissue samples and 96 of 160 contained all five of the esters measured (methylparaben, ethylparaben, n-propylparaben, n-butylparaben and isobutylparaben). In line with measurements in other body tissues, methylparaben and propylparaben were the two parabens detected at highest levels. Cell culture studies demonstrated that proliferation of human breast cancer cells could be increased by exposure to these five parabens either alone or in combination at some of the measured breast tissue concentrations. Forty-three of 160 human breast tissue samples contained at least one paraben at a concentration above that needed for an observed effect on proliferation (lowest observed effect concentration) [27].
On the other hand, another study on the population of breast cancer patients reported that patients who used more antiperspirant products were diagnosed with breast cancer at an earlier age. This study suggested a dose–response relationship to chemical exposure and sensitivity at a younger age, consistent with the patterns of breast cancer development, but it did not exclude other risk factors or consider the possibility that cosmetic use was simply higher in younger women [28].

The estrogenic activity of some cosmetic products with parabens has recently been confirmed again by the development of gynecomastia in 3 prepubertal boys as a consequence of the topical application of body oils [28].

Parabens and pregnancy

Exposure of pregnant women is of particular concern because of the potential health impact on the vulnerable fetus, in which exposure may inflict lifelong adverse health effects [31].

It has been already demonstrated that parabens are able to cross the placental barrier and reach the developing fetuses and the newborn through maternal milk [31,32]. Thus, a number of these preservatives measured in maternal urine, serum and breast milk have also been found in amniotic fluid, cord blood and meconium [31,33]. Studies have also suggested that use of personal care products are an important source of exposure to parabens in women and children [34–36].

A recent study which involved a total of 50 pregnant patients, demonstrated that 47 were found to have methylparaben in their blood, as well as in the cords bloods samples. For butylparaben, only 4 mothers showed detectable levels, whereas 8 cord blood samples were positive [33].

This study confirms the presence of methylparaben and butylparaben in maternal blood and, indeed, cross the placenta and enter fetal circulation. Further research is needed to determine what products are used by pregnant women that contain these preservatives and any possible long-term effects in the growth and development of exposed children [33].

Effects on Reproductive system

Although limited in scope and number, some studies demonstrated parabens effects on male reproductive organs, testosterone levels, and sperm production [17]. The issue of paraben effects on human reproductive toxicity was addressed by *Glander et al.* (1984), who studied primary microbiological contamination in human ejaculates, and also secondary contamination after cryopreservation using methylparaben. These authors found that not only methylparaben reduced microbiological contamination of the cryoprotective medium, but also decreased human sperm motility [10].

Due to the important role of mitochondria in testis metabolism, it is logical to assume that parabens may also interfere with mitochondrial energetics and thus disturb sperm function. Although no data exist on direct effects of parabens on testis mitochondria, it seems possible that tissue accumulation of such compounds would lead to toxicological relevant concentrations that would disturb mitochondrial bioenergetics. In fact, preliminary results indicate that several parabens present direct toxicity on isolated testis mitochondria at low concentrations [10].

A study concerning the effects of maternal exposure to butylparaben during gestation and lactation periods demonstrated that this exposure may adversely affect reproductive organ development of male F1 progeny. Also, and more importantly, male reproductive organ weights (testes, seminal vesicles and prostate glands), sperm counts and sperm motility were adversely affected. Vaginal opening also occurred earlier in female offspring, compared with the control group [10].

Methyl and propylparaben treatment of neonatal female rats produced impaired postnatal ovarian follicle development [17,37]. Prepubertal dosing of female SD rats with methyl- or isopropylparaben (1000 mg/kg bw/d but not 250 mg/kg/d) from postnatal days 21–40 was also associated with endocrine changes, markedly delaying the day of vaginal opening, decreasing serum estradiol levels, and shortening the estrous cycle length. These female rats also displayed pathology in several endocrine organs that included ovaries, adrenal glands, thyroid glands, liver, and kidneys [17].

Finally, a study which has assessed female reproductive health effects in relation to paraben exposure, provided evidence suggesting that exposure to parabens may lead to diminished ovarian reserve and contribute to ovarian aging among women [38].

SAFETY EVALUATION OF PARABENS

Parabens Sensitization

Parabens are practically nonirritating and nosensitizing in the population with normal skin. Paraben sensitization has occurred and continues to be reported in the case literature, but principally when exposure involves damaged or broken skin. Even when patients with chronic dermatitis are patch-tested to a parabens mix, parabens generally induce sensitization in less than 4% of such individuals [13].

Many patients sensitized to paraben-containing medications can wear cosmetics containing these ingredients with no adverse effects. Clinical patch testing data available over the past 20 years demonstrate no significant change in the overall portion of dermatitis patients that test positive for parabens. As reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel, the available acute, subchronic, and chronic toxicity tests, using a range of exposure routes, demonstrate a low order of parabens' toxicity at concentrations that would be used in cosmetics [13].
Parabens are rarely irritating or sensitizing to normal human skin at concentrations used in cosmetics. Although parabens do penetrate the stratum corneum, metabolism of parabens takes place within viable skin, which is likely to result in only 1% unmetabolized parabens available for absorption into the body [13].

Paraben-containing cosmetics and cancer
Harvey and Darbre (2004) suggested that cream- or lotion-based cosmetics, containing preservatives such as parabens, used on the underarm, chest, or breast area may be increasing breast cancer incidence in women [17]. However, in Darbre's study, no clear link was established between parabens and breast cancer [30,39]. In order to reach a true scientific conclusion, *Darbre* should have identified the route by which parabens enter the body (it might for instance have been from food or medicines taken by the patients); there was no information provided about the background of the patients, location and type of the tumor (ie, estrogen receptor positivity status), use of cosmetics, and so forth; absence of control tissue; and most importantly; blanks (no tissue) were also positive for parabens, suggesting contamination during the analytical process. Finally, this study was very small with only twenty tumour samples [18,30].
Darbre and Harvey's review article (2008) repeats the arguments that have all been refuted, and it does not add new data nor adds any conclusive evidence [39].
In 2012, *Barr et al* measured paraben levels in different regions of healthy breast tissue (without cancer). Except propyloparaben (which was observed at higher levels in the upper outer quadrant compared with other breast regions), the other parabens had similar concentrations in different breast regions [28]. Interestingly, 7 of these 40 patients had never used underarm cosmetics, suggesting they were exposed to parabens from other sources [17].

Parabens and reproductive system
Methyl, ethyl, propyl and butylparaben have been examined for effects on the reproductive organs [40]. Previous studies have shown that methylparaben was nonteratogenic in rabbits, rats, mice, and hamsters, and ethylparaben was nonteratogenic in rats. Parabens, even at levels that produce maternal toxicity, do not produce fetal anomalies in animal studies [13].
In 2004, *Cantox Health Sciences International* prepared an assessment of the endocrine disrupting/estrogenic potential of parabens. This assessment noted that parabens do not have genotoxic, carcinogenic, or teratogenic potential and are rapidly hydrolyzed to p-hydroxybenzoic acid and excreted [13].
Decreased sperm numbers and activity were reported in female rats given butylparaben by subcutaneous injection at 100 or 200 mg/kg day(-1), but there were no abnormalities in the reproductive organs [13]. Male neonatal Wistar rats were subjected to subcutaneous injection with butyl paraben at 2 mg/kg bw/day on postnatal days 2 to 18 showed no detectable effects on any reproductive parameter [40].
In another study it was revealed that pregnant and lactating dams presented no toxicity signs or body weight loss during butylparaben treatment and the number of live delivered pups and pups weight were also similar among experimental groups, indicating no toxic effects of parabens on the offspring and dams during gestation. In agreement, on other study showed that butylparaben, even in higher doses (400 mg/kg), did not caused alterations on maternal body weight, fetal weight, and number of fetuses [32].
Propylparaben and butylparaben were also administered subcutaneously at doses of up to 35 mg/d to pregnant mice during days 1 to 4 of pregnancy and this study found no adverse reproductive or other effects in mice, whereas the positive control substance, 17α-estradiol, produced the expected termination of pregnancy [18].

CONCLUSION
Preservatives are essential in cosmetics as they protect consumers from harmful pathogens that would otherwise invade the creams and products people use on a daily basis. Without preservatives all cosmetics would have a very short shelf life and would, in the most part, have to be stored in a fridge.

The group of chemicals known as parabens make up an important part of the preservatives which could be used in cosmetics. However, it is crucial to ensure that preservatives guarantee the maximum degree of protection to people.
In the past years, the safety of parabens has been challenged. Concerns have been raised about the possible adverse effects of the properties of parabens, as they are suspected to be potential endocrine disrupters that may contribute to the development of breast cancer and the occurrence of male infertility.
The SCCS confirmed that methylparaben and ethylparaben are safe at the maximum authorized concentrations as well as propylparaben and butylparaben. No concerns were raised on the safety of 4-Hydroxybenzoic acid and its salts (calcium paraben, sodium paraben, potassium paraben).
In addition, the Commission banned the use of five other parabens in cosmetic products due to the lack of data necessary for reassessment. As a result, for these compounds, the human risk cannot be evaluated. Therefore, more studies should be performed in humans, with larger sample sizes and with special focus on the male reproductive system and effects on the fetus that could occur during pregnancy or in later life.
Moreover, most of the toxicological studies for parabens were performed through the oral route, yet data on the effect of parabens or their intact esters via dermal administration, which is also a major route of exposure, are lacking and warrant thorough investigation. On the other hand, these studies should also address acute and long-term multiple parabens exposure (i.e., combinations of parabens).
In summary, some available studies showed endocrine-disrupting effects of parabens at environmentally relevant doses, which led several countries to already ban parabens, while others are working toward eliminating parabens in cosmetics as a precautionary measure. Although numerous studies involving parabens have been conducted, there are still significant gaps in knowledge regarding parabens exposure. For example, studies are designed under specific *in vitro* and *in vivo* experimental protocols when they are not reflective of human effects mainly because they fail to prove hormonal activity in humans and fail to consider the metabolism, degradation, and elimination of parabens in human subjects. Limited yet suggestive data highlight the need for further research on these chemicals.

REFERENCES

[1] *L.E. Maier, H.P. Lampel, T. Bhutani, S.E. Jacob, Hand Dermatitis: A Focus on Allergic Contact Dermatitis to Biocides, Dermatol. Clin. 27 (2009) 251–264. doi:10.1016/j.det.2009.05.007.*
[2] *J.A. Ocaña-González, M. Villar-Navarro, M. Ramos-Payán, R. Fernández-Torres, M.A. Bello-López, New developments in the extraction and determination of parabens in cosmetics and environmental samples. A review, Anal. Chim. Acta. (2014). doi:10.1016/j.aca.2014.07.002.*
[3] *C. Piao, L. Chen, Y. Wang, A review of the extraction and chromatographic determination methods for the analysis of parabens, J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 969 (2014) 139–148. doi:10.1016/j.jchromb.2014.08.015.*
[4] *D. Błędzka, J. Gromadzińska, W. Wąsowicz, Parabens. From environmental studies to human health., Environ. Int. 67 (2014) 27–42. doi:10.1016/j.envint.2014.02.007.*
[5] *M. Flasiński, M. Gawryś, M. Broniatowski, P. Wydro, Studies on the interactions between parabens and lipid membrane components in monolayers at the air/aqueous solution interface, Biochim. Biophys. Acta - Biomembr. (2016). doi:10.1016/j.bbamem.2016.01.002.*
[6] *C. Moreta, M.T. Tena, K. Kannan, Analytical method for the determination and a survey of parabens and their derivatives in pharmaceuticals, Environ. Res. 142 (2015) 452–460. doi:10.1016/j.envres.2015.07.014.*
[7] *H.-S. Kang, M.-S. Kyung, A. Ko, J.-H. Park, M.-S. Hwang, J.-E. Kwon, J.-H. Suh, H.-S. Lee, G.I. Moon, J.-H. Hong, I.G. Hwang, Urinary concentrations of parabens and their association with demographic factors: A population-based cross-sectional study, Environ. Res. 146 (2016) 245–251. doi:10.1016/j.envres.2015.12.032.*
[8] *S. El Hussein, P. Muret, M. Berard, S. Makki, P. Humbert, Assessment of principal parabens used in cosmetics after their passage through human epidermis-dermis layers (ex-vivo study)., Exp. Dermatol. 16 (2007) 830–6. doi:10.1111/j.1600-0625.2007.00625.x.*
[9] *M.G. Soni, I.G. Carabin, G. a Burdock, Safety assessment of esters of p-hydroxybenzoic acid (parabens)., Food Chem. Toxicol. 43 (2005) 985–1015. doi:10.1016/j.fct.2005.01.020.*
[10] *R.S. Tavares, F.C. Martins, P.J. Oliveira, J. Ramalho-Santos, F.P. Peixoto, Parabens in male infertility-Is there a mitochondrial connection?, Reprod. Toxicol. 27 (2009) 1–7. doi:10.1016/j.reprotox.2008.10.002.*

[11] *S. Ishiwatari, T. Suzuki, T. Hitomi, T. Yoshino, S. Matsukuma, T. Tsuji, Effects of methyl paraben on skin keratinocytes., J. Appl. Toxicol. 27 (2006) 1–9. doi:10.1002/jat.1176.*
[12] *J.J. Prusakiewicz, H.M. Harville, Y. Zhang, C. Ackermann, R.L. Voorman, Parabens inhibit human skin estrogen sulfotransferase activity: possible link to paraben estrogenic effects., Toxicology. 232 (2007) 248–56. doi:10.1016/j.tox.2007.01.010.*
[13] *Cosmetic Ingredient Review, Final amended report on the safety assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in cosmetic products., Int. J. Toxicol. 27 Suppl 4 (2008) 1–82. doi:10.1080/10915810802548359.*
[14] *M.J. Kim, S.J. Kwack, S.K. Lim, Y.J. Kim, T.H. Roh, S.M. Choi, H.S. Kim, B.M. Lee, Toxicological evaluation of isopropylparaben and isobutylparaben mixture in Sprague-Dawley rats following 28 days of dermal exposure., Regul. Toxicol. Pharmacol. 73 (2015) 544–51. doi:10.1016/j.yrtph.2015.08.005.*
[15] *K. Yoon, S.J. Kwack, H.S. Kim, B.-M. Lee, Estrogenic endocrine-disrupting chemicals: molecular mechanisms of actions on putative human diseases., J. Toxicol. Environ. Health. B. Crit. Rev. 17 (2014) 127–74. doi:10.1080/10937404.2014.882194.*
[16] *P.D. Darbre, A. Aljarrah, W.R. Miller, N.G. Coldham, M.J. Sauer, G.S. Pope, Concentrations of Parabens in human breast tumours, J. Appl. Toxicol. 24 (2004) 5–13. doi:10.1002/jat.958.*
[17] *E. Karpuzoglu, S.D. Holladay, R.M. Gogal, Parabens: potential impact of low-affinity estrogen receptor binding chemicals on human health., J. Toxicol. Environ. Health. B. Crit. Rev. 16 (2013) 321–35. doi:10.1080/10937404.2013.809252.*
[18] *D. Sasseville, M. Alfalah, J.-P. Lacroix, "Parabenoia" Debunked, or "Who's Afraid of Parabens?," Dermatitis. 26 (2015) 254–259. doi:10.1097/DER.0000000000000147.*
[19] *European Commission, Consumers: Commission improves safety of cosmetics, (2014). http://europa.eu/rapid/press-release_IP-14-1051_en.htm (accessed April 26, 2016).*
[20] *E. Yim, K.L. Baquerizo Nole, A. Tosti, Contact dermatitis caused by preservatives., Dermat. Contact, Atopic, Occup. Drug. 25 (2014) 215–31. doi:10.1097/DER.0000000000000061.*
[21] *D. Sasseville, Hypersensitivity to preservatives, Dermatol. Ther. 17 (2004) 251–263. doi:10.1111/j.1396-0296.2004.04028.x.*
[22] *P. González-Muñoz, L. Conde-Salazar, S. Vañó-Galván, Allergic Contact Dermatitis Caused by Cosmetic Products, Actas Dermo-Sifiliográficas (English Ed. 105 (2014) 822–832. doi:10.1016/j.adengl.2014.09.007.*
[23] *H. Brandin, O. Myrberg, T. Rundlöf, A.K. Arvidsson, G. Brenning, Adverse effects by artificial grapefruit seed extract products in patients on warfarin therapy, Eur. J. Clin. Pharmacol. 63 (2007) 565–570. doi:10.1007/s00228-007-0289-1.*
[24] *M.G. Kirchhof, G.C. De Gannes, The Health Controversies of Parabens, Ski. Ther. Lett. 18 (2013) 11–15.*
[25] *R. Golden, J. Gandy, G. Vollmer, A review of the endocrine activity of parabens and implications for potential risks to human health., Crit. Rev. Toxicol. 35 (2005) 435–458. doi:10.1080/10408440490920104.*
[26] *P.D. Darbre, Underarm antiperspirants/deodorants and breast cancer, Breast Cancer Res. BCR. 11 Suppl 3 (2009) S5. doi:10.1186/bcr2424.*
[27] *P.D. Darbre, P.W. Harvey, Parabens can enable hallmarks and characteristics of cancer in human breast epithelial cells: A review of the literature with reference to new exposure data and regulatory status, J. Appl. Toxicol. 34 (2014) 925–938. doi:10.1002/jat.3027.*
[28] *E. Konduracka, K. Krzemieniecki, G. Gajos, Relationship between everyday use cosmetics and female breast cancer, Pol. Arch. Med. Wewn. 124 (2014) 264–269.*
[29] *N.R. Janjua, G.K. Mortensen, A.M. Andersson, B. Kongshoj, N.E. Skakkebæk, H.C. Wulf, Systemic uptake of diethyl phthalate, dibutyl phthalate, and butyl paraben following whole-body topical application and reproductive and thyroid hormone levels in humans, Environ. Sci. Technol. 41 (2007) 5564–5570. doi:10.1021/es0628755.*
[30] *F. Castelain, M. Castelain, Parabens: a real hazard or a scare story?, Eur. J. Dermatol. 22 (2012) 723–7. doi:10.1684/ejd.2012.1835.*
[31] *K.T. De Renzy-Martin, H. Frederiksen, J.S. Christensen, H.B. Kyhl, A.M. Andersson, S. Husby, T. Barington, K.M. Main, T.K. Jensen, Current exposure of 200 pregnant Danish women to phthalates, parabens and phenols, Reproduction. 147 (2014) 443–453. doi:10.1530/REP-13-0461.*
[32] *M.T. Guerra, M. Sanabria, S.V. Cagliarani, G.A.A. Leite, C. dos S. Borges, W. De Grava Kempinas, Long-term effects of in utero and lactational exposure to butyl paraben in female rats, Environ. Toxicol. (2016).*

doi:10.1002/tox.22277.

[33] C. V Towers, P.D. Terry, D. Lewis, B. Howard, W. Chambers, C. Armistead, B. Weitz, S. Porter, C.J. Borman, R.C.M. Kennedy, J. Chen, Transplacental passage of antimicrobial paraben preservatives., J. Expo. Sci. Environ. Epidemiol. 25 (2015) 604–607. doi:10.1038/jes.2015.27.

[34] T.M. Sandanger, S. Huber, M.K. Moe, T. Braathen, H. Leknes, E. Lund, Plasma concentrations of parabens in postmenopausal women and self-reported use of personal care products: the NOWAC postgenome study, J. Expo. Sci. Environ. Epidemiol. 21 (2011) 595–600. doi:10.1038/jes.2011.22.

[35] J.M. Braun, A.C. Just, P.L. Williams, K.W. Smith, A.M. Calafat, R. Hauser, Personal care product use and urinary phthalate metabolite and paraben concentrations during pregnancy among women from a fertility clinic., J. Expo. Sci. Environ. Epidemiol. 24 (2014) 459–66. doi:10.1038/jes.2013.69.

[36] C. Philippat, D. Bennett, A.M. Calafat, I.H. Picciotto, Exposure to select phthalates and phenols through use of personal care products among Californian adults and their children, Environ. Res. 140 (2015) 369–376. doi:10.1016/j.envres.2015.04.009.

[37] H.J. Ahn, K.C. Choi, E.B. Jeung, Effect of parabens on the disruption of ovarian follicle maturation in a neonatal female rat model., Reprod. Fertil. Dev. 24 (2011) 178. doi:10.1071/RDv24n1Ab131.

[38] K.W. Smith, I. Souter, I. Dimitriadis, S. Ehrlich, P.L. Williams, A.M. Calafat, R. Hauser, Urinary Paraben Concentrations and Ovarian Aging among Women from a Fertility Center, Environ. Health Perspect. 121 (2013) 11–12.

[39] European Commission - SCCP, Opinion on Parabens, (2011) 1–50. doi:10.2772/30176.

[40] European Commission, Extended Opinion on the Safety Evaluation of Parabens, (2005) 1–39. http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_019.pdf.

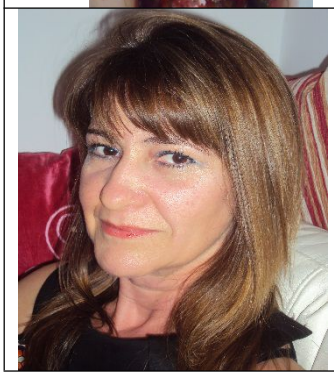
[41] L. Mathiesen, G. Zuri, M.H. Andersen, L.E. Knudsen, A Proposed Study on the Transplacental Transport of Parabens in the Human Placental Perfusion Model, (2013) 473–482.

[42] European Commission, Amending Annexes II and V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products, Off. J. Eur. Union. (2014). http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0358&from=EN (accessed June 16, 2016).

[43] European Commission - SCCP, Opinion on Parabens, (2008). http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_138.pdf.

Open Access Journal
International Journal of Medical Research and Pharmaceutical Sciences
Volume 3 (Issue 8) : August 2016 ISSN: 2394-9414
DOI: 10.5281/zenodo.61076 Impact Factor- 3.109

AUTHOR BIBLIOGRAPHY

	**Ana Patrícia Domingues Francisco** Ana Francisco is a pharmacy student in Escola Superior de Tecnologia da Saúde de Coimbra - Coimbra Health School at Coimbra, Portugal. Email: ana9francisco@gmail.com
	**Ana Paula Gomes Fonseca** Professor of Pharmacy Departament GIAF/ Investigation Applied in Pharmacy Coordinator Pharmacy Master Coordinator Pedagogic Council President Email: paula_fonseca@estescoimbra.pt