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SYSTEMATIC REVIEW

Can parabens be added to cosmetics without posing a risk to human health? A systematic review of its toxic effects

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Abstract

Objective: To summarize evidence regarding the toxic potential of administering parabens-containing cosmetics in humans. **Methods:** The systematic review followed the methodology proposed in Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA). Electronic searches of the PubMed, Virtual Health Library (BVS), and Science Direct databases were performed between October 1st and 31st, 2018. No language restriction was determined. Original articles reporting observational, *in vitro* and *in silico* studies of toxicity caused by parabens in human or human cells were considered for eligibility. Two independent reviewers performed data extraction and assessed the methodological quality and risk of bias of articles by using the Downs & Black Scale. Score levels greater than 70% were assumed to reflect good methodological quality. The Kappa coefficient was calculated. **Results**: A total of 254 studies were found. Following the eligibility evaluation, 22 studies were included for the qualitative synthesis. The concordance between the reviewers was substantial (Kappa coefficient = 0.650). The meaningful reported outcomes were: high concentrations of parabens in the body; apoptosis damage to sperm DNA; oxidative stress; DNA damage; irritative potential; interference in the control of adipogenesis; estrogenic activity; genotoxicity; necrosis; role in carcinogenesis of breast cancer; harmful effects on human skin when exposed to the sun; stimulation of oncogenes expression; and interference with DNA transcription. Despite most included articles presenting appreciable methodological quality, remarkable limitations were observed and the mechanisms by which parabens exert toxicity on humans remained unclear. **Conclusions:** The accumulation of parabens in the human organism following repeated cosmetics administration on the skin is noteworthy. However overall, the evidence so far does not make it possible to determine whether, and in what extent, the use of paraben-containing cosmetics can disturb human health. Further investigations are still required for clarifying these issues.

Keywords: Parabens. Drug-Related Side Effects and Adverse Reactions. Cosmetics.

How to cite

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INTRODUCTION

Parabens are esters derived from parahydroxybenzoic acid used as preservatives in the manufacture of several cosmetic, pharmaceutical and food products[1]. The parabens class of preservatives was introduced in the 1920s due to their broad spectrum of action against fungi, yeasts, and bacteria; remarkable compatibility with several raw materials; a wide range of pH and temperature stability; affordability; regulatory acceptance; and the need of low concentrations to exert antimicrobial effects, i.e., from 0.01 up to 0.3%[2].

Such class includes methyl, ethyl, propyl, butyl, pentyl, phenyl and benzylparabens. Methylparaben and propylparaben have been the first-choice preservative in cosmetic formulations, as they provide a synergistic and advantageous effect together with their attractive physicochemical properties (e.g. appreciable solubility in both aqueous and oily media). Due to these features, there are reports of their use in approximately 42% and 35% of products, respectively. The preservative properties of parabens are driven by a structure-activity relationship, and vary according to the extent of the carbon chain i.e., the greater the number of carbons and the length of the chain, the greater the antimicrobial activity, the greater lipophilicity, and the lower solubility in water[3,4].

The Brazilian determinations on cosmetics allow a maximum concentration of 0.4% expressed as individual acid and 0.8% expressed as acid for mixtures of salts or esters[5]. The European Union considers it safe to use at a concentration of 0.4% for individual acid or 0.8% when used in combination, however, considering propylparaben and butylparaben, the sum of their individual concentrations should not exceed 0.14%[6]. Long-chain parabens (isopropylparaben, isobutylparaben, phenylparaben, benzylparaben and pentylparaben) are banned in Europe[7]. In Japan, up to 1% of total paraben is tolerated for any cosmetic product[8]. In contrast, the US Food and Drug Administration (FDA) does not have specific standards applied exclusively to preservatives in cosmetics. Hence, they do not undergo approval before entering into the market[9].

From a safety point of view, typically the parabens incorporated in cosmetics do not lead to allergic reactions, and the majority of sensitizing reactions are due to the use of such products in previously injured skin. Even in the light of this low allergenic potential, there is growing concern regarding the estrogenic and endocrine disrupting activity caused by parabens. Despite the estrogenic activity *in vivo* and *in vitro* being considered weak, repeated exposures may lead to endocrine disruption and cancer development[10-12].

Recently, a study has shown that butylparaben is toxic to human trophoblastic cells, acting in the inhibition of cell proliferation, induction of apoptosis, and endoplasmic reticulum stress. Therefore, childbearing age women are easily exposed when using cosmetics; butylparaben may trigger problems related to early placental development[13].

A recent study has shown that exposure to parabens is related to metabolic changes and an increased risk of metabolic disorders in pregnant women. The results indicated that exposure to parabens in early pregnancy was associated with purine metabolism, beta-oxidation of fatty acids, metabolism of tryptophan and other pathways that were altered by parabens. Eighteen and three metabolites were correlated with exposure levels of methylparaben and propylparaben, respectively[14].

To date there is no consensus regarding the toxicity of parabens following topical administration of cosmetics on humans, which reflects the broad differences in the acceptance range for these chemicals in the cosmetics marketed worldwide, and sheds light on a great public health concern. Motivated by the large cosmetics consumption in Brazil and abroad, we report in this paper a systematic literature review of the toxic potential of the use of parabens as preservatives in cosmetic products.

MATERIALS AND METHODS

Study design

A systematic review of the scientific literature was conducted according to the methodology proposed in Preferred Reporting Items for Systematic reviews and Meta-Analyses – PRISMA[15].

Guiding question and definition of "PICOS"

The following guiding question was defined: "What are the toxic effects of parabens in cosmetics?" For the construction of the systematic review and elaboration of the guiding question the strategy of PICOS was used, being: "P" (population), humans or human cells; "I" (intervention), parabens-containing cosmetics; C (comparator), without comparison; "O" (outcome), toxic effects, side-effects, adverse reactions; "S" (study type), observational and experimental studies (in vitro and in silico).

Database and search strategy

The PubMed, Virtual Health Library (BVS), and Science Direct databases were accessed. The searches were performed by two authors (DFR/ GCSA) between October 1st and 31st, 2018. For all databases, the searches were conducted in the "advanced search" interface. The search terms were combined using the boolean logic terms 'OR' and 'AND'. The search strategy in Pubmed was: ((((“Parabens”[MeSH Terms]) OR ((4-Hydroxybenzoic Acids) OR (4 Hydroxybenzoic Acids) OR (para-Hydroxybenzoic Acids) OR (para Hydroxybenzoic Acids)))) AND ((“toxicity [Subheading]”) OR ((toxic potential) OR (margin of safety)))) AND ((“Cosmetics”[MeSH Terms]) OR ((Care Product*, Personal) OR (Personal Care Product*) OR (Product*, Personal Care))). For both BVS and Science Direct, the search strategy was "Parabens" AND "toxicity" AND "cosmetics".

Additional Analyzes

A manual search was also performed in the list of references of the included articles throughout the search for eligible publications, since they could not have been identified in the selection of the studies (gray literature). The authors of the unavailable articles were contacted twice by e-mail, through which access to these articles was requested.

Eligibility criteria

The inclusion criteria for the selection of articles were observational studies (performed in humans), experimental studies (*in vitro*), computational simulation studies (*in silico*), published up to September 30th, 2018. No language restriction was imposed. The starting date of the collection was not restricted, since the aim was to recover the maximum number of articles dealing with the toxicity of parabens. Reviews, comments, expert opinions, letters to the editor, supplements, conference abstracts, dissertations, editorials, theses, and studies on animals or on animal cells were excluded. The exclusion reasons were allocated into the following categories: wrong drug, wrong population, wrong study design, wrong publication type, and wrong outcomes.

Studies selection

The search and selection of articles were performed independently by two authors (DFR/ GCSA). Initially, duplicate articles were deleted. Subsequently, the titles related to the topic were evaluated and those that were not related to the subject were excluded. Afterwards, a detailed reading of the abstracts of the remaining articles was conducted, in order to select those that approached the proposed subject. Abstracts that did not address the topic in question were excluded. Thenceforward, articles were read in full, and those that were within

the inclusion criteria were inserted as search results. If there were any disagreements between the two authors, a third author was involved when necessary, to make the final decision. The Kappa coefficient[16] was determined to assess the degree of agreement between the two evaluators (DFR/ GCSA). In this pursuit, we considered a 95% confidence interval and used the Stata 11.0 software package (StataCorp LLC, Texas, USA).

Quality assessment

The Downs and Black Scale[17] was used in the analysis of quality and risk of bias. This is a scale which includes items that assess internal and external validity, reporting standards, and power of the studies. Such tool is considered prompt, useful, and can be used either to assess the quality of original or primary source research articles, as well as to synthesize evidence from quantitative studies. The "Checklist for Measuring Quality" contains 27 'yes' or 'no' questions distributed in five sections concerning: i) reporting (n = 10; questions 1 – 10) – the overall quality of the study; ii) external validity (n = 3; questions 11 – 13) – the ability to generalize findings of the study; iii) internal validity / bias (n = 7; questions 14 – 20) – to assess bias in the intervention and outcome measure(s); iv) internal validity / confounding and selection bias (n = 6; questions 21 – 26) – to determine bias from sampling or group assignment; and v) power of the study (n = 1; question 27) – to determine if findings are due to chance.

Herein, for observational studies in humans, five items from clinical trials were excluded, therefore, 22 items were evaluated (i.e., questions 1 – 13, 16 – 18, 20 – 22, 26 and 27). For *in vitro* and *in silico* studies, 15 specific items for studies performed in human populations were excluded, thus 12 items were considered for scoring (i.e., questions 1, 2, 5 – 7, 10, 16 – 18, 20, 25 and 27). In all cases, for a study to be individually considered as having good methodological quality, the sum of scores should be ≥ 70% of the total scores of evaluated items. The quality assessment was performed independently by two researchers (DFR / GCSA), and divergences between assessments were resolved by consensus between a third researcher.

Data extraction

After applying search criteria, the selected studies were arranged in electronic spreadsheets, and the data extracted from each study were: author and year, country, objectives, design, substance and / or cosmetic, and toxic effect caused by paraben. Moreover, the authors critically analyzed all the included papers and where described, the limitations were collected and summarized in the review. Data were divided into (i.e., Tables I and II), corresponding to human studies (observational) and *in vitro* / *in silico* studies.

RESULTS

A total of 254 studies were found. The total of articles resulting from the research in each database can be seen in Figure 1, which also summarizes the numbers and motivations for exclusion of the papers in each step of this review. Throughout the eligibility evaluation, the degree of agreement between the two researchers was considered substantial (good agreement) since the Kappa coefficient was 0.650[16]. Full analysis of these articles revealed that 22 studies fulfilled the inclusion criteria. From the selected articles, twelve were available in the Pubmed database, eight in BVS, one in Science Direct, and one was selected through search references of included studies.

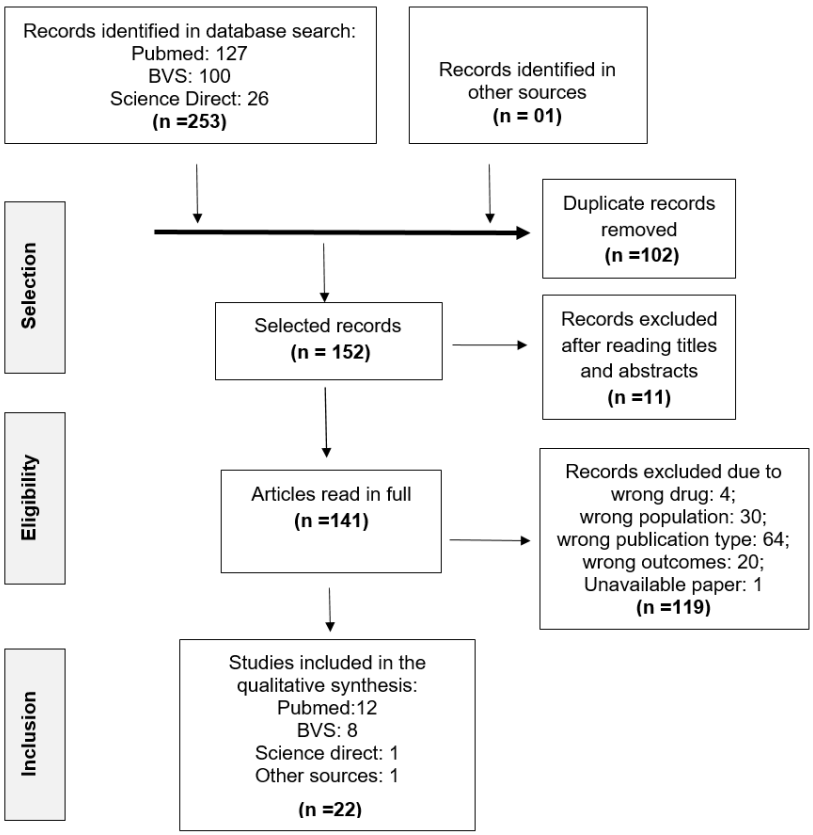

Figure 1- Flowchart of record selection based on PRISMA guideline (Moher et al.[15]).

The characteristics of the 22 studies included in the review are shown in Table I and II. From the analyzed studies, 31.8% (n = 7) were performed in humans, 63.6% (n = 14) were performed *in vitro* and 4.6% (n = 1) was performed *in silico*.

The publication time span of studies was between 2004 and 2018. The majority of the studies, 54.6% (n = 12), were published in the last seven years before the completion of the search. Regarding the country, the United States had the greatest number of published studies (n = 6), followed by Sweden, Poland, United Kingdom (UK), China (n = 2); and Denmark, Norway, India, Japan, France, Brazil, Romania and Germany (n = 1). From the included papers, 95.5% (n = 21) were published in the English language and 4.5% (n = 1) in Polish.

Concerning the methodological quality of the articles, of the seven studies in humans included (Table I), 85.7% (n = 6) presented scores greater than 16 points, with a response rate above 70%. They were therefore considered of great methodological quality according to the Downs and Black[17] score.

Considering the included studies performed *in vitro* (n = 14), 71.4% (n = 10) had a response rate greater than 70% (Table II). The other studies were considered well elaborated, however, as they were *in vitro* and *in silico* studies they had lower scores in some items evaluated, namely: description of the main confounding factors and possible adverse effects; characteristics of included and excluded patients; representative sample of the majority of the population; description of unplanned analyzes at baseline; adequate primary statistical analysis; and tests over the same period of time. No study was excluded due to methodological quality.

As displayed in Figure 2, the most prevalent parabens reported were methylparaben (90.9%), followed by butylparaben (86.4%), propylparaben (72.7%), ethylparaben (54.5%), benzylparaben (27.3%), isobutylparaben (18.2%), isopropylparaben (9.1%), and pentylparaben and phenylparaben (4.5%).

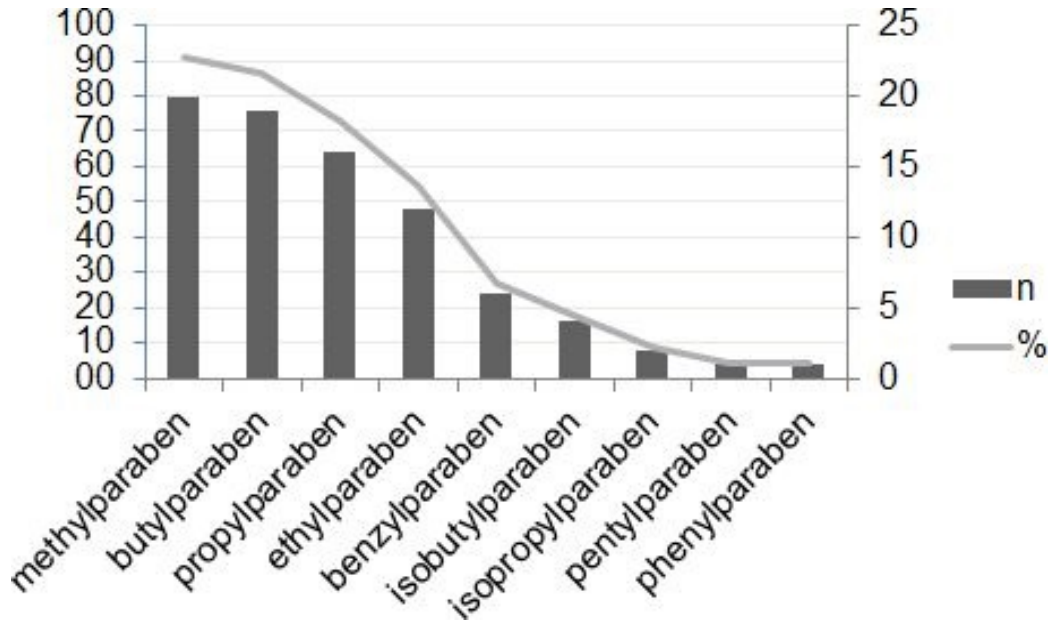

FIGURE 2: Prevalence of investigations with several parabens used in cosmetics according to a systematic literature review.

TABLE I: Characteristics of observational studies with humans included (n = 7).

STUDY	METHODS		RESULTS		
Author/ Year/ Country	**Objectives**	**Type of study (Quality assessment *)**	**Substance and / or cosmetic**	**Toxic effects of paraben**	**Limitation of the study**
Tefre de Renzy-Martin et al.[18]/ 2014/ Denmark	Describe the exposure of parabens to pregnant women in order to assess potential risks to the fetus	Cohort study (17 points)	methylparaben, ethylparaben, propylparaben, butylparaben, benzylparaben, isobutylparaben, isopropylparaben	No toxic effects were observed, only the presence of paraben metabolites in most of the analyzed urine samples	The toxicological risk assessments do not take into account the simultaneous exposures to parabens, potentially underestimating the true cumulative risk to the fetus
Larsson et al.[19]/ 2014/ Sweden	To estimate the exposure of parabens, phthalates, bisphenol A and triclosan in Swedish mothers and their children, and investigate potential predictors of exposure	Transversal study (17 points)	Make ups, lotions, sunscreens, and mouthwashes containing: methylparaben, ethylparaben, propylparaben, butylparaben, benzylparaben	No toxic effects were observed, but methyl, ethyl, propyl and butylparabens were found in a greater proportion in the urine samples of mothers than in the urine samples of the children	The number of participants and exposure factors reported in the questionnaire limited statistical power. A single urine sample would reasonably represent a person exposed over time
Scinicariello and Buser[20]/ 2016/ USA	To examine the association of bisphenol A, benzophenone 3, Triclosan, and	Transversal study (17 points)	methylparaben, propylparaben	The use of parabens in children and adolescents did not alter serum	The use of the single spot measurements of exposure is a limitation of this

TABLE I: Continued...

STUDY	METHODS			RESULTS	
	parabens, with serum levels of total testosterone in children and adolescents			levels of total testosterone	study. There may also have been other confounding factors that they did not control for in their analyses, including exposure to other environmental chemicals that are potentially anti-androgenic, such as phthalates.
Sandanger et al.[21]/ 2011/ Norway	To evaluate the levels of parabens in the plasma of women and to investigate a possible connection to the use of personal products	Cohort study (15 points)	methylparaben, ethylparaben, propylparaben, butylparaben, benzylparaben	Great plasma concentrations in women associated with daily use of different cosmetics	The questionnaire was not applied during the same period of collection of blood samples, so it is unlikely to know which women applied the products on the day of collection, and it is difficult to correlate these data
Kiec-Swierczynska et al.[22] 2006/ Poland	To evaluate the type of allergy to preservatives contained in cosmetics	Cohort study (16 points)	methylparaben, ethylparaben, propylparaben, butylparaben	Parabens were the components contained in the formulations with the lowest allergenic capacity	Not applicable
Meeker et al.[23]/ 2011/ USA	To assess the relationship between urine paraben concentrations and markers of the male reproductive system	Cohort study (18 points)	methylparaben, propylparaben, butylparaben	No evidence of the relationship between parabens in urine and hormone levels or semen quality was found, only butylparaben was associated with sperm DNA damage	Availability of only one blood or semen sample for the evaluation of hormone levels, semen quality, and sperm DNA damage.
Buttke et al.[24]/ 2012/ USA	To evaluate the relationship between paraben exposure and the menarche age in adolescents	Transversal study (17 points)	methylparaben, propylparaben, butylparaben, ethylparaben	The exposures to parabens were not significantly associated with the menarche age	Questionnaire data were self-reported and might be subject to misclassification. Exposures analyzed at a single time point

Quality assessment: * Downs and Black Scale – 21 scoring items

TABLE II: Characteristics of *in vitro* (n = 14) and *in silico* (n = 1) studies included.

STUDY	METHODS		RESULTS		
Author/ Year/ Country	**Objectives**	**Type of study (Quality assessment *)**	**Substance and / or cosmetic**	**Toxic effects of paraben**	**Limitation of the study**
Dubey et al.[25]/ 2017/ India	To assess the antimicrobial efficacy and photochemical mechanism of methylparaben under exposure to UVB radiation	*In vitro* experiments with *E. coli* culture for antibacterial activity, photocytotoxicity assay, oxidative stress and apoptosis study, and photogenotoxicity analysis (8 points)	methylparaben	Photodegraded methylparaben can lose its preservation properties and lead to oxidative stress, DNA damage, and apoptosis	Not applicable
Sonnenburg et al.[26]/ 2014/ Germany	To assess the irritant and sensitizing potential of preservatives that have come into contact with the skin through *in vitro* tests	*In vitro* experiment with co-culture of human keratinocytes and allogeneic dendritic cells (DC-rc); flow cytometric analysis of the DC-rc CD86 maturation marker. (9 points)	methylparaben, ethylparaben, propylparaben, isopropylparaben butylparaben, isobutylparaben, pentylparaben, benziparaben, phenylparaben	Methyl, ethyl, propyl and isopropylparaben were found to be weak sensitizers; butyl, isobutyl, pentyl and benzylparaben were found to be strong sensitizers; phenylparaben was classified as a mild sensitizer. Regarding the irritative potential, only phenylparaben was considered irritant	Potential lack of metabolic transformation of parabens with long side chains in the test used
Darbre et al.[27]/ 2004/ UK	To assess whether parabens can be found in human mammary tissue with tumor	Analysis of human breast tumors by high pressure liquid chromatography followed by tandem mass spectrometry (9 points)	methylparaben, ethylparaben, propylparaben, butylparaben, benzylparaben, isobutylparaben	Accumulation of parabens in human breast tissue with tumor	Low availability of material for analysis. There was no analysis of parabens in normal tissue, making it impossible to determine differences between normal and carcinogenic tissues
Hu et al.[28] 2012/ China	To assess the effects of parabens on the conversion of multipotent	*In vitro* experiments with cell culture, induction of adipocyte	methylparaben, ethyl paraben, butylparaben, propylparaben, benzylparaben	The results suggest that parabens may interfere with	The molecular mechanisms in which the parabens act on the

TABLE II: Continued...

STUDY	METHODS		RESULTS		
	stromal cells derived from human adipose tissue	differentiation, and treatment with parabens (9 points)		the control of adipogenesis	adipogenesis *in vitro* were not delineated
Wrobel and Gregoraszczu[29]/ 2014/ Poland	To characterize the mechanisms involved in the proliferative activity of breast cancer cells and to evaluate the expression of cell cycle regulatory genes when exposed to parabens	*In vitro* studies with MCF-7 and MCF-10A cells exposed to parabens and 17βestradiol; real-time polymerase chain reaction evaluation and protein expression by Western blot (9 points)	methylparaben, butylparaben, propylparaben	Methylparaben and butylparaben had no effect on the expression of selected apoptotic genes in breast cancer cells. Propylparaben increased both extrinsic and intrinsic apoptosis	Not applicable
Gomez et al.[30]/ 2005/ France	To investigate the estrogenic effects of substances added in cosmetic formulations	*In vitro* experiment using three cell lines: HELN, HELN ERα and HELN ERβ; analysis of estrogenic activity in relation to estrogen α and β receptors (ERα and ERβ) (7 points)	butylparaben, propylparaben, ethylparaben, methylparaben	Estrogenic activity of ethyl, propyl and n-butylparaben in the cell lines tested. Methylparaben had estrogenic activity only above 10^{-5} M	HELN cells have limited sensitivity for substance testing at concentrations below 10^{-4} M
Carvalho et al.[31]/ 2012/ Brazil	To assess and compare *in vitro* studies of apoptosis, necrosis, and potential inducer of genotoxicity of different types of preservatives	*In vitro* experiments were carried out on human dermal fibroblasts by a quantitative flow cytometry method, using specific cell markers (8 points)	propylparaben and methylparaben	Parabens caused genotoxicity, necrosis and apoptosis in a concentration dependent manner in the tested cells	Did not clarify the biochemical, physiological and cell death mechanisms induced by parabens in association with their clinical relevance
Zhang et al.[32]/ 2013/ China	To evaluate the activities related to parabens, salicylates, and benzoates via competitive antagonistic binding on the human estrogen receptor	Nuclear receptor coactivator recruitment test *in vitro*; evaluation of liaison activities of parabens via competitive antagonist binding to human estrogen-related	ethylparaben, methyparaben, propylparaben, butylparaben, benzylparaben	Parabens may play some role, through estrogen receptors, in breast cancer carcinogenesis	Not applicable

TABLE II: Continued...

STUDY	METHODS		RESULTS		
		receptory (ERRγ) (7 points)			
Pop et al.[33] 2016/ Romania	To evaluate by *in vitro* tests the antiandrogenic and androgenic activity of preservative additives for individual compounds and binary mixtures	*In vitro* experiments on MDA-kb2 cell line; evaluation of the individual and combined (of binary mixtures) (anti) androgenic effects (9 points)	butylparaben	None of the compounds showed androgenic activity and butylparaben proved to possess weak antiandrogenic effect	Need for EC_{50} or IC_{50} and Hill equation from the individual tests for all compounds. There is no possibility of predicting effects of the mixtures if a compound does not induce any effect on the test range concentration
Hu et al.[34] 2017/ USA	To investigate the effects of methylparaben and butylparaben on the differentiation of stem cells into adipocytes, chondrocytes, or osteoblasts	*In vitro* experiment modulated by C3H10T1 / 2 cells, adipogenic, osteogenic, and chondrogenic differentiation (9 points)	methylparaben, butylparaben	Butylparaben markedly promoted adipogenic differentiation but suppressed osteogenic and chondrogenic differentiation, while methylparaben had similar but less pronounced effects	The study used a fixed dose of parabens for most of its tests. The level of parabens detected in humans depends on age, gender, and ethnicity, probably reflecting the frequency of exposure
Handa et al.[35]/ 2006/ Japan	To investigate the effects of exposure to sunlight on keratinocytes treated with methylparaben	*In vitro* experiment on human skin keratinocytes treated with methylparaben; in this study, effects of exposure to ultraviolet B (9 points)	methylparaben	Methylparaben may cause harmful effects to human skin when exposed to sunlight.	Not applicable
Pan et al.[36]/ 2016/ USA	To investigate the hypothesis that the estrogenic potency of the parabens can be increased through the epidermal growth factor receptor ligands	*In vitro* experiment; Real-time PCR, Western blots, flow cytometry, and chromatin immunoprecipitation assays on human BT-474 ERα and HER2-positive breast cancer cells. (10 points)	butylparaben, methylparaben, ethylparaben, propylparaben	Epidermal growth factor receptor binders increased the potency of butylparaben by stimulating the expression of oncogenes and the cell proliferation of breast cancer *in vitro* via the	To determine whether there is potentiation of oncogenes expression in the ligands of the epidermal growth factor by parabens in normal breast cells

TABLE II: Continued...

STUDY	METHODS		RESULTS		
				estrogen receptor	
Cowan-Ellsberry and Robison[3] 2009/ USA	To portray the aggregate exposure of parabens using standard data of use and non-use of products, dermal penetration, and metabolism	Study of aggregate exposure to parabens (9 points)	Lotions and body creams, face mask, makeup, lipstick, facial serum, eye area cream, shampoo, conditioner and makeup remover, containing: methylparaben, ethylparaben, propylparaben, butylparaben	Methylparaben and aggregated exposures of propylparaben contributed more significantly to a cumulative exposure. Butylparaben had aggregate exposure inferior to the estimated aggregate exposure to the other parabens	Did not consider dermal absorption or metabolism of individual parabens and whether formulations of cosmetic products could affect dermal absorption
Charles and Darbre[37]/ 2013/ UK	To investigate to what extent the proliferation of breast cancer cells can be increased by the exposure of parabens	*In vitro* experiment with MCF-7 human breast cancer cells exposed to parabens (9 points)	methylparaben, ethyl paraben, propylparaben, butylparaben, isobutylparaben	Parabens isolated or in combination were present in breast tissue at concentrations sufficient to stimulate the proliferation of breast cancer cells	No parabens levels were measured in normal tissue to determine if there were differences between normal and carcinogenic breast tissue
Manzetti[38], 2018 Sweden	To evaluate a possible interaction of butylparaben with DNA	*In silico* study (6 points)	butylparaben	Butylparaben may interfere with transcription and DNA-related mechanisms, forming non-covalent interactions with DNA. The probability of a strong intercalation with DNA is low	Fine tuning of DNA restricts the formation of binding complex and impairs the stability of the molecule. This relationship between the effects of DNA positioning may limit the intercalation energy

Quality assessment: * Downs and Black Scale –12 scoring items

Abbreviations: $EC_{50:}$ concentration of a compound to which 50% of the effect is observed; $IC_{50:}$ average inhibition of a compound (50% inhibition); UVB: ultraviolet B radiation; DNA: desoxyribonucleic acid; M: molar

Most of the articles (31.8%) did not find toxic effects caused by the parabens[3,18-20,22,24,33]. The most reported toxic effects were the high concentration of parabens in breast tissue with tumor (9.1%)[27,37] and apoptosis (3.6%)[25,29,31]. The other effects evidenced were the high concentrations of parabens in the body[21], damage to sperm DNA[23], oxidative stress[25], DNA damage[25], irritative potential[26], interference in the control and differentiation of adipogenesis[28,34], estrogenic activity[30], genotoxicity[31], necrosis[31], role in breast cancer

carcinogenesis[32], harmful effects on human skin when exposed to the sun[35], stimulation of oncogenes expression[36], and interference in DNA transcription[38].

DISCUSSION

One of the great challenges of cosmetic conservation is the choice of safe and effective preservatives. This systematic review reports that there are few conclusive studies on the toxicity of parabens, explained by some factors such as a) the majority were conducted *in vitro* or *in silico*, making difficult a conclusive relation to humans, despite their quality; b) a wide diversity of substances evaluated; and c) diversity of toxic effects described.

The main route of exposure to parabens was dermal and only 4% of the aggregate exposure was from parabens in foodstuff. Estimates of aggregate exposure to parabens were less than 10 mg/kg/day. Methyl, propyl, and ethylparaben are present in 0.04% to 0.35% of the cosmetics and represent 74%, 75% and 70% of the aggregate exposure to parabens, respectively. Butylparaben was detected at very low concentrations after dermal use of cosmetics[4].

Topical allergic reactions to parabens are uncommon, ranging from 0.2 to 1.2%[22,39,40]. Fransway et al.[41] advocate that preservatives can be used safely in cosmetic formulations for application on the whole skin, since the possibility of allergy of contact is rare. Furthermore, significant plasma concentrations of parabens have been described after topical administration of hand cream, body lotion, and face cream with the repetitive use of these products increasing exposure[42,43].

For undergoing transdermal absorption, chemicals and drugs are supposed to equilibrate several physicochemical properties, i.e. (i) modest molecular weight (MW up to 500 Da); (ii) balanced lipophilicity (log octanol–water partition coefficient}, log P, ideally around 2 to 3); (iii) significant solubility in both oil and water; and (iv) be mostly in non-ionized form[44]. Most parabens satisfy those requirements such as methyl, ethyl, propyl and butylparaben[45,46].

Hence it is reasonable to consider that once administered through cosmetics, such parabens have prospects for breaching the lipophilic stratum corneum and resorption into the aqueous central compartment of systemic circulation. These features, together with that fact that vehicles (or co-vehicles) and botanical oils often used in the design of cosmetic formulations are assumed to enhance the permeability coefficients of methyl, ethyl, propyl and butylparaben[45], may support the trends observed for the plasmatic levels of these preservatives and cumulative effect in the body. Besides the effects of intrinsic physicochemical properties in the permeation of parabens, it would be of great relevance for future work devoted to predict and determine the role of other formulation aids with recognized permeation enhancement properties (e.g., moisturizers, surfactants, flavoring, etc.) in the bioavailability of these chemicals.

Moreover, skin integrity is a crucial issue concerning transdermal drug absorption[44], so that the injuries that skin could undergo day by day such as sun exposure, chemical peeling, depilation, friction, stetic treatments (e.g., infrared, sonophoresis and iontophoresis, etc.) may also contribute to favor the permeation of parabens through the skin following the exposure to cosmetics over a long time spam.

Concerning the hypothesis of sexual hormones or sperm alterations, Scinicariello and Buser[20] observed no significant relationship with serum levels of total testosterone by children and adolescents using total parabens (methylparaben and propylparaben). In animal models, exposed orally to parabens, no effects caused by methyl and ethylparaben[47-49] were observed, whereas propyl and butylparaben were associated with somewhat toxic effects, such as variations in spermatogenesis and dose-dependent reduction of serum levels of testosterone and activity-related estrogenic effects[48,49]. Conversely, in a similar investigation[47], the results did not express modifications for butylparaben. In an animal model, when exposed to butylparaben, sperm DNA methylation was observed in mitosis and post meiosis[50]. According to Buttke et al.[24], parabens were not significantly associated with the age of menarche in adolescents. However, James-Todd et al.[51] demonstrated the association between early

menarche and use of hair products before 13 years of age, but did not specify the ingredients involved. Therefore, sexual hormones or sperm alterations documentation seems to be poor related to parabens, and a slight evidence of butylparaben alteration should be investigated.

In the evaluation of the risks to the fetus of women exposed to parabens, despite the presence of parabens in plasma and urine of women or in the newborn, none of the parabens were consistently associated with maternal diseases or risk for fetal development[18,19,52,53]. The analyzes were not conclusive and more studies will be needed to characterize a more comprehensive scenario in relation to exposure while in the uterus.

Some studies have related the use of parabens in cosmetics with the presence of these compounds in breast tumor, which may not determine the cause of the disease but may be pre-conditions in its advance[25,28,52,54,55]. Darbre et al.[27], quantified methylparaben in 62% of tumors, at the mean concentration of 100 ng/g tissue. *In vitro* tests found that parabens activated estrogen receptors and that the activity increased with the size of the alkyl chain as described in trials with breast cancer cells[30]. Although parabens are considered estrogens in the environment, they are converted to parahydroxybenzoic acid, which is not an estrogenic substance[56].

In agreement with Pop et al.[33], by means of an androgen receptor mediated transcriptional activity assay, Chen et al.[57] found that at concentrations between 10^{-3} and 10 μM (1.0 nM to 10 μM), p-hydroxybenzoic acid and its derivatives revealed no androgenicity; and no statistically significant inhibition of the transcriptional activity of testosterone was detected for p-hydroxybenzoic acid, the major paraben metabolite. In contrast, at the highest concentrations tested (10 μM), methyl-, butyl- and propyl-4-hydroxybenzoate significantly inhibited the transcriptional activity of testosterone by 40%, 33%, and 19%, respectively ($P<0.05$).

It is noteworthy that when paraben-related activities were assessed via competitive antagonist binding on the human estrogen receptor, the results showed that they behaved as an inverse antagonist on the activities of the estrogen receptor, which may be an inducer of the development of breast cancer and a pharmacologic antagonist to tamoxifen[32]. It was found that human epidermal growth factor receptor (HER) increased the estrogenic capacity of butylparaben by increasing the expression of oncogenes and the proliferation of MCF-7 cells by means of estrogen receptor[36]. Although it was considered estrogenic, butylparaben was considered 10,000-fold less potent than estrogen[58]. Therefore there is a lot of evidence showing the estrogenic properties of parabens, but claims of carcinogenic activities are less argued in the literature and no human studies have certified these biological effects as relevant[59].

By using human dermal fibroblasts, it has been possible to analyze some cytotoxic mechanisms triggered by parabens and other preservatives. The parabens tested induced necrosis in 65% of the cells and apoptosis in 95%, when at the concentration of 1%, and in smaller concentrations, necrosis and apoptosis decreased. Methylparaben caused genotoxicity in 0.8% of cells at all concentrations and propylparaben 1.5% in the presence of parabens (1%)[31]. According to Martín et al.[60], propylparaben caused changes in cellular proliferation values, but not in cell viability, and led to DNA breaks. These effects confirm that oxidative damage is implied by the cytostatic effect on the cultured cells.

An *in silico* approach showed that butylparaben bound the terminal part of the DNA with 20% probability, which resulted in a stable binding energy with DNA, estimated to be 80 to 300 times weaker than the positive control, benzopyrene, considered to be a carcinogen[38]. However, there is evidence pointed out by other authors that parabens interact with the Golgi complex and potentially with DNA[61].

Regarding the effects on adipocyte differentiation, parabens have been shown to modulate and activate glucocorticoid receptors, which are involved in the mechanism of adipogenesis[28]. The adipogenic potential increases as the length of the linear chain increases and the presence of an aromatic ring further increases adipogenic capacity. Butyl and benzylparaben, besides having the most notable adipogenic effects, caused toxicity when used in the

concentration of 100 μM in the cells tested. Hu et al.[34] have presented results in agreement with these previous findings.

Handa et al.[35] investigated the effects of methylparaben at concentrations ranging from 0.003% to 0.3%. It was observed that at concentrations of 0.003% there was no effect on the cell viability of keratinocytes exposed to sunlight, but at higher concentrations the cell viability significantly decreased in 6 h, demonstrating that the harmful effect is dose and time dependent. Similarly, Dubey et al.[25] demonstrated that methylparaben presented time-dependent photodegradation and reduced its antimicrobial activity by 40%.

Despite the great relevance of the findings reported by the included articles, there were several remarkable limitations in their methodological designs, which definitely impair the robustness of most of their conclusions. Assessing the studies for the quality of their findings is within the main strengths of a systematic review over traditional narrative reviews. This may provide a more precise estimate of a treatment effect and explain heterogeneity between the results of individual studies[62]. Accordingly, it may guide defining limits of what is known and unknown and helps to formulate hypotheses for further investigation. For example, even with these findings it was not possible to describe a mechanism of toxicity to the parabens, and further studies would be required.

Overall, the conflicting results obtained, and the limitations of the studies performed so far, do not make it possible to draw an accurate answer to the guiding question of this review. There remain many inquiries to be clarified and research to be completed, since there are insufficient supporting studies on the toxicity of parabens to patient health. In turn, this issue exposes a great gap to be solved by upcoming generations of pharmaceutical scientists.

Consumers' concerns regarding the safety and toxicity of cosmetics are genuine and understandable. From a market point of view, as long researchers do not move forward to obtain high-level scientific evidence as regards the safety of parabens, this may increasingly shift prescriber and consumer preferences for paraben-free products. In practice, by reading this report patients may increase their empowerment concerning the issues involved in the self-care process. Also, prescribers, health surveillance agents, and cosmetics manufacturers are invited to be aware and much more conscious of this uncertain and challenging scenario. Finally, regardless of the composition, the safety and quality of cosmetics must be utmost sought and achieved, rather than only market share and financial gain.

CONCLUSION

This work gathers, summarizes, and critically analyses scientific evidence as regards the risks for human health following the exposure to parabens used in cosmetics. There is evidence that after being repeatedly applied on the skin, parabens can permeate, reach the systemic circulation and accumulate in the human organism. However, it is still premature to determine whether the use of paraben-containing cosmetics must be avoided or contraindicated for humans. Considering the worldwide market growth trends for cosmetics and the prevalence of using parabens in their composition, addressing responses to this issue remains crucial to assure rational use of these products and to promote human health and wellbeing. Therefore, the immediate, conscious, and systematic toxicological evaluation of these products is fully justified.

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Authors' contributions

DFR, GCSA and FMDC: Conceived, planned and carried out the data collect presented in the manuscript or interpreted the data, or both; DFR, GCSA, ROC, CS and FMDC: Wrote the paper, or reviewed successive versions; DFR, GCSA, ROC, CS and FMDC: Approved the final version.