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Allergic Contact Dermatitis after the Use of Cosmetics Containing Parabens: Systematic Review and Meta-analysis

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HIGHLIGHTS

- There are few studies with a control group evaluating the incidence of ACD in the healthy population.
- Skin reactions to cosmetic products containing parabens in their formulations are rare.
- In the few cases in which ACD was associated with the use of cosmetics containing parabens, the reaction was often attributed to the application of parabens on already damaged skin.

Abstract: Parabens are among the most widely used preservatives in cosmetic formulations. The aim of this study was to investigate the relationship between allergic contact dermatitis (ACD) and the use of parabens in cosmetics. A systematic review was performed with searches in PubMed, Scopus and Science Direct, in addition to a manual search. Interventional or observational studies that assessed the incidence of ACD in individuals using parabens were included. The quality of the articles was assessed and the data were extracted for a qualitative synthesis and single-arm meta-analysis. Fourteen studies (8 longitudinal, 3 cross-sectional, 1 quasi experimental and 2 case reports) were included in the systematic review and had their data extracted. Twelve studies reported ACD after the use of parabens and were included in the single-arm meta-analysis, resulting in an ACD incidence of 0.9%[95%CI: 0.4-2.0%], thus classified as a rare event. This result was related to already sensitized skin in most cases. In addition, the concentration of parabens in the contact test was above that recommended in cosmetics. The incidence of ACD due to parabens is rare, but further studies with control groups and at the usual concentrations of parabens are needed to better evaluate the results.

Keywords: Dermatitis; Allergic Contact; Parabens; Systematic review; Safety.

INTRODUCTION

Among the most common preservatives in cosmetic and pharmaceutical formulations are the alkyl esters of parahydroxybenzoic acid, classified as methylparaben, ethylparaben, propylparaben, butylparaben and benzylparaben (the latter banned in the new cosmetic ingredient review – CIR expert panel because it is considered unsafe). However, according to the CIR expert panel, 21 types of parabens are currently known [1]. According to the food and drug administration (FDA), the parabens most commonly used as preservatives are methylparaben, ethylparaben, propylparaben and butylparaben [2].

Due to the high efficiency of parabens, their concentrations in formulations often do not exceed 0.3% individually, or 0.3% methylparaben and 0.1% propylparaben [3]. Despite this, there is a worldwide controversy over the safety of these products regarding human health. A study published in 2005 showed that the use of parabens in cosmetic products can cause skin allergies [4]. However, in a retrospective observational study published in 2014 evaluating 69,487 individuals already suspected of having allergic contact dermatitis (ACD), only 1% had positive reactions to parabens [5].

ACD is an inflammatory dermatosis of exogenous etiology; it is more frequent in industrialized countries, and is considered one of the most common occupational diseases [6, 7]. It is caused by external agents that trigger an inflammatory reaction in contact with the skin, and the disease is usually manifested as eczema [7]. External agents that can trigger ACD include preservatives, acidulants or emulsifiers, which are commonly found in cosmetic formulations [8].

Considering the contradictions in several countries regarding the safety of using parabens as preservatives in cosmetic products, the objective of this study was to conduct a systematic review of the literature in order to assess the incidence of ACD related to the use of parabens in cosmetics.

MATERIAL AND METHODS

The research was designed using the cochrane collaboration recommendations for systematic reviews [9] and reported according to the preferred reporting items for systematic reviews and meta-analysis (prisma) [10].

Study search

Electronic searches were performed in pubmed, scopus and science direct, in addition to manual searches in the references of included studies and in non-indexed records. The following descriptors were used: dermatitis, paraben, 4-hydroxybenzoic acid, toxicity, safety and allergy. The terms were combined using the Boolean operators “and” and “or”. The detailed search can be found in supplementary material 1 (https://osf.io/v4fuy/?view_only=3a076c1726ec4cfd86e852cc964f7c3a).

Inclusion and exclusion criteria

The acronym “PICOS” was used to assess study eligibility criteria [9]. (P) participants: participants with healthy skin or with suspected allergic contact dermatitis or other dermatological reactions. (I) intervention: parabens in any concentration. (C) comparator: placebo or without comparator. (O) outcome: allergic contact dermatitis. (S) study design: observational or interventional studies. Articles published until February 2021 were included.

Studies that were not available in full in any database and that were not found after attempts to contact the authors were excluded, as well as articles published in non-roman characters. Studies conducted in patients with already diagnosed dermatological reactions (including ACD) were also excluded from this systematic review.

Study selection

After the search, two independent reviewers read the titles and abstracts of the studies retrieved (screening). Then, the articles selected in the screening stage were read in full by the two reviewers (eligibility stage), again independently, and those that met the established inclusion criteria were selected for data extraction. Disagreements between reviewers were resolved by consensus or by the decision of a third independent reviewer. For the organization of references and screening, the EndNote version X7 was used.

Data extraction and synthesis

Studies that met the inclusion criteria were used for data extraction, which was also performed in duplicate by two independent reviewers with the help of pre-prepared spreadsheets in Microsoft Excel®. Baseline information was extracted from the studies (authors, year of publication, country), type of study, number of individuals, age, sex, type of cosmetic, type of paraben, percentage and characteristics of the paraben, time of exposure, type of test and outcomes.

Quality assessment

Observational studies and quasi-experimental studies were evaluated regarding their methodological quality using the Newcastle Ottawa scale (NOS). This scale contains eight items segmented into three parts: selection, comparability, exposure (case-control) or outcome (cohort study) [11]. Studies scored ≥7 were considered to be of high quality.

To assess the quality of case reports, the tool proposed by Murad et al. Was used, composed of eight questions that can be separated into four domains: selection, investigation, causality and reports. In this tool, the suggestion is not to use an aggregate score, instead making an overall judgement about methodological quality based on the questions deemed most critical [12].

Meta-analysis

The quantitative analysis of the studies included in this systematic review was performed using CMA® software (comprehensive meta-analysis version 2.0 Biostat, Englewood, NJ), in a single-arm meta-analysis using a random effects model and 95% confidence interval (ci). Heterogeneity was assessed by calculating the i-square (i2); values of i2>75% were considered to indicate high heterogeneity [9].

Subgroup analyses were performed according to the country of the study.

Publication bias

Publication bias was assessed with the CMA® software (comprehensive meta-analysis) - (version 2.0 biostat, Englewood, NJ) using a funnel plot graph.

This study was recorded on the PROSPERO database (registration number CRD42019135888 - https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019135888).

RESULTS

A total of 3,570 records were initially identified by searching electronic databases (Figure 1). After removing 44 duplicates, the titles and abstracts of 3,526 articles were screened, 113 of which were selected for reading in full. After this stage, 14 articles were eligible for analysis, comprising 8 longitudinal studies [5, 13-19], 3 cross-sectional studies [20-22], 2 case reports [23, 24] and one quasi-experimental study [25]. No study was retrieved through the manual search. The reasons for the exclusion of studies after reading in full are described in supplementary material 2:
(https://osf.io/v4fuy/?view_only=3a076c1726ec4cfd86e852cc964f7c3a).

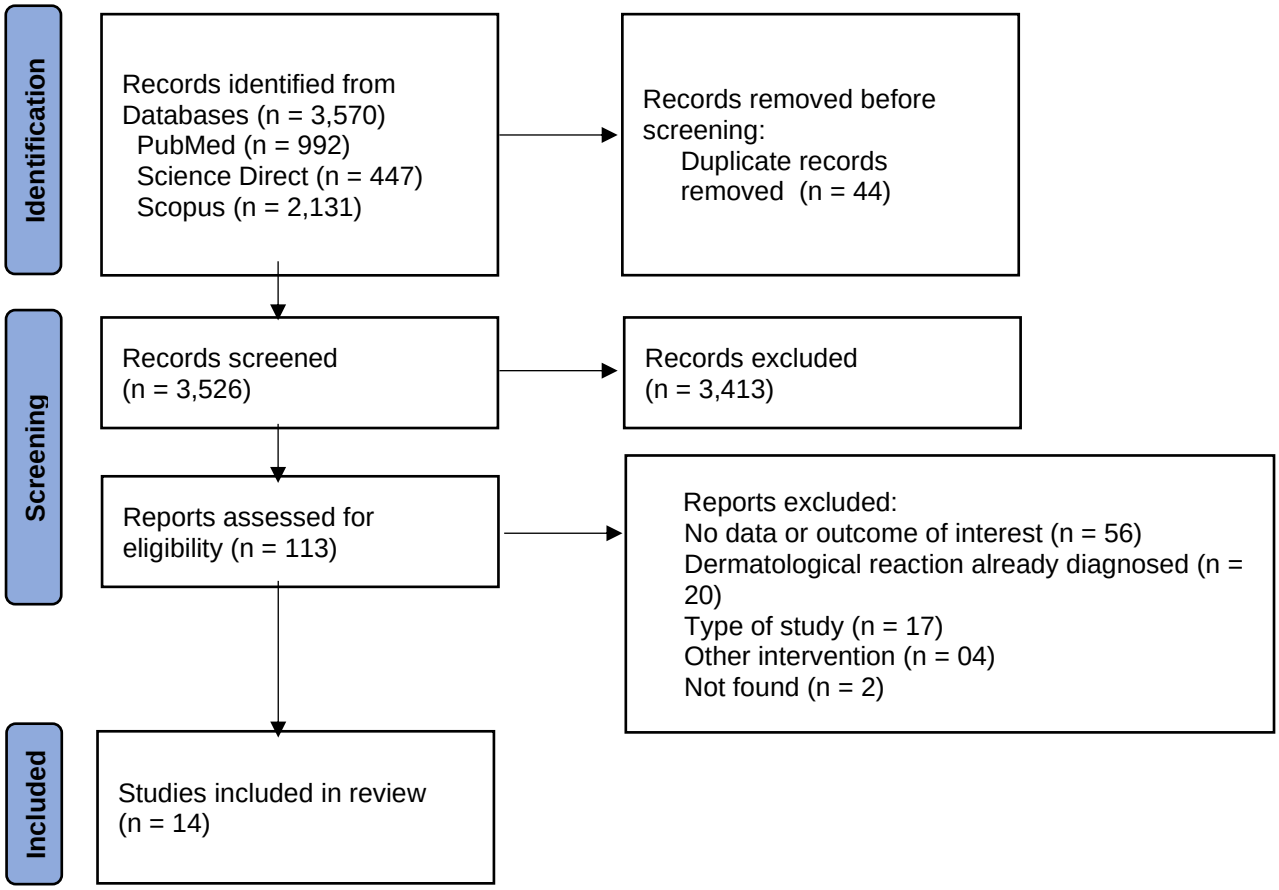

Figure 1. Flowchart of the article selection process.

The study characteristics and participants baseline characteristics are described in Table 1.

Table 1. Studies and patients baseline characteristics.

Author	Year	Country	Study desing	Participants (N)	Mean Age (years)	Sex (% female)	Study period (Year)	Time between application of the paraben and evaluation of ACD
Cooper [23]	1998	United Kingdom	Case Report	1	74	100	NR	Immediately
Henry [24]	1979	Mexico	Case Report	1	31	0	NR	15-20 minutes
Adams [13]	1985	United States	Longitudinal	281,100	20 to 60	NR	1977-1983	NR
Akasya-H [14]	2002	Turkey	Longitudinal	542	33.5	55.9	1996-1999	NR
Dinkloh [5]	2015	Germany, Switzerland and Austria	Longitudinal	69,487	NR	NR	2006–2011	NR
Duarte [15]	2011	Brazil	Longitudinal	2,618	NR	NR	1999-2009	NR

Cont Table 1

Romaguera [16]	1983	Spain	Longitudinal	58,128	NR	NR	NR	NR
Sarma [17]	2010	India	Longitudinal	70	1 to 15	58.6	2005-2008	2 days
Schnuch [18]	2011	Germany, Switzerland and Austria	Longitudinal	200,000	NR	NR	1996-2009	NR
Zhao [19]	2015	China	Longitudinal	481	18 to 33	69	2014	2 days
Gómez [20]	2002	Spain	Cross-sectional	351	40.6 (14 to 70)	NR	2000	NR
Lee [21]	2012	Korea	Cross-sectional	584	16 to 83	82.2	2010-2011	2 days
Rodrigues [22]	2015	Brazil	Cross-sectional	125	1 to 19	76.8	2003-2010	2 days
Dogra [25]	1994	India	*Quasi*-experimental	200	21 to 30	100	NR	NR

N=participants; ACD = allergic contact dermatitis NR=not related.

Two studies were conducted in three countries, and the rest of the studies were conducted in only one country each. The publication period varied between 1979 and 2015. Two studies evaluated only one individual (case reports), and among the other 12 studies the number of individuals ranged between 70 and 281,100. The age of the individuals included ranged from 1 to 83 years. One of the case reports refers to a man and the other to a woman. Of the other studies, five reported the gender of the individuals, and of these, 69.5% (1,252) were women. The time elapsed between the application of the paraben and the evaluation of the skin reaction varied between immediately and 2 days after the application (eight studies did not provide this data).

Of the studies detailing which paraben was used (eight studies), all used more than one paraben, or a mixture of parabens (table 2). Four studies used parabens at a concentration of 16%, two studies 15%, one study 12% and one study 5%. Only two studies have been carried out in healthy patients [19, 24]; the other studies included patients with suspected allergic skin reactions.

Table 2. Characteristics of parabens used and incidence of allergic contact dermatitis.

Author	Year	Participants (N)	Type of paraben	Paraben concentration (%)	Incidence of ACD (N)
Cooper [23]	1998	1	Propylparaben, ethylparaben and butylparaben	NR	1
Henry [24]	1979	1	Methylparaben, ethylparaben and propylparaben	5%	1 for methylparaben and ethylparaben; 0 for propylparaben
Adams [13]	1985	281,100	Mixture of parabens	NR	19
Akasya-H [14]	2002	542	Mixture of parabens	12%	negative
Dinkloh [5]	2015	69,487	Mixture of parabens	16%	695
Duarte [15]	2011	2,618	NR	NR	28

Cont. Table 2

Romaguera [16]	1983	58,128	Mixture of parabens	NR	37
Sarma [17]	2010	70	NR	NR	30
Schnuch [18]	2011	200,000	NR	16%	1,752
Zhao [19]	2015	481	Mixture of parabens	16%	2
Gómez [20]	2002	351	NR	NR	2
Lee [21]	2012	584	NR	16%	18
Rodrigues [22]	2015	125	Mixture of parabens	15%	negative
Dogra [25]	1994	200	Ethylparaben and methylparaben	15%	77 (40 for ethylparaben and 37 for methylparaben)

N=number of participants; ACD = allergic contact dermatitis.

Quality assessment

For observational and quasi-experimental studies, the average of the results obtained was 6.3, and only two studies were considered of high quality with a score of 9 [5, 21]. The other studies scored 5 or 6, indicating moderate quality.

The results obtained in the evaluation of the methodological quality of the case reports indicate that the studies were of good quality, as both presented the answer “no” in only one of the items.

Meta-analysis

Twelve studies (1,802 individuals) were selected for the single-arm meta-analysis. As these were heterogeneous studies, the random effects model was chosen in the analysis. Figure 2 shows the result of the overall ACD occurrence rate (0.9% [95%ci 0.4-2.0%]. The results demonstrate high heterogeneity (99.4%) among the studies.

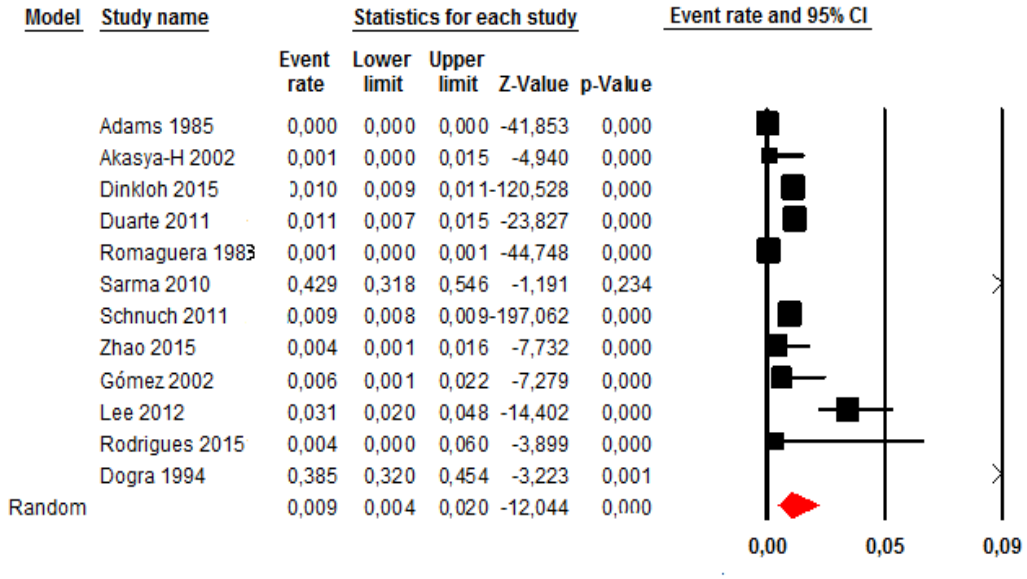

Figure 2. Single-arm meta-analysis of the incidence of allergic contact dermatitis. CI = confidence interval.

In the subgroup analyses according to the country of the study (Table 3), it was not possible to evaluate the studies conducted in North America as this comprised only one study. Studies conducted in Asia had an incidence of ACD of 48 positive cases per 1000 individuals (i2 = 97.79%). Studies conducted in South America resulted in an incidence of 11 positive cases per 1000 individuals (i2 = 0). In the European region, the incidence was 4 positive cases per 1000 individuals (i2 = 98.883%).

Table 3. Subgroup analysis by country of study.

Country	Number of studies	Estimate Point	Inferior limit	Superior limit	(I^2)	p
North America	1	0,000	0,000	0,000	NA	0,000
South America	2	0,011	0,007	0,015	0,000	0,000
Asia	5	0,048	0,009	0,221	97,790	0,001
Europe	4	0,004	0,002	0,007	98,883	0,000
Total	12	0,002	0,001	0,002	99,432	0,000

Publication bias

Figure 3 presents the funnel graph, suggesting the presence of publication bias.

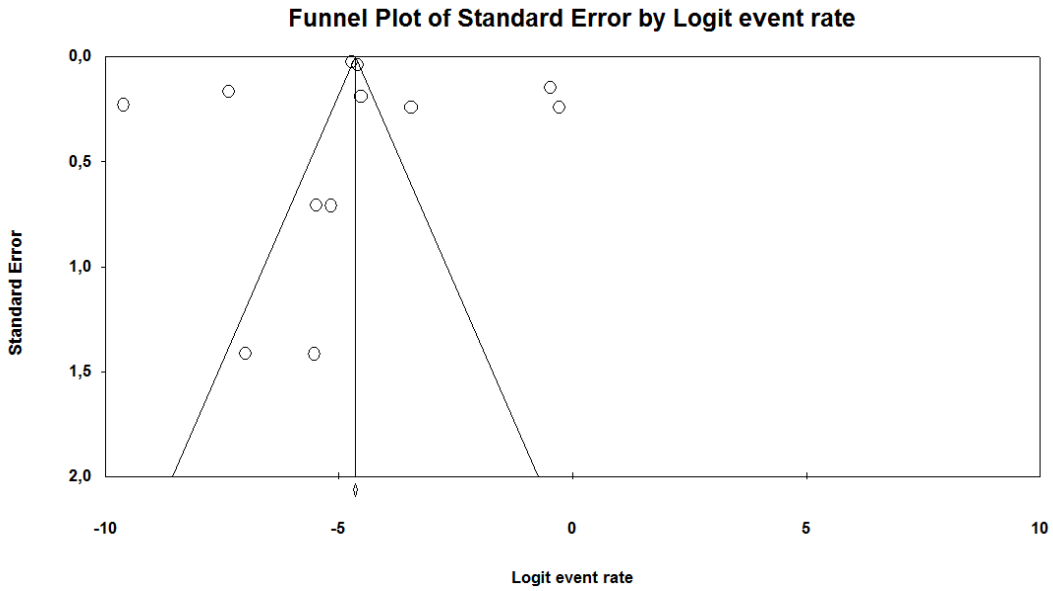

Figure 3. Publication bias analysis.

DISCUSSION

Although parabens are popular, since the 1960s, their use and safety according to ACD is questionable. Therefore, its use as a preservative in cosmetic, pharmaceutical and industrial products raises concerns about the possible risk to human health [4, 26]. Although there is controversy regarding the use of parabens in cosmetics, this class of chemical preservatives has withstood extensive tests carried out by some north american and european organizations. It is noticeable that the use of a “claim” (paraben-free) has been highlighted in the media, but the use of this term may be limited to marketing, since the use of these substances within the indicated concentration is allowed by competent agencies. However, the fear that parabens may induce ACD has remained persistent [15, 27]. Therefore, the FDA continues to assess the safety of parabens [2].

This is the first systematic review published in the literature on the safety of parabens regarding the incidence of ACD. We evaluated 14 studies that addressed the use of some type of cosmetic containing parabens as a preservative and its possible relationship with ACD. The included studies were carried out in different countries on different continents, showing that studies assessing these substances have been conducted in different regions of the world. Most of the studies found in the present systematic review showed low ACD rates in individuals using parabéns [5,13,15,16,18-21,24], both for individuals with suspected ACD and healthy subjects.

Two studies included in this systematic review were carried out in a population in India, totalling 270 individuals. Of these, 89% were women. In these studies, the incidence rates of ACD in relation to exposure to parabens were approximately four times higher when compared to the other studies [17, 25]. This may have occurred because the concentration of parabens used in Indian goods may be above the permitted standard level (0.1-0.3%), leading to greater skin sensitization, so these results obtained need to be validated in further studies [17].

Sensitization to parabens, whether immediate or delayed hypersensitivity, presents a difficult diagnosis and a therapeutic challenge for physicians. When detected, individuals should be advised to avoid cosmetics or other products containing these preservatives [24]. There are reports that ACD caused by parabens contained in shampoo formulations is uncommon, except for damaged skin. Therefore, it is possible to conclude that on skin already damaged by some type of irritation, dermatitis is more likely to occur due to contact with the use of cosmetic products containing parabens, since the skin is already sensitized [23].

In the single-arm meta-analysis, the incidence of ACD was 0.9%. As recommended by the Council for International Organizations of Medical Sciences (CIOMS), this is considered a rare reaction [28]. In addition, it was observed that the heterogeneity among the studies included in the analysis was high. The cause of this heterogeneity may be related to clinical, methodological and statistical variations of the included studies. The subgroup analysis carried out by region showed that Asia had a higher prevalence of ACD associated with parabens, which can be explained by the studies carried out in India that presented a significant number of positive cases. In addition, all studies used doses of parabens above recommended levels, which may overestimate the incidence of ACD.

One of the latest studies carried out by the CIR panel of experts concluded that 20 different types of parabens are safe in cosmetics, as long as they are within the current practice of use and in concentrations considered safe [1]. Although the different types of parabens evaluated through contact testing in the studies included in this systematic review are within the list of parabens allowed by the CIR panel, it is known that the concentrations used in contact tests are much higher than those recommended by the agencies, which leads us to conclude that the incidence of ACD would be even lower if recommended concentrations of parabens were used.

The CIR panel of experts is concerned about the bioaccumulation potential of parabens, which can be distributed throughout tissues. In addition, despite recent studies using sensitive analytical tests demonstrating the presence of parabens in different human tissues, the data are still unclear about permanent accumulation in tissues, so further studies are needed. It has been shown that, after parabens are applied to the skin, they are metabolized into 4-hydroxybenzoic acid, which is safe under the typical conditions of use [29].

Limitations

The present study was limited to investigating the relationship between the use of parabens in cosmetics and the incidence of ACD; therefore, other problems related to parabens were not the subject of this study.

Another limitation of this study is that only two of the studies had a control group. Thus, the meta-analysis was conducted without comparison with another group. For more robust results, controlled studies are necessary.

In view of all the data collected and analyzed in this systematic review with a meta-analysis, we observed that, in the few cases in which ACD was associated with the use of cosmetics containing parabens, the reaction was often attributed to the application of parabens on already damaged skin and at concentrations much higher than recommended. Therefore, skin reactions to cosmetic products containing parabens in their formulations are rare and, when they occur, it is recommended to discontinue use of the product containing this preservative. This fact does not justify the interruption of the use of this class as preservatives in cosmetics. These data would be better evaluated in studies with a control group, at the usual concentrations of parabens and in individuals without suspected ACD.

CONCLUSION

According to the results obtained in this study, considering the advantages, facility of use, compatibility with different cosmetic formulations, low cost and good effectiveness, the incidence of ACD after using cosmetics with parabens is observed as a rare event. Therefore, we can consider that paraben-free products do not appear to be advantageous to the consumer, since they generally have a higher cost on the market. However, as a safety measure, consumers who have already been diagnosed with ACD can be advised to

avoid the use of cosmetic products containing parabens, since the chance of increasing dermatitis with the use of parabens may be greater because the skin is already be sensitized.

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