REVIEW

Parabens: A Review of Epidemiology, Structure, Allergenicity, and Hormonal Properties

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Parabens are the most commonly used preservatives in cosmetic, pharmaceutical, and industrial products. The epidemiology, structural properties, allergenicity, hormonal properties, and hypotheses regarding the "paraben paradox" are addressed in this review.

PARABENS were first introduced in the 1930s and currently are the most widely used preservatives in cosmetic, pharmaceutical, and industrial products.[1–4] Parabens are found worldwide in creams, pastes, beauty products, glues, fats, and oils.[5] Methyl and ethyl parabens are the most frequently used parabens and, with the exception of water, the most commonly used ingredients in cosmetic preparations.[1,6–8] Parabens are popular because they are inexpensive, colorless, odorless, and nontoxic; effective over an extensive range of hydrogen ion concentration (pH); and have a wide spectrum of antimicrobial activity.[3,9–11]

The antimicrobial effect of parabens and their use as preservatives were first established in 1924 by Sabalitschka.[12] In 1995, the US Environmental Protection Agency granted GRAS (Generally Recognized as Safe) status to parabens, and current European Union cosmetic regulations permit a total concentration of 0.8% for methyl-, ethyl-, propyl-, and butylparaben in cosmetic products.[9] However, as a result of recent evidence suggesting a link between parabens and breast cancer and testosterone levels, the Cosmetic Ingredient Review Expert Panel has elected to reevaluate their safety.[13,14] This evidence, as well as the structural properties, metabolism, antimicrobial properties, and allergenicity of parabens, will be discussed in this review.

Structure, Formulation, and Metabolism

The term "paraben" is an abbreviation for para-hydroxybenzoic acid. Parabens are a family of alkyl esters of para-hydroxybenzoic acid that differ at the para position of the benzene ring by various chemical substitutions.[1,8] There are five widely marketed para-hydroxybenzoic acid esters: methylparaben, ethylparaben, propylparaben, butylparaben, and benzylparaben (Fig 1). The chemical substitutions provide each paraben ester with a different solubility and spectrum of antimicrobial activity. As the alkyl chain length increases, water solubility decreases and oil solubility increases.[15] The greater the paraben's lipid solubility, the greater the penetration through the epidermis. Therefore, penetration increases with ester chain length.[15,16]

In the United States, the average total paraben exposure per individual is estimated to be approximately 76 mg per day (1.3 mg/kg/d for a person weighing 70 kg). Cosmetics and personal products provide the bulk of exposure at 50 mg per day, drugs supply 25 mg per day, and food accounts for approximately 1 mg per day.[17] The concentration of parabens in foods is usually less than 1%.[17] In the past, concentrations of parabens in topical over-the-counter products were as high as 5% in the United States.[17] Currently, however, the concentrations of parabens in cosmetics are generally less than 0.3% but may range up to a total concentration of 1%.[11,18,19] The bioavailability of all parabens is greater in oil-in-water preparations than in petrolatum.[8,20] The potential for the percutaneous absorption of parabens is influenced by the relative distribution of the oil/water phases of formulation, and this is further altered by the addition of various surfactants.[21,22] All parabens partition into the oil phase, but those with longer chains are more soluble in oil, and those with shorter chains are more soluble in water. Therefore, in oil-based formulations, methylparaben requires a higher concentration to maintain effectiveness.[23] The effect of variable concentrations of parental formulations on the development of paraben hypersensitivity reactions has not been examined.

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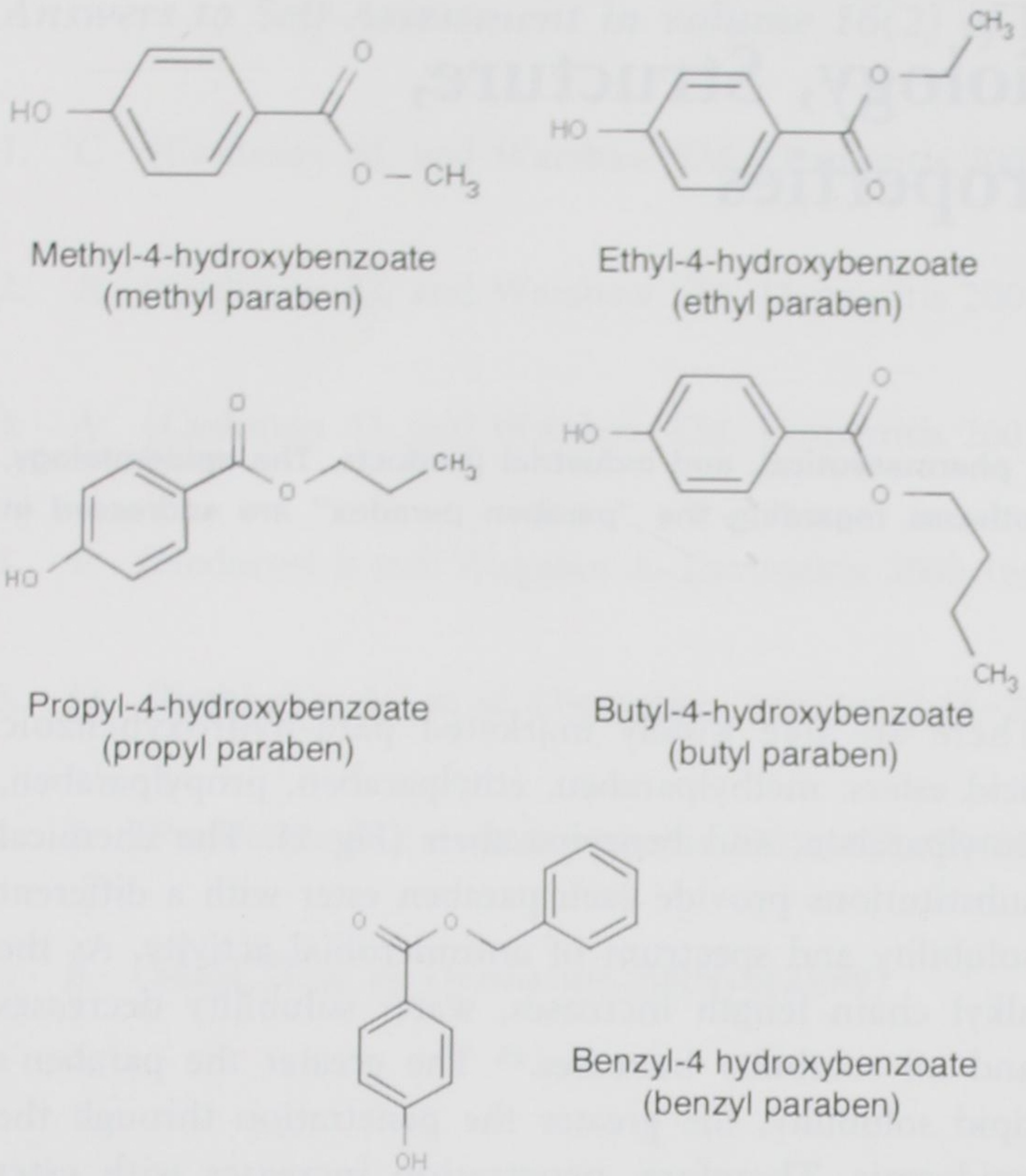


Figure 1. Structure of the parabens.

Parabens applied to skin are partially metabolized by four carboxyl esterases found in skin and subcutaneous fat. These esterases hydrolyze the parabens to para-hydroxybenzoic acid and their respective side chains.[24] The carboxyl esterases found in the subcutaneous fat are more active against parabens with short chains whereas esterases localized to keratinocytes are more active against parabens with longer chains.[24] Parabens absorbed by the body were once thought to be fully metabolized by esterases in the liver and kidney, excreted in the urine, and not to accumulate in the body; however, recent evidence points to the contrary. Nakazawa and colleagues found that individual parabens were not detected in human blood and milk but that para-hydroxybenzoic acid, the main metabolite of parabens, was detected in all patient blood and milk samples tested.[25] In addition, a study by Oishi demonstrated that a portion of parabens can be absorbed and retained in human body tissues without hydrolysis by tissue esterases.[14]

Antimicrobial Spectrum and Microbial Resistance

Parabens have a broad spectrum of activity against yeasts, molds, and bacteria. The antimicrobial activity of parabens increases with increasing alkyl chain length. As a result, they are typically combined to enhance antimicrobial efficacy. Parabens are more effective against fungi than against bacteria; their antibacterial activity is greatest against gram-positive organisms and poorest against *Pseudomonas* species.[10,26] Enhancement of antimicrobial coverage is achieved by combining parabens with other biocides such as formaldehyde releasers, isothiazolinones, or phenoxyethanol.[1,10,26]

Cladosporium resinae, *Pseudomonas aeruginosa*, and *Burkholderia cepacia* have been reported to be resistant to parabens.[27–29] Certain microorganisms, such as the gram-negative bacteria *Enterobacter cloacae*, *Acinetobacter*, *Rhodopseudomona palustris*, and *Burkholderia cepacia*, contain specific enzymes that degrade parabens.[30–34] A recent study showed a para-hydroxybenzoate hydroxylase gene (*POBA/PRBA*) in *Enterobacter cloacae* and *Enterobacter gergoviae* strains.[35] This enzyme catabolizes para-hydroxybenzoic acid to the central intermediate protocatechuate, which is ultimately degraded to form tricarboxylic acid intermediates.

Burkholderia cepacia and *Enterobacter cloacae* known to degrade parabens have led to systemic infections by resistant organisms. Hutchinson and colleagues reported on six patients with serious infections that were caused by an ultrasound gel contaminated with *Burkholderia cepacia*.[33] The *B. cepacia* strain that was isolated from the patients' blood was identical to the isolates in the ultrasound gel and demonstrated the ability to degrade parabens in vitro. *Enterobacter cloacae* was isolated from the ultrasound gel and also demonstrated the ability to degrade parabens. Other cases of nosocomial infections from paraben-containing products contaminated with *Enterobacter* have been reported, including an outbreak of *E. cloacae* sepsis in a newborn unit, traced to contaminated total parenteral nutrition solution[36]; an outbreak of *E. cloacae* and *Pseudomonas aeruginosa*, traced to a contaminated vial of dextrose[37]; and cases of gram-negative bacteremia in hemodialysis patients, traced to contaminated drain ports.[38]

Allergic Reactions

Type IV Delayed-Type Hypersensitivity Reactions to Topical Parabens

The first case of delayed-type hypersensitivity reaction to parabens was described in 1940 by Bonnevie and described a woman who reacted to ethylparaben in her antifungal preparation.[39] The prevalence of allergic contact dermatitis from parabens is low; in most studies, it ranges

Table 1. Prevalence of Paraben Allergy in Patch-Test Populations

Investigator or Study	*Year Published*	*No. of Patients Tested*	*Positive Reactions (%)*
Fregert[42]	1969	4,825	1.9
Bandmann[43]	1972	4,000	2.0
Burry[44]	1973	1,000	0.5
Marsulli[45]	1974	397	0.3
Brun[46]	1975	1,000	1.7
NACDG[47]	1975	1,900	3.7
NACDG[48]	1976	900–2,000	2.7
Lepine[49]	1976	131	1.5
Husain[50]	1977	1,312	3.0
Camarasa[51]	1977	2,806	1.5
Calas[52]	1978	500	1.8
Blondeel[53]	1978	330	10.9
NACDG[54]	1982	1,753–2,145	2.1
Romaguera[55]	1980	4,600	1.2
Edman[56]	1982	8,933	0.3
de Groot[57]	1986	627	0.3
de Groot[58]	1986	501	0.2
Vestey[59]	1986	501	6.5
Broeckx[60]	1987	5,202	1.4
Gollhausen[61]	1988	11,962	2.0
Hogan[62]	1988	542	4.2
Enders[63]	1989	1,845	1.9
Macfarlane[64]	1990	403	0.7
George[65]	1990	63	8.0
Seidenari[66]	1990	593	0.7
Shehade[67]	1991	1,753–4,721	1.3
Fransway[12]	1991	4,270	3.8
NACDG[68]	1997	NR	2.3
Perrenoud[69]	1994	2,295	1.7
NACDG[70]	1998	3,120	1.7
Schnuch[71]	1998	28,349	1.6
Lestringant[72]*	1999	373	5.1
NACDG[73]	2000	NR	1.7
NACDG[74]	2003	5,800	1.0
NACDG[75]	2000–2002	4,913	0.6

NACDG = North American Contact Dermatitis Group; NR= not reported.
Adapted from Fransway AF.[12]
*Suspected cosmetic allergy.

from 0 to 4.2%.[10,18,40] A meta-analysis by Krob and colleagues that evaluated 15 years of published Thin-Layer Rapid Use Epicutaneous (TRUE) Test (Mekos Laboratories A/S, Hillerød, Denmark) data established that paraben mix was one of the least prevalent allergens tested (only 0.5% of tested patients had reactions).[41] Table 1[42–75]. shows the prevalence of positive paraben results in routine patch testing from 1968 through 2002.

Numerous individual reports describing cases of contact dermatitis as a result of contact with parabens in topical products have been published.[76–80] Two cases reported by Mowad[11] and one case reported by Simpson[80] were recurrent reactions to facial cosmetic products and formulations. Sporadic case reports describing young children reacting to parabens in gel-like toy products called "Let Rip! Fun Pot"[79] and "Slimy"[81] are present in the literature. There has been one report of contact dermatitis from ultrasound gel[82] and a report of four cases from Unna boots.[83] Fisher reported a case of paraben dermatitis caused by a medicated bandage[84] and two cases involving paraben-containing topical steroid creams.[85] All of these affected individuals were patch-tested and had positive reactions to a paraben mixture.

Occupational cases of paraben contact dermatitis (among cooks and food handlers with hand dermatitis caused by paraben-containing foods) have also been reported.[86] Recently, Foti and colleagues reported a 42-year-old nonatopic male who presented with a severe eczematous reaction in the genital area after using a condom containing a retarding cream formulated with benzocaine and parabens. Patch testing yielded positive reactions to the retarding cream, benzocaine, and paraben mixture.[87]

Allergic contact dermatitis has most commonly been reported when paraben-containing products are used on damaged skin.[84] Patients with long-standing dermatitis and leg ulcers may become sensitized when topical preparations containing parabens (such as topical corticosteroids or Unna boot bandages) are applied, even preparations with low paraben concentrations of 0.1 to 0.3%.[18,19,84,85,88] This process is perpetuated with frequent re-application and can present as a stubborn recalcitrant dermatitis that is unresponsive to treatment.[89] The rate of sensitization to parabens in patients with chronic leg ulcers is higher than that of the general population. Machet and colleagues reported that of 3,043 leg ulcer patients, 8.5% had contact sensitivity to any allergen and of that 8.5%, 5.7% were sensitized to the paraben mixture.[90]

Although parabens are frequently found in cosmetics, they are considered weak sensitizers in these formulations. Paraben-sensitive individuals are often able to tolerate paraben-containing cosmetics when applied to normal intact skin. Sites of healed dermatitis occasionally flare when a sensitizer is applied whereas skin that has never been the site of dermatitis does not react. This puzzling aspect of the use of paraben-containing products was termed the "paraben paradox" by Fisher.[91]

Table 2. Parabens in Foods

Food Category	*Use Level (ppm)*
Tomato pulp	1,000
Tomato puree	1,000
Catsup	1,000
Pickles	1,000
Relishes	1,000
Fruit juices	1,000
Packaged meats, fish, and poultry	1,000
Gelatin and pudding	0.01
Alcoholic beverages	0.02
Soft candy	0.06–0.08
Frozen dairy foods	0.06–0.08
Sugar substitutes	0.25
Fats and oils	0.32
Baked goods	0.97
Processed vegetables	1.00

ppm = parts per million.
Adapted from Soni MG et al[17]; Rietschel RL, Fowler JF Jr.[26]

Type IV Hypersensitivity Reactions to Ingested Parabens in Orally Administered Products

Most paraben-sensitive persons do not require a restrictive diet because ingestion of products containing parabens does not result in a dermatitis.[92] There are a few reports, however, of a systemic allergic contact dermatitis presenting as a generalized eczematous eruption after ingestion of paraben-containing medications or foods (Table 2).[18,93] Kaminer and colleagues reported a patient who, after receiving an oral preparation of haloperidol syrup containing methylparaben, developed a generalized eczematous eruption; testing by macrophage migration inhibitor factor indicated paraben sensitivity.[94] Veien and colleagues conducted a study involving 14 paraben-sensitive patients who ingested placebo and paraben-containing capsules. Only 2 (14%) of the 14 patients reacted: one patient with hand eczema developed vesicles on the sides of fingers within 24 hours of ingesting the capsule, and the other patient had a localized flare at the paraben patch-test site.[95]

Type I Immediate Hypersensitivity Reactions to Topical Parabens

The same paraben compounds that cause delayed-type reactions can also cause type I immediate reactions such as contact urticaria. In a study by Katsarou and colleagues, 664 patients were tested to determine the incidence of immediate contact reactions to European Standard series allergens. Within 30 minutes, 30 patients (4.5%) reacted positively to the paraben mixture. The clinical relevance of these reactions, however, was not described.[96] Most reports of type I reactions to parabens describe localized cutaneous urticarial plaques present in the distribution of exposure to the paraben-containing product,[8,39,97] but a few cases with systemic symptoms have been described. Carr reported a case of anaphylaxis from an intraurethral lignocaine preparation containing paraben preservative. The authors attributed the reaction to parabens; however, this patient was not patch-tested.[98] Henry and colleagues described a 31-year-old man who developed hives, itching, and redness within 15 minutes of applying different cosmetic products and who subsequently developed immediate cutaneous wheal and flare reactions when tested with topical applications of 5% methylparaben and 5% ethylparaben.[99]

Although not currently performed in the clinical setting, positive passive transfer (to produce the Prausnitz-Küstner reaction) was performed in the past. This procedure involved injecting a small amount (0.1 mL) of a paraben-sensitive patient's serum into a healthy volunteer's forearm. If the recipient reacted, the test result was considered positive and indicative of a type I immunoglobulin E (IgE)–mediated sensitivity.[100] Henry and colleagues reported a patient with contact urticaria from paraben-containing moisturizers who had both a positive open patch-test reaction to parabens and a positive passive transfer reaction.[99]

Type I Immediate Hypersensitivity Reactions to Parenteral Parabens

Paraben-containing parenteral products include antibiotics, corticosteroids, local anesthetics, radiopharmaceuticals, vitamins, antihypertensives, diuretics, insulin, heparin, and chemotherapeutic agents.[36] The prevalence of type I immediate hypersensitivity to parenteral parabens was investigated by Kajimoto and colleagues, who conducted a double-blind study of intravenous regional anesthesia using 0.5% prilocaine with or without 0.1% methylparaben in 200 patients. Seventeen (8.5%) of the patients developed an immediate reaction after injection with the methylparaben-containing compound whereas only 4 (2%) of the patients reacted to the paraben-free anesthetic.[101]

Several cases of immediate hypersensitivity reactions (including bronchospasm, pruritus, localized angioedema, and generalized dermatitis) to parenterally administered compounds containing parabens have been reported.[10,102–111] Reactions to local anesthetics and intravenous infusions of hydrocortisone preserved with parabens are the most commonly reported immediate IgE-mediated reactions.[106–108] Nagel and colleagues described a patient who developed

bronchospasm and pruritus after intravenous infusion of a hydrocortisone preparation containing methylparaben and propylparaben. Subsequent challenge determined that this patient could tolerate parenteral hydrocortisone preparations without parabens.[104] Sato and colleagues described a 24-year-old woman on chronic dialysis who complained of generalized itching immediately after an intracatheter injection of a heparin agent. She was able to tolerate a heparin preparation without parabens but not the heparin preparation containing parabens. Through testing with a leukocyte migration inhibition test, she was found to be sensitive to methylparaben and propylparaben and able to tolerate heparin.[111] In 1969, Aldrete and Johnson reported a type I immediate hypersensitivity reaction in a patient after subcutaneous injection with lidocaine preserved with parabens. A subcutaneous skin test showed a negative response to lidocaine and a positive reaction to methylparaben. Additionally, the Prausnitz-Küstner reaction test result was positive.[102] Reports of three other local anesthesia–related cases described similar patients' reacting to methylparaben but not to lidocaine after subcutaneous injections.[106–108]

Type IV Hypersensitivity Reactions to Parenteral Parabens

Fine and Dingman reported one case of generalized eczematous dermatitis following suction-assisted lipectomy when a local anesthetic containing methylparaben was used. The eruption began overlying the surgical site and progressed to the patient's upper extremities and neck.[105]

Patch Testing

Responses to Different Paraben Concentrations

Several different concentrations of individual parabens, as well as paraben mixes, have been used for patch testing. Several paraben mixes are currently commercially available and are listed in Table 3. In the United States, the individual esters were typically tested at 5% until December 1984, when the concentration was decreased to 3%.[2]

Today, patch testing is usually performed with methylparaben, ethylparaben, propylparaben, and butylparaben combined in petrolatum, each at a 4% concentration for a total of 16%.[8] There is controversy over which concentration is the most sensitive and/or specific. Higher concentrations of a paraben mixture are often more irritating than individual esters are.[9,112] Most practitioners initially patch-test patients with a paraben mix and then, if the result is positive, test with individual paraben esters. Cross-reactions between the paraben esters are fairly common. One of the largest reported studies evaluating cross-reactions was by Menne and Hjorth. They performed routine patch testing on 8,020 patients from 1971 to 1986. Positive reactions (+, ++, or +++) to the paraben mixture were found in 2% of patients. Of the 76 patients who reacted positively to the paraben mixture, 60 were tested with the individual paraben esters. Two-thirds of the patients (40 of 60) reacted to one or more of the individual esters, including butylparaben (30 of 60 patients [50%]), propylparaben (21 of 60 [35%]), and benzylparaben (12 of 60 [20%]). All patients who reacted to propylparaben reacted to ethylparaben or butylparaben or both.[2]

Paraben-containing therapeutic agents that cause allergic contact dermatitis in paraben-sensitive patients often produce false-negative patch-test reactions. This is thought to occur because the paraben concentration in the commercial product is too low (typically < 0.3%) to induce a positive reaction on normal skin.[98] Several studies have indicated that lower concentrations of parabens used for patch testing result in a lower number of positive reactions. In the study by Menne and Hjorth, individual

Table 3. Paraben Patch-Test Formulations

Formulation	*Total Concentration in Petrolatum (%)*	*Paraben Concentration (%)*				
		Ethylparaben	*Methylparaben*	*Propylparaben*	*Butylparaben*	*Benzylparaben*
TRUE Test	15	3	3	3	3	3
Chemotechnique Diagnostics (Sweden)	16	4	4	4	4	0
Trolab* (Canada)	16	3	3	3	3	0
NACDG	12	3	3	3	3	0

NACDG = North American Contact Dermatitis Group.
Adapted from Rastogi et al.[9]
*Trolab (Hermal, Reinbek, Germany) test, recommended by the International Contact Dermatitis Research Group and the European Environmental and Contact Dermatitis Research Group, and 16% formulations were used in Swedish standard, European standard, and Hungarian standard.

parabens were tested at 5% until December 1984, when the concentration was reduced to 3%. They reported that after the concentration was reduced, there were no +++ reactions, unlike what had been witnessed with the 5% concentration.[2] Hjorth and Trolle-Lassen described 19 patients who reacted to a 5% paraben mixture and who were subsequently tested with four paraben esters (methyl-, ethyl-, propyl-, and benzylparaben), each at four different concentrations (5%, 1%, 0.5%, and 0.1%). All patients reacted to one or several of the individual paraben esters at 5%, but lower concentrations induced fewer reactions. Positive reactions to the 1%, 0.5%, and 0.1% concentrations were found in 13 of 19 (67%) patients, 11 of 19 (58%) patients, and 5 of 19 (27%) patients, respectively.[113]

Epidermal Penetration of Parabens in Patch Testing

The efficacy of topical allergy screening systems relies on the ability of the allergens to separate from the vehicle, penetrate the stratum corneum, and activate Langerhans' cells. It is known that occlusion of the patch-test site increases the penetration of topical allergens.[114,115] Although there are no studies that have evaluated the impact of vehicle preparation or occlusion specifically in patch testing with parabens, some studies have indirectly indicated an effect. Occlusion increases hydration of the stratum corneum, from 5% to 50%.[115] Parabens are lipophilic, so their penetration should increase from the change in partitioning between the stratum corneum and viable epidermis during occlusion. This theory was tested by Cross and Roberts, who evaluated (1) the in vitro human epidermal penetration of a mixture of paraben ester preservatives in ointment, ethanol, and acetone vehicles and (2) the effect of a 10-hour occlusion period on the rate of delivery in each system. The occlusion increased diffusion eightfold in ethanol and 16-fold in acetone. Surprisingly, however, decreased diffusion and flux were reported in the ointment formulation. Additionally, there was a significant difference in the epidermal flux of the parabens when applied without occlusion in ointment, ethanol, or acetone compounds, indicating a role of the actual vehicle in the penetration of the allergen.[116] These results have notable implications regarding the use of the optimal topical allergy screening system, its vehicle, and occlusion.

Cross-Reactions

The "para" group of antigens are frequent sensitizers and consist of chemicals with a free amino group in the para position of a benzene ring. Table 4 lists chemicals in this group. There is debate about the cross-reactivity of parabens and the "para" group because parabens have a hydroxyl group instead of an amino group in the para position. Rudzki and Kleniewska reported that of 144 patients sensitive to para-phenylenediamine, 20 (14%) were allergic to parabens, and that in a separate group of 62 benzocaine-sensitive individuals, 20 (32%) were allergic to the parabens.[117] Although para-aminobenzoic acid (PABA) itself does not cross-react with parabens, the esters of PABA may show cross-reactivity.[92] According to Fisher, there have been no reported cases of cross-reactions between PABA ester and the other "para" compounds or with benzoic acid.[91] However, Rietschel and Fowler noted several unpublished cases of positive patch-test reactions to parabens, PABA, and para-phenylenediamine that appeared to be true cross-reactions.[18] In addition, Johnson and DeStigter reported a woman with demonstrated hypersensitivity to procaine, tetracaine, mepivacaine, and methylparaben.[106]

Table 4. para-Amino Group Chemicals

Class	*Chemical*
Diabetic medications	Carbutamide sulfonamides, sulfonylureas
Sunscreens	PABA
	PABA derivatives (glycerol para-aminobenzoate, isobutyl-p-aminobenzoate)
Diuretics	Hydrochlorothiazide
Hair dyes	PPD/para-aminophenol
Anesthetics	Benzocaine
	Chloroprocaine hydrochloride
	Procaine
	Phenacaine
	Ecocaine
	Butethamine
	Tetracaine
	Butacaine (topical anesthetics)
Antibiotics/antiinfectives	para-Aminosalicylic acid
Cardiac drugs	Procainamide
Azo and aniline dyes	Disperse Orange 3 Blue
	Disperse Yellow 3 Red
	Chrysoidine brown
	Bismarck brown
	Acid fuchsin
	Aminoazotoluene

PABA = para-aminobenzoic acid; PPD = para-phenylenediamine.
Adapted from Marks JG, DeLeo VA, editors. Contact and occupational dermatology. Chicago: Mosby Year Book; 1992. p. 183, and Rietschel RL, Fowler JF. Fisher's contact dermatitis. 5th ed. Philadelphia: Lippincott, Williams & Wilkins; 2001.

The Paraben Paradox and Suggested Hypotheses

The term "paraben paradox" was first used by Fisher in 1973 to describe two phenomena. The first paradox is that paraben-containing personal products, which are the cause of an allergic contact dermatitis, often produce false-negative patch-test reactions when applied to the skin of the back.[84] The second paradox is that paraben-sensitive persons, who react to parabens on patch testing and develop a dermatitis when paraben-containing products are used on compromised skin, may continue to use paraben-containing products on other areas of the body that have intact uninvolved skin, without any adverse reactions. Fisher provided two explanations for these paradoxes: (1) the patch testing is being performed on normal skin and (2) the concentration of the vehicle ingredient is too low.[84]

While these hypotheses provide partial explanations for these phenomena, other factors may play a role. We propose two additional hypotheses for the "paraben paradox," namely, the "esterase" and the "microbial metabolite" hypotheses.

Esterase Hypothesis

Long-chain parabens (eg, butylparaben) are metabolized by esterases in the subcutaneous tissue and are the least reactive. Short-chain parabens (methylparaben and propylparaben) are metabolized by esterases in keratinocytes and are the most reactive. Damaged epithelium could adversely affect the metabolism of parabens by esterases in this layer, thereby altering the final concentration of parabens that reach the dermis. It is possible that the short-chain highly reactive parabens, therefore, can penetrate damaged skin more readily because of impaired metabolism by keratinocyte esterases. It is also possible (as has been proposed for other antigens in dermatitic or traumatized skin where the stratum corneum barrier is impaired) that this disruption alone may allow greater absorption and penetration of all paraben esters. Either impaired metabolism of short-chain highly allergenic parabens by damaged keratinocytes and/or greater penetration of all paraben esterases by a disrupted stratum corneum could play a role in the development or elicitation of allergic contact dermatitis.

Microbial Metabolite Hypothesis

Most reports of allergic contact dermatitis from parabens describe the development of an allergic reaction in damaged skin after repeated applications of a paraben-containing therapeutic agent. It is possible that repeated applications produce or allow the cultivation of paraben-resistant microbes on the skin. These paraben-resistant organisms hydrolyze parabens to hydroxybenzoic acid and their respective side chains, which could in turn induce or accentuate sensitization. To our knowledge, the role of paraben-resistant microbial breakdown products in causing an allergic reaction to chemicals or in enhancing sensitization to the parent paraben has not been evaluated.

Hormonal Activity of Parabens

The estrogenic activity of parabens was first described by Routledge and colleagues in 1998[118] and has subsequently been substantiated by several in vitro and in vivo studies.[118–125] Methyl and ethyl esters have less potent in vitro and in vivo estrogenic activity than either butylparaben or propylparaben.[120,122,123] Parabens have been shown to bind to rodent uterine estrogen receptors[86] and to human estrogen receptors.[123] Because estrogen is a major etiologic factor in the development of human breast tissue and breast cancers, Darbre proposed that parabens and other chemicals that are used in underarm cosmetics may contribute to the increasing incidence of breast cancer.[126] In an uncontrolled study of 20 patients with breast tumors, the mean concentration of parabens was 20.6 $\pm$ 4.2 ng per gram of tissue, and methylparaben was present at the highest level.[127]

In addition to studies of estrogenic activity, several studies have evaluated the antispermatogenic potential of parabens. Oishi reported that exposure of postweaning rats and mice to butylparaben or propylparaben (but not methylparaben or ethylparaben) adversely affected the secretion of testosterone and the function of the male reproductive system.[14,128,129] Because these studies indicated a possible relationship between paraben exposure and breast cancer and/or male reproductive function, the Cosmetic Ingredient Review Expert Panel in 2004 announced its intention to reevaluate the safety of parabens.[13]

Summary

Allergic reactions to parabens, the most commonly used preservatives, are rare. More research is needed to further elucidate the best formulations for patch testing, the potential effects of parabens on human hormonal function, and potential explanations of the "paraben paradox."

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