

ALLERGEN Focus



Focus on T.R.U.E. Test Allergen #8: Parabens

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The thin-layer rapid-use epicutaneous (T.R.U.E.) test is a valuable first-line screening tool used by many dermatologists and allergists. Although the test focuses on common allergens, frequent questions have arisen from colleagues and patients as to where a specific allergen is derived or what products patients should avoid. With this in mind, this column was developed to provide educational information about the T.R.U.E. test allergens.

This month, the column explores T.R.U.E. test allergen #8: parabens, a preservative agent commonly added to cosmetics, body care products and foods.

THE CONTACT DERMATIDES

The contact dermatides include allergic contact dermatitis (ACD), irritant contact dermatitis and contact urticaria.



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Irritant contact dermatitis, the most common form of contact dermatitis, accounts for approximately 80% of environmental-occupational-based dermatoses.

Contact urticaria (wheal and flare reaction) represents an IgE and mast cell-mediated immediate-type hypersensitivity reaction that can lead to anaphylaxis, the foremost example of this being latex hypersensitivity. While this is beyond the scope of this section, we acknowledge this form of hypersensitivity due to the severity of the potential reactions and direct the reader to key sources.^{1,2}

ACD is an important disease with high impact in terms of patient morbidity and economics. ACD represents a T-helper-cell Type-1 (Th1)-dependent delayed-type (Type IV) hypersensitivity reaction.

The instigating exogenous antigens are primarily small lipophilic chemicals (haptens) with a molecular weight less than 500 Da. On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated, which leads to the clinical picture of ACD.

The primary focus of this section is to highlight the educational component of this important inflammatory disorder.

CLINICAL ILLUSTRATION

A patient presented with penile dermatitis to the University of Miami Contact Dermatitis Clinic. Of note, he related worsening of his dermatitis with trials of a variety of over-the-counter topical therapeutics.

EARLY USE OF COSMETICS

“A woman without paint is like food without salt,” once wrote the Roman philosopher Platus.³ In fact, makeup has played a key role in societies’ perceptions of beauty for centuries, with archaeological evidence of cosmetics use dating back to Ancient Egypt, circa 4000 BC.⁴

Ancient Greek, Egyptian and Roman women were known to have used mercury and lead to lighten their skin and kohl (a substance linked to lead poisoning in children) for darkening eyelashes and eyelids.³⁻⁵ It is believed that these Egyptian traditions were passed down to the Jews because references to face painting can be found in the Bible.⁴

During both the European Middle Ages and the Italian Renaissance there was a resurgence of the *pale-faced* look as a sign of wealth and affluence, being that the wealthy did not work outside.³ Women at times sought drastic measures, such as inducing anemia, to achieve the ultimate wealthy pale look by either blood letting or, during the Renaissance, through the more *civilized* consumption of arsenic complexion wafers.^{3,5}

The *pale-glazed* look became very popular in the late 1500s during Elizabethan England. Egg whites were applied to the face for glazing.³⁻⁵ Concern over the health hazards of glazing led to the first consumer alert on the possible health threat of cosmetics. Many feared that glazing would block vapors and energy from circulating properly.³

By the reign of Charles II (1630-1685), Europe was in recovery from the black plaque epidemic. The gripping fear of going outdoors meant that regardless of class, all suffered from the pallor from being kept indoors. This led to widespread use of makeup, especially by the affluent to achieve a 'healthy' look.³⁻⁵ Specifically, the French were known to use an excessive amount of red rouge and lipstick to imply good health and a fun-loving spirit, which led Europe at large to tout the painted French as "unattractive, with something to hide."³⁻⁵

Of interest around this same time, a high-society Italian woman of historical note, Signora Toffana, designed a face powder for herself and her friends that contained both lead and arsenic.^{3,5} Toffana instructed these women to apply the powder to their cheeks only when their husbands were around — so that they would kiss their cheeks.

Her most notorious invention, however, was called *Agua Toffana*. This poi-



sonous liquid, containing the deadly arsenic, was purportedly decorated with a small picture of a saint and an inscription to seek out Signora for instructions.⁵ The high demand for Aqua Toffana was eventually what led to her demise, as Signora Toffana was arrested, imprisoned and hung in 1709 for having been an accomplice in the killings of more than 600 husbands who ingested her deadly liquid.⁵

FLEDGLING COSMETIC INDUSTRY SUFFERS SETBACK, THEN ROARS AHEAD

In the late 1800s, the young and growing cosmetic industry suffered a major setback when Queen Victoria publicly declared that wearing makeup was "impolite." The stigma of makeup became widely dispersed, and it became regarded as vulgar and obscene — "a prop for actors and prostitutes alike."³⁻⁵ Queen Victoria's socio-political effects were so grand that makeup didn't regain public acceptance until late in the 19th century.³

Of note, the "Victorian face" maintained a stronghold, until mass marketing led to a resurgence of makeup use in the 1920s.³⁻⁵ On August 26, 1920, the Nineteenth Amendment to the United States Constitution became law, and American women with their newly gained right to vote, flaunted their independence by wearing bright red lipstick.³

THE EVOLUTION OF COSMECEUTICALS

It is known that before the commercialization of makeup, women formulated their own. For example, women would add hot beads of wax to the tips of their eyelashes to lengthen them. In fact the word "mascara" was originally imported into English language from the Spanish word *mascaro* (meaning soot mask) circa 1890.⁵

The first modern-type mascara was formulated in 1913 by a chemist named T.L. Williams. Notably, he named the product after his sister *Mabel*, the first to utilize this new method. Variations of this mascara are still marketed today as *Maybelline*.⁵

During this time the Russian Ballet had a big influence on American film actors. A Polish makeup artist to the Russian Ballet by the name of Max Factor was to make great strides in the cosmeceutical industry, following his cosmetic arts debut at the World Fair in 1904.⁶ And, by 1914, Max Factor introduced his pancake makeup foundation to movie actors, which unlike traditional theatrical makeup resisted cracking and caking under the lights.⁷

Movie stars loved the new formulations so much that Max Factor decided to make his formulations available to the public with accompanying advertisements insisting that every girl could look like a movie star, just like Joan Crawford, if she wore clear red lipstick by Max Factor.

Russian dancers with their dramatic eye makeup also did not go unnoticed, and with this new appeal came an increased demand for kohl and mascara — at least for the privileged classes and movie stars. The Ballet also inspired the fad of colored eye shadow color-coordinated with couture evening dresses. The beauty artists behind these advances were none other than Helena Rubinstein and Elizabeth Arden.⁸

In 1917, film actress Theda Bara asked Helena Rubinstein to find a way to emphasize her eyes, which she did with mascara and color. “The effect was tremendously dramatic,” Rubinstein later wrote. “It was a sensation reported in every newspaper and magazine — only less of a sensation than when Theda first painted her toenails!”^{7,8}

The 1920s, 30s and 40s marked the glamour and glory years of Hollywood, and movie stars became the poster definitions of vogue. Max Factor opened his beauty salon on Hollywood Boulevard and Hollywood’s elite became his regular clientele, from Jean Harlow to Bette Davis.

Mary Pickford’s baby-doll-like pale-skinned face and small cherry red lips and Audrey Hepburn’s cat-eyes eyeliner made huge appearances on the big screen, and the makeup artists behind the looks even began to appear in movie credits and even make cameo appearances.^{3,5}

THE ERA OF REGULATION

Worldwide, women wanted to achieve the look of their favorite movie stars. With this, there was a mass demand for retail cosmetics, a trend that brought with it something else: cosmetic regulation.

The Food and Drug Administration (FDA) and a new generation of consumer protection organizations worked with Congress to pass a bill that legally mandated quality and identity standards for foods, prohibition of false therapeutic claims for drugs, coverage of cosmetics and medical devices, clarification of the FDA’s right to conduct factory inspections, and the control of product advertising.⁹

Before meeting in front of Congress, the FDA assembled a collection of products that exemplified consumer harm from manufactured products. This col-

lection included Lash-Lure, an eyelash hair dye that blinded some women after use and resulted in one death.⁷



PARABENS OWE THEIR POPULARITY TO BEING INEXPENSIVE, COLORLESS, ODORLESS, AND HIGHLY EFFECTIVE OVER AN EXTENSIVE RANGE OF PH WHILE MAINTAINING A WIDE SPECTRUM OF ANTIMICROBIAL ACTIVITY.¹¹

President Franklin D. Roosevelt signed the Food, Drug, and Cosmetic Act on June 25, 1938, which brought cosmetics and medical devices under review by the FDA.⁹

PRESERVATIVES IN COSMETICS

In addition to federal regulations, the vast growth of the cosmetic industry in the 20th century brought with it a greater need for new ingredients and ways to preserve the shelf life of these items and decrease bacterial contamination.

One such group of preservatives was parabens, whose anti-microbial effects in cosmetics, pharmaceuticals and foods were first described by Sabalitschka in 1924.¹⁰ By the 1930s, parabens were routinely added to creams and cosmetics, and were

well on their way to becoming the most widely used preservatives in the products of the cosmeceutical industry.^{11,12}

Parabens owe their popularity to being inexpensive, colorless, odorless, and highly effective over an extensive range of pH while maintaining a wide spectrum of antimicrobial activity.¹¹ It is no wonder that they are commonly added to shampoos, moisturizers, shaving gels, cleansing gels, personal lubricants, topical pharmaceuticals, and even foods.¹¹ It is estimated that more than 90% of all cosmetic and body care products today contain some form of paraben preservation.¹²

A CLOSER LOOK AT PARABENS

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.¹³

There are five widely marketed paraben esters:

1. **methylparaben**
2. **ethylparaben**
3. **propylparaben**
4. **butylparaben**
5. **benzylparaben**

Each has a different chemical substitution on the benzene ring, and each of these chemical substitutions leads to different solubility and spectrum of antimicrobial activity.¹³ As a result, parabens are typically combined to enhance antimicrobial efficacy.¹¹ Lipid solubility (which increases with ester chain length) also allows for greater penetration through the epidermis.¹³

Topically applied parabens 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.¹⁴ In addition, further metabolism by the liver and kidney and quick excretion in the urine, lead to the thought that parabens do not accumulate in the body.¹⁵

However, recent evidence may point to the contrary. Nakazawa et al found that while individual parabens were not detected in human blood and breast milk, para-hydroxybenzoic acid, the main metabolite of parabens, was detected in all patients.¹⁶

Even more recently, Oishi demonstrated that a portion of parabens can be absorbed and retained in human body tissues without hydrolysis by tissue esterases.¹⁷

A recent study measured the urinary concentrations of methyl, ethyl, propyl, butyl, and benzyl parabens in a demographically diverse group of 100 anonymous adults with an unknown exposure to paraben.¹⁸ They detected methyl and *n*-propyl parabens at the highest median concentrations (43.9 ng/ml and 9.05 ng/ml, respectively) in nearly all (>96%) of the samples, and detected other parabens in more than half of the samples (ethyl, 58%; butyl, 69%). They further found that parabens in urine appear predominantly in their conjugated or broken down forms. These authors, suggested that urinary conjugated parabens could be used as exposure biomarkers.¹⁸

PARABENS AND CANCER

Recently, the possibility of systemic side effects of preservatives has come into question.¹⁹ The greatest concern regarding parabens has focused on the estrogen-like effects. This is based on recent evidence from more than a dozen scientific studies indicating that several types of parabens can bind to estrogen receptors and can cause estrogen-like responses when tested in laboratory animals.²⁰⁻²³

The estrogenic activity of parabens was first described by Routledge et al in 1998,²⁰ and has subsequently been substantiated by several *in vitro* and *in vivo* studies.²¹⁻²³ Parabens have been shown to bind not only to rodent uterine estrogen receptors but also to human estrogen receptors as well.²⁴ In whole-animal studies, the estrogenic effects were not seen when the animals were fed the parabens, but rather when they were applied to or injected under the skin.²⁰

Since estrogen is a major etiologic factor in the development of human breast tissue and breast cancers, Darbre et al proposed that parabens and other chemicals that are used in underarm cosmetics may contribute to the increasing incidence of breast cancer.²⁵ In an uncontrolled study of 20 patients with breast tumors published in the *Journal of Applied Toxicology* in 2004, parabens were claimed to have been found in all 20 of the tissue samples.²⁶ According to the authors, methyl-

paraben was the most commonly observed paraben (18/20) and was detected at the highest average level.²⁶

Skeptics questioned these results as similar concentrations have been detected in blank control samples where there was thought to be "contamination of the samples from the hand soap used by technicians or detergents used in cleaning the glassware."²⁰



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To date, there is no concrete scientific evidence to support a link between parabens and breast cancer.^{12,13} Nevertheless, these studies brought to light the possibility that parabens might affect endocrine function and breast cancer development. Given that underarm deodorants or antiperspirants that contain these parabens are used daily for millions of people and the close proximity of the axilla and breast tissue this possibility should be considered and further work done in this area.²⁷

GOVERNMENTAL INPUT

The U.S. Food and Drug Administration (FDA), which regulates product safety, and the Cosmetic

Toiletries and Fragrance Association (CTFA), which provides specific ingredient safety through the Cosmetic Ingredient Review Board (CIR), have researched the use of parabens in cosmetics.

The CIR, an independent panel of renowned physicians and scientists that has reviewed ingredients used in cosmetics since 1976, reviewed the safety of methylparaben, propylparaben, and butylparaben in 1984 and concluded they were safe for use in cosmetic products at levels up to 25%, well above the concentration found in cosmetics.²⁸ With the more recent questions regarding paraben exposure and breast cancer, the CIR again reevaluated the safety of parabens.²⁹

And, in December 2005, after considering all the evidence for exposure to women and infants, the panel determined that there was no need to change its original conclusions.²⁸

The current FDA conclusion is that, "They are aware that estrogenic activity in the body is associated with certain forms of breast cancer, and although parabens can act similarly to estrogen, they have been shown to have much less estrogenic activity than the body's naturally occurring estrogens."²⁸⁻³⁰

Furthermore, at the present time the position of the FDA is that there is no reason for consumers to be concerned about a link between cancer and the use of cosmetics containing parabens.²⁸ It believes that the estrogenic potential or effect on the male reproductive system of parabens is not relevant to the cosmetic use of these ingredients because the level of parabens used in cosmetics is extremely low.²⁸

All this being said, there is little to no information in existence on the effects of the use of products with low levels of parabens over many years, which could result in accumulation of parabens in body tissue.²⁰

Ultimately, more comprehensive studies over a longer range of time are needed to explore these possibilities.

CONSUMER CONCERN

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.¹¹

And consumers are still concerned about the potential side effects. In fact, at one point, Avon's shareholders requested that Avon remove all parabens from the 82 cosmetic products that contained them. The request was denied by the Avon Board of Directors which cited the FDA's conclusion on the low risk potential of parabens and decided to continue their use.

This important interchange between consumer, industry and government regulation body demonstrates the increasing public awareness and request for more accountability from the cosmeceutical industry.³¹

SENSITIVITY TO PARABENS

While parabens have been shown to cause skin irritation and contact dermatitis in allergic persons, the prevalence, is relatively low.^{32,33-38} There have been three cases reported of recurrent reactions to facial cosmetic products and formulations.³⁵⁻³⁶ There is one report of contact dermatitis from ultrasound gel,³⁹ and a report of four cases from Unna boots.⁴⁰

Parabens also affect children. For example, reactions have been reported to parabens in gel-like toy products.³⁷⁻³⁸ In addition, paraben dermatitis has been also attributed to paraben-containing topical steroid creams and food additives.^{41,42} They are notably present in several food products such as mayonnaise, ketchup, salad dressings, jelly, fruit juices, and packaged meats. (See Table 1.) Occupational cases of paraben contact dermatitis, among cooks and food handlers, caused by paraben-containing foods have also been reported.⁴²

A recent meta-analysis of the overall prevalence and relevance of contact dermatitis reactions, found the prevalence of paraben allergies to be relatively low at 0.5% compared to other preservative chemicals.⁴³ (See composite data in Table 2.) Recently, a severe eczematous reaction in the genital area after using a condom containing a retarding cream formulated with benzocaine and parabens was reported. Patch testing yielded positive reactions to the ejaculation-retarding cream, which contained a benzocaine and paraben mixture.⁴²

TABLE 1

PRODUCTS THAT CONTAIN PARABEN⁵¹

COSMETICS	PERSONAL HYGIENE PRODUCTS	FOODS
<ul style="list-style-type: none"> • Bronzers • Concealers • Eye Makeup (Liners, Shadows, Mascara) • Facial Makeup (Blushes) • Foundations, Powders • Lipstick • Makeup Removers • Quick-Dry Nail Products 	<ul style="list-style-type: none"> • Anesthetics • Antiperspirants and Deodorants • Bandages (Unna) • Condoms • Dentifrices • Ear, Eye, and Nose Drops • Emollients, Lotions, and Creams • Rectal, Vaginal Medications • Soaps • Sunscreens • Toothpastes 	<ul style="list-style-type: none"> • Baked Goods • Frozen Dairy Products • Jams and Jellies • Mayonnaise • Mustard • Salad Dressings • Soft Drinks and Fruit Juices

TABLE 1: Adapted from Allergy to Parabens — available at dermnetnz.org

THE PARADOX

A notable aspect of ACD to parabens is that higher sensitivity to paraben-containing products is seen when they are used on damaged skin.⁴⁴ These paraben-sensitive individuals are often able to tolerate paraben-containing cosmetics when applied to normal intact skin. Interestingly, sites of healed dermatitis occasionally flare when the paraben sensitizer is applied to intact skin, which notably does not react. This aspect of the use of paraben-containing products was termed the "paraben paradox" by Fisher in 1973.⁴⁵

CROSS-REACTIVITY

The "para" group of allergens are defined by an alkyl group and consist of chemicals with a free amino group in the para position on a benzene ring. There are several chemicals in this group that have the potential to cross react with *para*-hydroxybenzoic acids via metabolites. These include: *para*-aminobenzoic acid (PABA) esters in sunscreens, *para*-phenylenediamine (PPD) in hair dye, sulfa medications, hydrochlorothiazide, ester anesthetics, *para*-aminosalicylic acid, and disperse dyes. Rudzki and Kleniewska reported that of 144 patients sensitive to *para*-phenylenediamine, 20 (14%) were also allergic to parabens, and that in a separate group of 62 benzocaine-sensitive individuals, 20 (32%) were allergic to the parabens.⁴⁶

Although *para*-aminobenzoic acid (PABA) itself does not cross-react with

TABLE 2

SENSITIZING POTENTIAL OF PRESERVATIVES IN COSMETICS^{43,51}

Iodopropylbutylcarbamate	0.3%
Paraben	0.5%
Methylchloroisothiazolinone	2.3%
Methyldibromoglutaronitrile	2.7%
DMDM Hydantoin (FRP)	2.8%
Imidazolidinyl urea (FRP)	3.0%
Diazolidinyl urea (FRP)	3.2%
Bromonitropropane diol (FRP)	3.3%
Quaternium 15 (FRP)	9.3%

parabens, the esters of PABA may show cross-reactivity.⁴⁷

Rietschel and Fowler noted several cases of positive patch-test reactions to parabens, PABA, and *para*-phenylenediamine that appeared to be true cross-reactions.⁴⁸ In addition, Johnson and DeStigter reported a woman with demonstrated hypersensitivity to procaine, tetracaine, mepivacaine, and methylparaben.⁴⁹

Patients with paraben allergies should be aware of these cross reactive chemicals and when possible try to avoid them.

TESTING FOR PARABEN SENSITIVITY

Paraben mix is included on the T.R.U.E. test panel 1.1, site # 8. The component consists of a mixture of methyl *p*-hydroxybenzoate, ethyl *p*-hydroxybenzoate, propyl *p*-hydroxy-

benzoate, butyl *p*-hydroxybenzoate, and benzyl *p*-hydroxybenzoate combined in petrolatum.

THE VALUE OF THIS PATIENT CASE

This patient was found to be allergic to the **parabens**, which were found to be ingredients in his topical creams and medicaments. Upon further inquiry, the patient disclosed having previously used condoms with ejaculation retardants, which we believe may have contained parabens and benzocaine (and sensitized the patient). The patient was educated on **avoidance** of products containing these allergens. (See Table 1.) Alternative product substitutions were recommended through the Contact Allergen Replacement Database — C.A.R.D. program (www.contactderm.org) and the patient was able to remain dermatitis-free. ■

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DEDICATION

This column is dedicated to a master mentor in contact dermatitis, Dr. David E. Cohen, for his inspiration and guidance. Thank you.

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