

# AN UPDATE ON PARABENS

This article provides an updated review of exposures, absorption, health implications, and regulatory issues pertaining to parabens.

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Allergic contact dermatitis (ACD) is a significant disease that is estimated to affect up to 18 million Americans each year.<sup>1</sup> The economic impact of this disease is high in terms of both patient morbidity as well as loss of income, school, and work—not to mention significant expenditures for visits to health care providers and for medicaments.<sup>1</sup> Patch testing—the gold standard for ACD diagnosis—is utilized to confirm relevant allergens.

Once patch testing is performed and an inciting allergen has been identified, education of the patient is critical to ensure adherence to an avoidance regimen. With avoidance, remission of the dermatitis is possible. If the patient is unable to comply with the avoidance regimen, they are at risk for recurrent or sustained dermatitis or progression to a systematized presentation.<sup>2,3</sup> In fact, education of the patient often begins before the diagnostic patch test is conducted to make sure that the patient has an appropriate understanding of potential outcomes and his or her central role in both disease and treatment. During the initial consultation, providers must educate patients about the pathophysiology of ACD, including its delayed presentation, its relationship with the immune system (sensitization to a chemical and then elicitation of dermatitis with re-exposure), and its frequent recurrence rate.

The differential diagnoses will also need to be considered, especially with contact dermatitis where there are often confounders. It is important to note that irritant contact dermatitis (ICD), the most prevalent form of contact dermatitis, can, at times, precede or be a concomitant diagnosis with ACD.<sup>4,5</sup> Unlike ACD, ICD does not require prior sensitization and occurs from direct contact with an irritating or abrasive substance. Contact urticaria (a type I, IgE-mediated, wheal- and flare-type hypersensitivity reaction), on the



other hand, represents the least prevalent form of contact dermatitis. However, contact urticaria has the potential to evolve into a fully systemic, anaphylactic reaction. Sources for supplementary reading on this topic are available.<sup>6-8</sup> This article highlights ACD and explores top relevant allergens, regional- and topic-based presentations, and clinical tips and pearls for diagnosis and treatment. Additionally, the article provides a concise, updated review of exposures, absorption, health implications (specifically ACD including relevant cross-reactors), and regulatory issues pertaining to parabens.

## PARABENS AS PRESERVATIVES

Parabens, also known as *p*-hydroxybenzoic acids, are a class of alkyl ester preservatives found in a wide range of products encountered daily.<sup>9</sup> The naming of the individual parabens refers to the varied chemical composition at the para position of their associated benzene ring.<sup>10</sup> Specific names include methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben.<sup>11</sup>

Originally, as early as the 1920s, parabens were noted to be useful antibacterial and antifungal agents leading to their use as a preservative.<sup>12,13</sup> The odorless, colorless, and inexpensive qualities inherent to parabens make them an easy choice when trying to extend the shelf life of cosmetics, pharmaceuticals, and other consumer goods.<sup>10</sup>

## EXPOSURES

Evidence demonstrates the ever-increasing dependence on preservatives in industrialized society from sunscreens to paper currency to sanitary wipes. Methylparaben, propylparaben, and butylparaben are most often used in cosmeceutical and personal hygiene preparations due to effectiveness throughout a broad-spectrum of pH levels.<sup>10,14</sup> Yu and colleagues found that 9.5% of diaper wipes and 24.4% of topical diaper rash treatments contained methylparaben.<sup>15</sup> In light of the previous, Nardelli and colleagues reported a case of a 10-month-old girl who developed a type IV ACD reaction after using Broekies (Intigena AG, Zug, Switzerland) baby tissues.<sup>16</sup> A study done by Gosens and colleagues performed a novel risk assessment study to parabens in children aged 0 to 3 years. They concluded that propylparaben and butylparaben, were above the proposed “safe” margins of exposure at levels of 13% and 7%, respectively.<sup>17</sup> Another study done in China reported that out of 105 children’s cosmetic products purchased at a local market in Beijing, 69% of those contained at least some element of parabens, ranging in concentration from 0.02% to 0.75% as deduced through the use of high-performance liquid chromatography.<sup>18</sup> The aforementioned levels were all under the restricted levels in the region.

In 2014, Liao and colleagues tested 253 paper products (including paper currency bills) for parabens using liquid chromatography-tandem mass spectrometry. The results indicated that 98% of the products they tested contained at least one paraben. One interesting comparison relayed in the study showed that the median concentrations of parabens in paper currency was greater than the median concentrations found in sanitary wipes, although sanitary wipes had a greater array of recorded concentrations.<sup>19</sup> One year later, intrigued by

the continued endorsement of recycled products in an attempt to conserve the environment, Pivnenko and colleagues found that recycled paper, containing as many as 10,000 various chemicals, may in fact be harboring parabens, a direct result of lax monitoring at treatment plants.<sup>20</sup> However, they also stated that butylparaben and propylparaben would be the only constituents that could persist through modern recycling practices and they had limited concern in regards to parabens as an individual hazardous chemical.<sup>20</sup>

Parabens are used in a number of both ingested and injectable medications, isotretinoin and multiuse vials of injectable lidocaine are examples of frequently used dermatologic preparations that contain parabens.<sup>21,22</sup> Parabens can also be found naturally occurring in rabbiteye blueberries in a concentration of up to 104/100 g fresh weight product as well as the cell walls of carrots in a concentration of up to 2.09µg/mg.<sup>23,24</sup> **Table 1** outlines select results presented in a study by Liao and colleagues,<sup>25</sup> in which 267 food samples were analyzed for 5 types of parabens in beverages, dairy products, fats and oils, fish and shellfish, grains, meats, fruits, and vegetables. According to the study, grains and beverages contained the highest concentrations of combined parabens constituents.<sup>25</sup> Several case reports in the literature have reported a systemic contact dermatitis (SCD) from oral exposure to parabens.<sup>26</sup>

Interested in the newly found possibility of SCD caused by parabens, Veien and colleagues performed a placebo-controlled, double-blind study in 24 patients by giving 220 mg of methylparaben and propylparaben orally. Two patients who were given the oral paraben preparation had a flare of their vesicular hand dermatitis, but the placebo-controlled group did not.<sup>27</sup> The utility of this information is still highly debated because the amount of paraben given in the study was far more than is orally ingested by the everyday consumer. Further, larger studies are warranted to provide a clearer picture of how much ingested paraben is needed to trigger a reaction.

Other environmental exposures include various aquatic environments. It has been stated that greater than 90% of parabens are removed during processing at waste water treatment plants. However, chlorinated parabens were shown to be

**Table 1. RESULTS OF PARABENS IDENTIFIED FROM FOOD GROUPS<sup>a</sup>**

Parabens <sup>b</sup>	Combined Mean (ng/g)	Frequency
Beverages (n = 33)	14.2	72.7%
Dairy products (n = 31)	9.6	90.3%
Fats and oils (n = 5)	0.271	60%
Fish and shellfish (n = 23)	1.43	100%
Grains (n = 54)	18.6	100%
Meat (n = 52)	7.67	100%
Fruits (n = 20)	0.830	95%
Vegetables (n = 49)	7.43	100%

<sup>a</sup>Data adapted from Liao and colleagues.<sup>25</sup>

<sup>b</sup>Types of parabens analyzed included methylparaben, ethylparaben, propylparaben, butylparaben, and benzylparaben.

more persistent than those found in the indigenous form. Postprocessing concentrations of chlorinated parabens as by products in water have been reported at concentrations up to about 4000 ng/L. So far, no studies suggest that posttreatment chlorinated parabens are contained in the drinking water. Instead they are most often reported in low levels at swimming pools and rivers.<sup>28</sup> The pervasive presence of parabens has also been shown in air, dust, soil, and other sediments.<sup>28,29</sup>

## ABSORPTION

The majority of topical parabens are absorbed after being acted upon by carboxylesterases typically found in the skin and subcutaneous tissues. *P*-hydroxybenzoic acid and its associated side chain iterations are created as a result of the hydrolysis. Lipid solubility is directly proportional to the length of the alkyl chain on each paraben ester. Fat soluble products traverse the epidermis more easily. Therefore, the longer the paraben, the easier it gets past the first layer of human defense. The types of parabens ordered from greatest to least penetrable are: butylparaben, propylparaben, ethylparaben, and methylparaben.<sup>30</sup> It has been proposed through a variety of estimations using reported paraben concentration data that total individual paraben exposure in the United States is approximately 1.3 mg/kg/day.<sup>31</sup> In an in vitro study by Seo and colleagues, a dose-dependent absorption pattern was found in both hairless mice and human cadaver skin using the Franz diffusion cell method.<sup>32</sup> Patients who have a history of epidermal damage such as those with active wounds or atopic dermatitis have been

noted to have an increased sensitivity to topical compounds containing parabens.<sup>10</sup> Even without esterase manipulation, parabens have also been shown to be absorbed in their whole form through the skin in rat models.<sup>33</sup>

## ACD TO PARABENS

In 1940, the first case of ACD to ethylparaben was reported as a result of continued topical application of an antifungal preparation resulting in intractable eczematous dermatitis in a highly unsuspecting middle-aged woman.<sup>10</sup>

Since, parabens has been implicated in enough cases of ACD that it has been incorporated into patch test preparations used for patients with specific recalcitrant dermatitis. Positive patch test (PPT) reactions to paraben mix were reported at 1.4% (4231 tested) by the North American Contact Dermatitis Group (NACDG) between 2011-2012, which marks an increase from prior testing periods. The same group had PPT reactions to parabens at 0.9% (4304 tested) from 2009-2010 and 1.1% (5082 tested) from 2007 to 2008.<sup>34-36</sup> This may be related to substrate preferences of the incumbent members, as the NACDG pediatric data also demonstrated an increase from a 0% PPT rate between 2001-2004 to 0.9% between 2005-2012, with the same transition of members.<sup>37,38</sup> Although an uptrend was noted, the overall sensitization rate remains low enough to gain endorsement as a lesser evil by the NACDG as evidenced through a recent quote, "Of the common and effective preservatives, parabens, because of its low sensitization rate, remains the preferred choice of the NACDG."<sup>34</sup>

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Krob and colleagues performed a meta-analysis of 15 years of Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test (SmartPractice, Phoenix, AZ) data and reported only 0.5% of patients had a positive result to parabens mix.<sup>39</sup> These results reiterate the already assumed low sensitizing potential of paraben as causing clinically relevant ACD. It is also important to take into account the report by Saripalli and colleagues that states that only 28% of all clinically relevant cases of ACD they analyzed were caught with the T.R.U.E. Test alone.<sup>40</sup> Also of importance, prevalence rates can be regionally based due to higher indices of exposure locally, for example, Sarma and colleagues<sup>41</sup> tested 70 Indian children and found a total PPT rate of 43%, with 36.15% of the PPT determined to be a clinically relevant allergy. The authors attributed this large increase in paraben reactivity to increased levels of the chemical in common food sources, although larger studies are needed to confirm this assumption.<sup>41</sup>

#### PATCH TESTING TO PARABENS

Paraben mix is one of 36 allergens represented on T.R.U.E. Test and is composed of methyl *p*-hydroxybenzoate, ethyl *p*-hydroxybenzoate, propyl *p*-hydroxybenzoate, butyl *p*-hydroxybenzoate, and benzyl *p*-hydroxybenzoate at a total dose of 1000 µg/cm applied via a povidone gel vehicle containing 162 µg/cm each of the aforementioned paraben substituents.<sup>42</sup> In contrast, paraben mix is also available through Chemotechnique Diagnostics (Dormer Laboratories, Toronto, CA) and Allergeaze (SmartPractice) on a standardized petrolatum-based substrate containing 4% equal parts of methyl-, ethyl-, propyl-, and butyl-4-hydroxybenzoate in petrolatum, for a total of 16% with Chemotechnique Diagnostics and either 16%, 15%, or 12% with Allergeaze.<sup>43,44</sup>

Parabens can cross-react with other compounds. Chemicals known to cross-react with parabens contain a free amino group (instead of a hydroxyl group) in the para position of their associated benzene ring.<sup>10</sup> Two specific probable cross-reactors include *p*-phenylenediamine (PPD) and benzocaine. As reported in a study by Turchin and colleagues at the Contact Dermatitis Clinic of the Royal Victoria Hospital in Montreal, Canada, 2% of a group of PPD and benzocaine patch test positive patients were also found to be sensitized to

parabens.<sup>43</sup> This could also represent the possibility of co-sensitization.

Local anesthetic solutions may be preserved with methylparaben and reports of local delayed-type hypersensitive anesthetic reactions have been traced to the paraben preservative.<sup>22,45</sup> In 1984, the FDA banned the addition of parabens to single-use local anesthetic cartridges, but it still remains in multiuse preparations.<sup>46</sup> Delayed reading epicutaneous patch testing is most suitable to evaluate patients who have reaction occurring at least 24 hours after injection. In addition, if clinical suspicion for delayed reaction remains high despite negative patch testing, an intradermal test for both the methylparaben and the active ingredient in the anesthetic may be performed. If the patient develops a relevant positive reaction on either patch testing or intradermal injection, care should be taken to list parabens as an allergy in the medical record and avoid use of products containing it as a preservative.<sup>45</sup>

#### ENDOCRINE AND OTHER HEALTH CONCERNS

Paraben molecules have a low affinity estrogenic effect.<sup>47</sup> Although the effect has been reported as less than that induced by endogenous estrogen, public health concerns remain, especially a previously proposed correlation with breast carcinogenesis.<sup>47</sup> In a study by Barr and colleagues, out of 160 breast tissue samples obtained from women who had mastectomies for primary breast cancer, 99% contained at least one paraben and notably 60% contained all 5 types of parabens evaluated in the study. Highest levels were of the methylparaben and propylparaben types.<sup>48</sup> In an *in vitro* analysis, Khanna and Darbre noted that parabens were able to induce anchorage-independent growth of MCF-10A breast epithelial cells. The authors conclude this is an important predictor of tumor growth *in vivo*.<sup>49</sup> The aforementioned studies have come under critical review as there continues to be a question as to how well the evidence correlates to overall *in vivo* environments and studies to date have not shown causation or validated interactions *in vivo*.

Other health uncertainties pertaining to parabens include studies concerning P450 (CYPs) enzyme inhibition, direct cytotoxicity, and maternal fetal transfer. There is some evidence towards P450 inhibition presented in a new study by

Ozaki and colleagues.<sup>50</sup> The study used rat liver microsomal enzymes and assayed specific substrates in order to portray possible inhibition as a result of 11 different parabens found in cosmetic preparations. They found that the parabens had a strong inhibition of 7-methoxy-4-trifluoromethylcoumarin dealkylase, one of the specific substrates analyzed. They attributed the bulk of inhibition was taking place with the CYP2C enzyme.<sup>50</sup> The mechanism of action for parabens as a preservative depends on the ability of the molecule to interact and disrupt bacterial and fungal membranes. However, Flasinski and colleagues found that parabens actually had a predilection for mammalian membranes as opposed to bacterial membranes, thus indicating a possible mechanism for direct cytotoxic occurrences taking place *in vivo*.<sup>51</sup> Due to concerns over possible developmental disruption as a result of paraben exposure, Pycke and colleagues analyzed maternal urine and human cord blood plasma from an urban immigrant population in the United States. They concluded that parabens are likely transmitted through the human umbilical cord, but the extent of paraben load could vary drastically in different populations. The authors proposed the population variation could be due to “education, socioeconomic status, geography, and culture-dependent diet.”<sup>52</sup> The worry is that developmental exposure to the estrogenic properties of parabens might cause reproductive problems in adult life, a hypothesis linked to current studies done using mice, and a significant study by the Danish Environmental Protection Agency (DEPA) expressing additional developmental endocrine concerns from the use of certain sunscreens and lotions.<sup>13,53,54</sup> More *in-depth* study on the result of *in utero* exposure on fetal development is warranted.

#### REGULATORY BODIES AND DECISIONS

In the past, a considerable amount of pressure has been placed on the Cosmetic Ingredient Review (CIR) and the FDA to help regulate the use of parabens in consumer cosmetics and other goods. In 1984, the CIR stated that parabens could be used safely in cosmetics in a concentration of up to 25%.<sup>55</sup> With most cosmetic preparations composed of only 0.1% to 0.3% parabens, this original assessment indicated that parabens are relatively safe.<sup>55</sup>

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In 2005, the CIR again looked at the possible harmful nature of parabens but felt no need to modify their original conclusion from 1984.<sup>55</sup> The FDA also published a statement on their website in 2014 refuting any need for further reform or concern regarding parabens because the amount in consumer goods has yet to be completely proven to have harmful sequelae at such small doses. This continues to be the FDA's current stance.<sup>55</sup>

During 2011, Denmark banned the inclusion of propylparaben and butylparaben in any cosmetic product meant for children aged 3 or younger due to worrisome endocrine developmental disturbance data gathered by the DEPA.<sup>13</sup> Initially, the European Union (EU) Scientific Committee on Consumer Safety (SCCS) did not heed any possible warnings toward harmful consequences stemming from parabens in cosmetics. In light of what was being published from Denmark, the EU revisited their original stance in 2011, and eventually enacted a law in July 2013 that prohibited the use of isopropylparaben, isobutylparaben, phenylparaben, benzylparaben, and pentylparaben in cosmetics. However, the original EU SCCS statement expressing no association between breast cancer and exposure to parabens was never rescinded, claiming the compound to have no carcinogenic or co-carcinogenic nature based on current evidence.<sup>13,54,56</sup>

## A NEW PROBLEM

The American Cancer Society maintains the view that paraben containing cosmetics and antiperspirants do not increase the risk of breast cancer in women.<sup>57</sup> With the phase out of parabens, new replacement preservatives such as methylisothiazolinone came into high frequency use. Methylisothiazolinone has caused epidemic sensitization rates worldwide and has proven to present a significant health and economic burden.<sup>12,58,59</sup> Svedman and colleagues found that quaternium-15, imidazolidinyl urea, diazolidinyl urea, formaldehyde, methylidibromo glutaronitrile, and methylchloroisothiazolinone/methylisothiazolinone all had much higher rates of patch test proven sensitization as opposed to parabens.<sup>60</sup> However, data including 120,000 patch tests in the general population in Britain provided by Schnuch and colleagues<sup>61</sup> painted a slightly different picture as shown in **Table 2**.

**Table 2. SENSITIZATION RATES TO PRESERVATIVES STANDARDIZED FOR AGE IN BRITISH TEST POPULATION<sup>a</sup>**

Preservative (Concentration: Number Tested)	Age Standardized Sensitization Rate
<b>Methylidibromo glutaronitrile (0.3%: 53,545)</b>	<b>4.5%</b>
<b>Methylisothiazolinone/methylchloroisothiazolinone (0.01%: 121,136)</b>	<b>2.2%</b>
<b>Formaldehyde (1%: 121,558)</b>	<b>1.54%</b>
<b>Paraben mix (16%: 121,247)</b>	<b>1.33%</b>
<b>Diazolidinyl urea (2%: 78,711)</b>	<b>0.71%</b>
<b>Quaternium-15 (1%: 79,745)</b>	<b>0.66%</b>
<b>Imidazolidinyl urea (2%: 78,670)</b>	<b>0.6%</b>

<sup>a</sup>Data adapted from Schnuch and colleagues.<sup>61</sup>

Hughes and colleagues recently reported on safety with and safety without preservation and stated: "Due to the widespread use of cosmetic products, the prevalence of allergy, the need for proper prevention of product contamination, and concerns over safety of preservatives, further investigations into alternative agents to create successful preservative-free products is warranted."<sup>62</sup>

Awareness of paraben associated ACD, SCD, and other the potential health effects of preservation with this group of preservatives are necessary. Longitudinal human studies are also necessary for continued strengthening of already presented deleterious developmental endocrine changes as a possible result of exposure to parabens.<sup>47-49</sup> Ultimately, it is important to be cognizant of the ability of parabens, a compound found heavily in the elective use of cosmetics, to be absorbed into the skin and interact both locally and systemically.

## PEARLS OF TREATMENT: EVERY DOSE COUNTS

A person might be exposed to and subsequently sensitized to a contact allergen (eg, a fragrance) for days to years before demonstrating the clinical picture of ACD. With each exposure, there is an increased risk of reaching a point at which the immune system meets its metaphorical "threshold" and subsequent exposures can lead to elicitation of a cutaneous response.<sup>63</sup> Just as repeated contact over time led to this immune response, repeated avoidance of the majority of exposures over time will be required to induce remission. Avoidance of specific allergens in personal care products can prove to be a tedious task; however, there are programs

available to aid in this endeavor. Both the Contact Allergen Management Program, a service offered through the ACDS,<sup>64</sup> and the Contact Allergen Replacement Database, developed by Mayo Clinic,<sup>65</sup> allow for a provider to enter a patient's known contact allergens, and produce a "shopping list" of products to avoid with those particular chemicals. The programs also can exclude cross-reactors. Additionally, education for patients can be accessed through online programs, such as the Dermatitis Academy ([www.dermatitisacademy.com](http://www.dermatitisacademy.com))<sup>66</sup> and through the ACDS website ([www.contactderm.org](http://www.contactderm.org)). ■

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