

# ALLERGEN Focus



## Focus on T.R.U.E. Test Allergen #15: Carbamates

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*This expert provides an enlightening, practical look at common allergens so that you can better educate your patients about the basis for their allergy and what products they need to avoid.*



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**T**he thin-layer rapid use epicutaneous (T.R.U.E) Test of 23 common allergens is a valuable, first-line screening tool used by many dermatologists. 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.

A rich, interesting history accompanies each of the 23 allergens, and understanding these historic perspectives can help to

better educate patients. Each column will also highlight appropriate products that patients should avoid when they are allergic to a specific allergen.

### CONTACT DERMATIDES

Allergic contact dermatitis is an important disease with high impact on 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.<sup>1</sup>

On direct antigen exposure to the skin or mucosa, an immunologic cascade is initiated that includes cytokines, i.e., interleukin 2 (IL-2) and interferon gamma (IFN-gamma), T cells and Langerhan cells. This complex interaction leads to the clinical picture of ACD.

The contact dermatides include allergic contact dermatitis, irritant contact dermatitis and contact urticaria.

*Irritant contact dermatitis*, the most common form, 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 would be latex protein 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.<sup>1,2</sup>

The primary focus of this section is to highlight the educational component of allergic contact dermatitis.

### CLINICAL ILLUSTRATION

We report a case of a professional painter with an avid outdoor basketball hobby. He presented to the Contact Dermatitis Clinic at the University of Miami with severe hand dermatitis, which he attributed to his latex paint products. He related that despite wearing protective rubber gloves, his hand dermatitis had continued to worsen. Allergen-specific IgE antibody test (RAST) for latex demonstrated a normal IgE level.

## THE HISTORY OF RUBBER AND CARBAMATES

On Columbus's second voyage to Haiti in 1493, he observed natives playing with high bouncing balls, a noteworthy discovery that improved the enjoyment of ball games. He learned that the natives made these balls from procured tree sap which was then cured over the smoke of palm nuts.<sup>3</sup> Rubber trees, especially *Hevea brasiliensis*, produce a milky fluid from the lactiferous cells: the latex. The natural rubber latex (NRL) has a high composition of poly-cis-isoprene, an organic polymer that confers strength and elasticity.<sup>4</sup> It also contains a variety of proteins, such as hevamine, hevein and rubber elongation factor among the more than 10 *Hevea brasiliensis* allergens known to initiate type I (IgE-mediated) wheal and flare (hives) and anaphylactic reactions.<sup>5</sup>

Early Mesoamerican cultures (Mayans) found that rubber sap mixed with morning glory vine juice would become more durable with increased elasticity.<sup>6</sup> The natives of the Amazon valley made shoes of this gum called "caoutchouc," and Spanish soldiers had spread their cloaks with it to waterproof them.

Caoutchouc was derived from the Indian word "cahuchu" meaning "weeping wood". It is the root of the commonly used Spanish word for rubber, "Caucho".<sup>3</sup>

The modern world is highly dependent on rubber and rubberized products. Indonesia, Malaysia, Thailand and South America are the current-day main suppliers of freshly harvested latex.

To enable mass transport to worldwide factories, the harvested latex is treated with ammonia preservatives to prevent autocoagulation and bacterial contamination.<sup>4,6</sup>

At the factories, the long polymer chains are broken by mastication (applying mechanical forces to the rubber with rollers or rotating blades) to allow for further organic chemical compounding with antioxidants, accelerators and vulcanizing additives.<sup>7</sup>

The accelerators, such as carbamate chemicals (zinc-dithiocarbamates and diphenylguanidine) are added to speed



This patient is suffering from a contact dermatitis to carbamates.

EARLY MESOAMERICAN CULTURES (MAYANS) HAD DISCOVERED THAT RUBBER SAP MIXED WITH MORNING GLORY VINE JUICE WOULD BECOME MORE DURABLE WITH INCREASED ELASTICITY.

the cross-linking of the natural rubber latex particles for proper alignment in producing a heat-stable, elastic, strong, and durable product, also known as vulcanization.

The compounded rubber is then sheeted, extruded into the desired shapes and molded.<sup>7</sup> Finally, once the vulcanized rubber is dried and rinsed, it is dry-

lubricated with cornstarch or talc powders to bind residual latex proteins.<sup>4,8</sup>

Charles Goodyear first made the observation that rubber mixed with sulphur produced an elastic and weatherproof compound, when these ingredients were accidentally dropped onto a hot stove. Ultimately, he patented the process for vulcanized rubber in 1844.<sup>3,7</sup> The process was subsequently refined, and by the 1920s the role of accelerators was defined. The sulphur atoms, within the dithiocarbamates, were determined to participate in the cross-linking of the natural rubber latex molecules in the vulcanized endproduct with definitive improvement of the final physical properties of the rubber.

The carbamate acceleration chemicals are present in almost every rubber product, in addition to medicinal and agricultural uses. (See Table 1.)<sup>4,8</sup> Ironically, this highly used chemical was once a royalty restricted product. Carbamates were originally extracted from the Guinean Gulf calabar bean (*Physostigma venenosum*) grown near the mouth of the Old Calabar River.

TABLE I

## PRODUCTS CONTAINING CARBAMATES

### FREQUENT USES

Condoms, cosmetic applicators, diaphragms, pacifiers, pillows and mattresses, rubberized toothbrush handles, shoe soles, tires, underwear.

### MEDICAL EQUIPMENT

Bandages, blood pressure cuffs, dental dams, disposable gloves, intravenous ports, microscope eyepieces, safety goggles, stethoscopes, surgical masks, syringe plungers, thiuram (anti-abuse drug), tourniquets.

### LAWN AND GARDEN PRODUCTS

**COMMERCIAL:** Aldicarb, Mancozeb, Methomyl.  
**HOUSEHOLD:** Bendiocarb (Ficam), Propoxur (Baygon).

### OFFICE SUPPLIES

Adhesive tape, carpet backing, electrical cords, envelopes, erasers, glue, mouse pads, pen grips, rubber bands, stamps.

### SPORTS SUPPLIES

Handgrips, rubber balls, shoes, swimwear, swimming goggles and caps.

This exotic West African plant, called *Doomsday Plant* by the natives, was originally an "ordeal poison". People suspected of committing a crime were obligated to swallow an infusion of the seeds.

According to the native ordeal test, depending on the cholinomimetic effect produced on the accused, a verdict was given. A guilty verdict was placed if the imbiber passed away, designating them to a life of servitude. The accused were found innocent and liberated, if the seed was vomited.<sup>9</sup> To consecrate this royal crime judgment, the native king ordered massive destruction of community crops of the *ordeal seed*.

This monopolization of the calabar bean plant barred early attempts at botanical classification.<sup>9</sup> The classification of the calabar seed, however, finally became possible when a British missionary in Africa sent dark brown kidney-shaped seeds back to Edinburgh, for identification. Of medical historical note, these (*Physostigma venenosum*) seeds also became the source of a valuable alkaloid, Physostigmine (aka eser-

ine). In 1863, Dr. Argyll Robertson first described the ophthalmologic miotic effect of this alkaloid, which is still in use today for treating glaucoma.<sup>9</sup>

On another note, carbamates are important agricultural fungicides and are an occupational hazard for pesticide handlers, field workers and gardeners.<sup>10</sup>

Carbamates, as reversible inhibitors of acetylcholinesterases, are among the most popular pesticides for home use, both indoors and for lawns and gardens.

Carbaryl is the best-known and most applied carbamate pesticide. Commercially, the fungicide Maneb (a dithiocarbamate) is used in the Midwest to prevent ginseng weed from producing potato blight<sup>11</sup> and related compounds such as Oxamyl, among others, are used by tobacco growers in North Carolina. Contact dermatitis to carbamate fungicides is well known.<sup>4,8,10-12</sup>

An important note regarding the allergenicity of carbamate compounds was the discovery that these compounds can become greater antigens when exposed to common household bleach.

In 1975, Jordan and Bourlas<sup>12</sup> reported the *bleached rubber syndrome* by which exposure of underwear elastic to hypochlorite (bleach) caused new chemical byproducts. For example, the rubber accelerator zinc dibenzylthiocarbamate (ZDC) became N,N-dibenzylcarbanyl chloride when exposed to hypochlorite. This change in configuration proved to make a potent allergen that undoubtedly caused allergic dermatitis in the exposed subjects.

### TESTING FOR CARBAMATE SENSITIVITY

Patch testing for Carbamate allergy can be accomplished with the T.R.U.E. test [site # 15]. The T.R.U.E test recognizes only 23 of the more than 3,700 possible allergens that can cause allergic contact dermatitis. Therefore, it needs to be known that this test is a mere screening tool that could be used by general dermatologists everywhere.

Unfortunately, we are faced with important workforce economics. There are roughly 14,500 U.S. members of the American Academy of Dermatology and many of these dermatologists serve remote locations. In contrast, the Allergic Contact Dermatitis Society ([www.contactderm.org](http://www.contactderm.org)) has about 450 members. This ratio translates to one comprehensive patch tester to every 33 dermatologists, if the distribution was evenly cast, which it isn't.

Thus, in geographic areas with limited access, the T.R.U.E. test should be recognized and utilized as a basic and necessary screening tool and its limitations understood as such.

The American Contact Dermatitis Society (ACDS) recognizes the need for comprehensive patch testing and patch test support for general dermatologists and patients suffering from allergic contact dermatitis.

The ACDS is actively engaged in maintaining access to this important testing modality by training new providers (ACDS-Fujisawa mentorship program) and providing patient education materials through the Contact Allergen Replacement Database (CARD).

### THE VALUE OF THIS PATIENT CASE

Our patient with allergy to carbamates underscores the importance of

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**CONTRAINDICATIONS:** LUSTRA ULTRA is contraindicated in any patient that has a prior history of hypersensitivity or allergic reaction to hydroquinone or any of the other ingredients. The safety of topical hydroquinone use during pregnancy or on children (7 years and under) has not been established.

## WARNINGS:

**A. CAUTION:** Hydroquinone is a depigmenting agent which may produce unwanted cosmetic effects if not used as directed. The physician should be familiar with the contents of this sheet before prescribing or dispensing this medication.

**B. Test for skin sensitivity before using LUSTRA ULTRA** by applying a small amount to an unbroken patch of skin and check within 24 hours. Minor redness is not a contraindication, but where there is itching, vesicle formation, or excessive inflammatory response, further treatment is not advised. Close patient supervision is recommended. Contact with the eyes should be avoided.

If no lightening effect is noted after two months of treatment, use of LUSTRA ULTRA should be discontinued. LUSTRA ULTRA is formulated for use as a treatment for dyschromia and should not be used for the prevention of sunburn.

**C. Sunscreen use is an essential aspect of hydroquinone therapy, because even minimal sunlight sustains melanocytic activity.** During treatment and maintenance therapy, sun exposure should be avoided on treated skin by application of a broad spectrum sunscreen (SPF 15 or greater) or by use of protective clothing to prevent re-pigmentation. The sunscreens in LUSTRA ULTRA provide the necessary sun protection during therapy. During and after the use of LUSTRA ULTRA, sun exposure should be limited or sun-protective clothing should be used to cover the treated areas to prevent re-pigmentation.

**D. Keep this and all medications out of the reach of children.** In case of accidental ingestion, contact a physician or a poison control center immediately.

**E. WARNING:** Contains sodium metabisulfite, a sulfite which may cause serious allergic reactions (eg. hives, itching, wheezing, anaphylaxis, severe asthma attack) in certain susceptible persons.

**F. In rare occasions, a gradual blue-black darkening of the skin may occur in which case, use of LUSTRA ULTRA should be discontinued and a physician contacted immediately.**

## PRECAUTIONS: SEE WARNINGS

**A. Pregnancy Category C:** Animal reproduction studies have not been conducted with topical hydroquinone. It is also not known whether hydroquinone can cause fetal harm when used topically on a pregnant woman or can affect reproductive capacity. It is not known to what degree, if any, topical hydroquinone is absorbed systemically. Topical hydroquinone should be used in pregnant women only when clearly indicated.

**B. Nursing mothers:** It is not known whether topical hydroquinone is absorbed or excreted in human milk. Caution is advised when hydroquinone is used by a nursing mother.

**C. Pediatric usage:** Safety and effectiveness in pediatric patients below the age of 17 years have not been established.

## ADVERSE REACTIONS:

No systemic reactions have been reported. Occasional cutaneous hypersensitivity (localized contact dermatitis) may occur, in which case the medication should be discontinued and the physician notified immediately.

## OVERDOSAGE:

There have been no systemic reactions reported from the use of topical hydroquinone. However, treatment should be limited to relatively small areas of the body at one time, since some patients experience a transient skin reddening and a mild burning sensation which does not preclude treatment.

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appropriate patch testing and subsequent patient education. The presence of carbamates/rubber in such a wide variety of products makes it an especially common, difficult to avoid, contactant in daily activities. Rubber products can be tested for carbamate content by extraction with a methylisobutylketone and cuprous acetate solution (a positive reaction turns olive green).

To the greatest extent possible, we advised the patient to remove rubber products from his daily routine, including protective rubber gloves, rubberized toothbrush, paint roller gripper and the basketball. With these changes, the patient dramatically improved, consistent with the fact that the mainstay of treatment for allergic contact dermatitis is avoidance. ■

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