

T.R.U.E. TEST® CLINICAL STUDIES

In the United States and worldwide, more than 25 clinical studies involving over 4,500 patients have been conducted to evaluate the consistency, reproducibility, optimal dose, performance, safety, efficacy, and clinical relevance of T.R.U.E. TEST (Allergen Patch Test). T.R.U.E. TEST has been shown consistently to provide a safe, effective, clinically relevant method of diagnosing allergic contact dermatitis.



GENERAL PERFORMANCE AND ADVERSE EVENTS

T.R.U.E. TEST was evaluated for overall performance in 422 patients in four clinical studies in the United States (see package insert). Patients with suspected allergic contact dermatitis, based on history or clinical signs, were tested in all studies.

Clinical study #1: In an open, multi-center clinical study designed to evaluate T.R.U.E. TEST Panel 1, 128 patients were screened prospectively for allergic contact dermatitis. Positive reactions to 11 of the 12 allergens were observed in 45 patients. Positive test reactions to all allergens except chromium were observed. The most common allergic reactions were to nickel (n=21), fragrance mix (n=9), and cobalt dichloride (n=9). As expected, itching and burning sensations were reported in some patients.

Clinical study #2: T.R.U.E. TEST Panel 1 with 11 allergens and a negative control was applied to 122 patients with suspected contact dermatitis for 48 hours. Test results were evaluated at either 72 or 96 hours. Forty-seven positive test reactions were observed in 33 patients, and included all allergens except quinoline mix and paraben mix.

Clinical study #3: Of 122 patients referred for patch testing, T.R.U.E. TEST Panels 1 and 2 were applied for 48 hours and read at either 72 or 96 hours. In total, 122 positive test reactions were elicited in 71 patients, 14 doubtful (?) reactions were observed in 11 patients, and irritant reactions were found in 3 patients. Positive reactions were recorded for all allergens.

Clinical study #4: In an open, multi-center study T.R.U.E. TEST Panel 1 and 2 were evaluated in 50 patients with suspected contact dermatitis. Results were evaluated after 72, 96, 120, or 168 hours. Test sites also were reassessed after 21 days for late and persistent local reactions.

A total of 66 reactions were observed in 32 patients. All allergens except, caine mix, epoxy resin, and quinoline mix, elicited at least one reaction in these patients. The most common reactions were to nickel sulfate (14%) and quaternium-15 (11%), followed by equal numbers of reactions to balsam of Peru, cobalt dichloride, formaldehyde, and thimerosal (8% each).

Ten persistent local reactions were observed in 8 patients after 21 days, including a late strong positive (++) reaction to Cl⁺ Me-isothiazolinone. Although most patients (34 of 50) did not experience any itching or burning, 14 patients reported mild and 2 patients reported moderate itching or burning sensations. No other adverse events were reported, other than a mild adhesive irritation reported by one patient. Otherwise, the surgical tape adhered perfectly in 45 patients (90%).

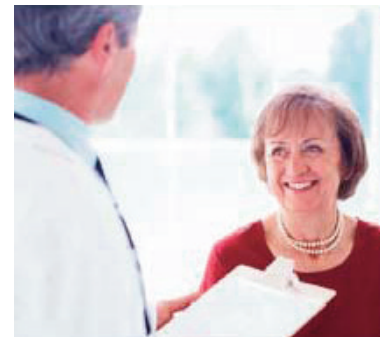
Note: Except as noted in Study #2, the above studies were conducted using a 24-allergen T.R.U.E. TEST product. In this product, the allergen configuration quinoline mix replaced the negative control (an uncoated polyester patch), and the positions of epoxy resin and paraben mix patches were reversed. The change in configuration did not affect the results of the reaction frequencies observed for T.R.U.E. TEST.

Post-marketing study: A survey conducted from January 1995 through the end of December 1995 supports the results of the above clinical trials. This survey evaluated a total of 1,772 data collection forms completed by physicians using T.R.U.E. TEST in 1995.

According to survey results, allergens with the highest reaction rate frequency included nickel (17.6%), quaternium-15 (11.0%), thimerosal (9.1%), and formaldehyde (9.0%). When clinical relevance was addressed (in 27% of surveys), test results corresponded to the patient's contact history in 75.9% of these cases.

The survey also reaffirmed the observed minimal adverse events and irritation. Tape irritation and adhesion problems were reported infrequently (2.5% and 4.6%, respectively). The number of adverse events reported was also very small and centered around the typical symptoms of an allergic reaction.

Published studies in adult patients: Krob et al., (*Journal of the American Academy of Dermatology 2004*) published a meta-analysis of previously published T.R.U.E. TEST clinical data. Consistent with earlier results, nickel (14.7%) was reportedly the most prevalent allergen, followed by thimerosal (5.0%), cobalt (4.8%), fragrance mix (3.4%) and balsam of Peru (3.0%). Although there were differences in prevalence, T.R.U.E. TEST results are in general agreement with other patch test methods and with data from the North American Contact Dermatitis Group.



Over 3,700 allergens have been identified to date as associated with allergic contact dermatitis. With only 23 allergens, at the time, included in the panels licensed for sale in the United States, Krob et al. suspect that without supplemental allergens, T.R.U.E. TEST may miss other highly relevant allergies.

Sherertz et al., (*Journal of the American Academy of Dermatology 2001*) reported that T.R.U.E. TEST might miss some positive reactions to fragrance mix, thiuram mix and carba mix. In a study of 318 patients evaluated simultaneously with T.R.U.E. TEST and allergens in Finn Chambers®, multiple discordant reactions were noted. The limited results of this study suggested that some negative reactions to fragrance mix, thiuram mix and carba mix might be false.

Postmarketing surveys and published studies in pediatric patients: Since the premarket approval testing of T.R.U.E. TEST, which excluded patients younger than 16 years of age, some studies have reported on its use in pediatric patients ranging from 6 months to 14 years of age. Postmarketing surveys have shown that physicians in the United States occasionally patch test children using T.R.U.E. TEST. Of 3,200 reports filed in a two-year period, 19 were for patients under the age of 13, and 74 were for patients between the ages of 13 and 19.

Johnke et al., (*Contact Dermatitis 2004*) reported on the use of T.R.U.E. TEST patches in infants up to 18 months of age. Of the 543 infants tested, 8.6% had positive nickel reactions. However, of these, only one was considered clinically relevant. These investigators also cautioned that the adult level of nickel allergen in T.R.U.E. TEST (0.2 mg) may elicit more transient false positive reactions in infants.



Mortz et al., (*Acta Derm Venereol 2002*) used T.R.U.E. TEST panels on 1,146 schoolchildren in the 8th grade. Tests adhered well in 93% of patients, and reactions to the tape were seen in only 2% of those tested. In this pediatric population, 15% tested positive to one or more of the T.R.U.E. TEST allergens. However, more of these schoolchildren had a history of atopy or hand dermatitis.

Bruckner et al., (*Pediatrics* 2000) patch tested 85 children from 6 months to 5 years of age using T.R.U.E. TEST. They reported the overall prevalence of contact allergies in these children at 24.5%. Irritant reactions to the tape were reported in 7.4% of the tested children, and 6% removed the patches early due to discomfort.

Romaguera and Vilaplana (*Contact Dermatitis* 1998) patch tested 141 children with T.R.U.E. TEST. Of these, 45% were determined to have allergic contact dermatitis, most commonly to nickel, cobalt, mercurials, fragrance and rubber-based chemicals.

Note: This information is not intended to advise medical professionals to use T.R.U.E. TEST in a manner inconsistent with product labeling. Application of T.R.U.E. TEST in children is considered an off-label use even when supported by current medical care guidelines.

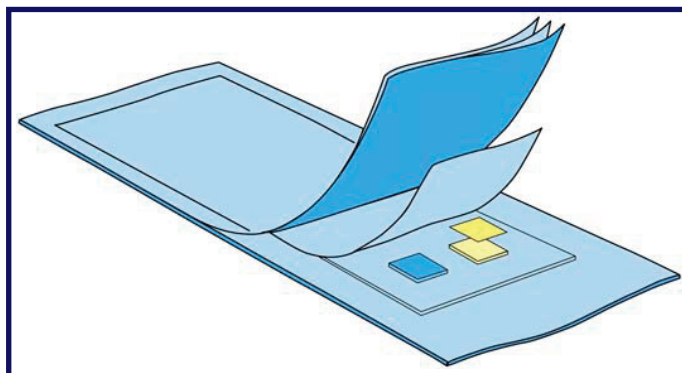
ALLERGEN DOSE OPTIMIZATION

The optimal dose for T.R.U.E. TEST allergens has been determined through controlled clinical testing. The goal was to ensure a consistent allergen dose that is sufficient for a response, yet low enough to minimize the potential for irritation and sensitization. Examples of this testing are discussed below.

For *p*-phenylenediamine (PPD): The optimal dose was determined to be 0.09 mg/cm². Per the recommendations of the International Contact Dermatitis Research Group and the European Environmental Contact Dermatitis Research Group, the PPD allergen is provided as PPD base, rather than hydrochloride salt. In a controlled, dose-response and irritation study of base in 211 patients, the PPD base was tested at 0.20, 0.15, 0.10, and 0.05 mg/cm². In the 14 patients allergic to PPD, the 0.10 mg/cm² dose was the minimum concentration that consistently elicited an allergic reaction with the lowest frequency of irritant reactions. In comparison, the PPD hydrochloride salt previously used (0.05 mg/cm²), elicited positive reactions in only five patients.

For formaldehyde: A formaldehyde-releasing compound, N-hydroxymethyl succinimide (HMS) was developed to overcome the inherent instability of formaldehyde patches. For HMS, the optimal dose was evaluated in healthy volunteers and allergy patients. In initial safety evaluations in 9 healthy volunteers, HMS was found to be non-irritating when used at 0.12 mg/cm². However, HMS elicited irritant reactions in 3 of the 9 volunteers at 0.57 mg/cm², and in 5 of the 9 at 1.12 mg/cm². An initial dose-response study was also conducted in 25 patients with previously confirmed formaldehyde allergy. In this study, HMS at 0.16 mg/cm² was sufficient to detect formaldehyde allergy.

The current HMS concentration (0.18 mg/cm²) used in T.R.U.E. TEST was established in a larger dose-finding study. In a controlled, multicenter study, 255 patients with suspected allergic contact dermatitis were tested with HMS in concentrations equal to 0.4, 0.3, 0.2, and 0.1 mg formaldehyde/cm². For comparison, a 1% aqueous solution of formaldehyde was tested. The apparent dose-response relationship indicated that the threshold for irritant reactions was 0.25 mg formaldehyde/cm², which is well above the HMS concentration in T.R.U.E. TEST of 0.18 mg/cm². Moreover, the 0.18 mg/cm² dose was found to elicit consistent allergic reactions with minimal irritation among the patients tested.



OVERALL REPRODUCIBILITY AND BATCH CONSISTENCY

T.R.U.E. TEST was previously tested for batch consistency in several clinical studies. In each study, three separate production lots of allergens were evaluated for uniform reactivity. All patients had previously confirmed allergy to the test allergens. Results of these studies are summarized below. Taken together, the results of these studies demonstrated good reproducibility from different production lots of allergens contained in T.R.U.E. TEST.

Clinical Study #1: Thirty-nine patients were tested with nickel sulfate, ethylenediamine dihydrochloride, and epoxy resin. Similar positive results developed in 90% to 100% of reactions. Evaluations were performed at 72, 96, or 120 hours.

Two discordant reactions were recorded in patients with documented nickel allergies. One patient showed strong (++) reactions to batch No. 1 and 2, but a negative (-) reaction to batch No. 3. A second evaluator interpreted the reactions similarly.

Another patient had a weak (+) reaction to batch No. 2 and 3 with a negative (-) reaction to batch No. 1. A second evaluator interpreted the reactions as strong (++) for batch No. 2 and 3, and weak (+) for batch No. 1.

Clinical Study #2: A randomized, double-blind, placebo-controlled study was conducted in 47 patients, 42 of whom responded. Balsam of Peru, black rubber mix, Cl+ Me- isothiazolinone, and thiuram mix produced consistent positive reactions in 93% of cases (39/42). No discordant reactions to these allergens were observed. Two independent observers interpreted reactions.

Clinical Study #3: A randomized, double-blind, placebo-controlled trial was conducted with three batches of *p*-phenylenediamine. Consistent reactions developed in 90% of patients (9/10), and no discordant reactions were observed.

Published studies: Ale and Maibach (*Contact Dermatitis 2004*) reported excellent concordance of T.R.U.E. TEST results. Duplicate patch tests were performed on 491 patients using T.R.U.E. TEST panels. Of these, 289 patients tested positive to at least one allergen and 76% of these reactions were considered clinically relevant.

Concordance of duplicate positive reactions was 95%, with 413 of 435 reactions in agreement. Positive reactions were observed for all allergens included in T.R.U.E. TEST, and were most prevalent for nickel, thiuram mix, potassium chromate, cobalt, *p*-phenylenediamine and carba mix.

Of the 22 discordant reactions, most were observed for nickel (4), lanolin (3), cobalt (3), carba mix (2), thiuram mix (2), and fragrance mix (2). One discordant reaction each was also reported for balsam of Peru, *p*-phenylenediamine, thimerosal, potassium chromate, formaldehyde and colophony. When retested, over half the discordant reactions proved positive. In addition, discordant reactions were clinically relevant in only 3.1% of patch test positive patients.

Please consult the T.R.U.E. TEST package insert for complete safety, clinical test data and prescribing information.