Assessment of Contact Allergens in "Hypoallergenic" Athletic Shoes by Mass Spectrometry

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Abstract: ***Background:*** **Identification of athletic shoes for patients with contact allergy is difficult. Company reports of allergen content are often incorrect.**

Objectives: **To determine whether chemical analysis of 4 athletic shoes, previously reported to be free of the most common contact allergens, contain quantifiable allergen levels.**

Methods: **Samples from the uppers and insoles of 4 shoes believed to be free of common allergens were assessed by mass spectrometry. A total of 4 rubber accelerators and 2 adhesives were directly quantified and additional 7 rubber accelerators were assessed using semiquantitative measures.**

Results: **Aside from carbamates (assayed as 59 ppm zinc in insoles) in SeaVee's Sixty-Six sneakers, paratertiarybutylphenol formaldehyde resin (PTBFR) (assayed as 7.6 ppm paratertiary butylphenol or 4-tertiary butylphenol [4TBP] in uppers) in Allbirds Tree Runners and rosin (assayed as 628 ppm sodium abietate in uppers) and carbamates (24 ppm zinc in uppers) in Saucony Jazz sneakers, these shoes had low levels of all allergens assayed in this study. Tom's Carlo sneakers contained rosin (127 ppm sodium abietate in insoles), PTBFR (6.5 ppm 4TBP in uppers), and carbamates (112 ppm sodium abietate in insoles) but had low levels of all other assayed allergens.**

Conclusions: **Although identifying allergen-free shoes is challenging, the results of this analysis will help patch testing physicians recommend athletic shoes to patients with specific allergies.**

Capsule Summary

- Identifying shoes free of specific contact allergens is challenging.
- SeaVee's Sixty-Six sneaker, Tom's Carlo sneaker, Allbirds Tree Runner, and Saucony Jazz sneakers may be safe for patients depending on their specific allergies, but they may not be safe for all patients with shoe allergic contact dermatitis.

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INTRODUCTION

Allergic contact dermatitis (ACD) is a type IV hypersensitivity reaction. Individuals with contact allergy are instructed to select products free of their allergens. For cosmetic products, reading product labels or the American Contact Dermatitis Society (ACDS) Contact Allergen Management Program (CAMP) can help patients select safe products. However, noncosmetic products, such as clothing and shoes, present unique challenges. Companies are not required to list, and many not even know, all chemicals used during manufacturing. This poses unique challenges for helping patients identify safe shoes.

In 2019, the American Contact Alternatives Group (ACAG) published a comprehensive list of safe products for patients with contact allergies.[1] The group contacted the technical departments of a number of shoe manufacturers to determine whether certain common shoe allergens are used in the manufacture of any shoes in their product lines. The manufacturers were asked about the use of rubber accelerators (thiurams, carbamates, benzothiazoles, thioureas), black rubber, chromates, rosin (colophony), and paratertiary butylphenol formaldehyde resin (PTBFR). Several manufacturers provided information suggesting that their shoes were free of at least

some of the most common shoe allergens. The purpose of this study was to determine whether these claims are true.

METHODS

Representative shoes from 4 manufacturers were selected: (*a*) Saucony Jazz, (*b*) Tom's Carlo Sneaker, (*c*) Allbirds Tree Runner, and (*d*) SeaVees Sixty-Six. These 4 shoe manufacturers were specifically selected as they can be easily purchased and represent practical everyday shoes. All 4 shoes, based on ACAG data, are known to be free of leather.[1]

Six chemicals of interest were selected for quantitative analysis: tetramethylthiuram disulfide (TMTDS; Sigma Aldrich, St. Louis, MO, USA), tetramethylthiuram monosulfide (TMTMS; Sigma Aldrich), tetraethylthiuram disulfide (TETDS; TCI America, Portland, OR, USA), 1,3 diphenylguanidine (DPG; TCI America), the colophony derivative sodium abietate (NAB; TCI America), and 4-tertiary butylphenol (4TBP; Thermo Fisher Scientific, Waltham, MA, USA).

Sodium abietate and 4TBP were chosen as markers for rosin and PTBFR, respectively, since the latter are complex compounds that are difficult to directly quantify using mass spectrometry. Acetonitrile, water, ethanol, formic acid, and ammonium acetate all used as dilution solvents and buffers for liquid chromatography were purchased at LC grade or higher (Sigma Aldrich).

Owing to technical and cost limitations, several additional chemicals were suspect screened and reported using semiquantitative estimates. These chemicals were *n*,*n*-diethylthiourea (DET), *n*-isopropyl-*n*-phenyl-4-phenylenediamine (IPPD), 2-mercaptobenzothiazole (MBT), dibenzothiazyl disulfide (DBTD), *n*-cyclohexyl-2-benzothiazolesulfenamide (CBTS), and 2-(4-morpholinylmercapto)benzothiazole (MOR). Finally, the presence of zinc was used as a marker for the presence of zinc dibutyldithiocarbamate (ZDBC) since carbamates are difficult to detect with mass spectrometry analysis.

Shoes were purchased from Amazon. Two core samples from the "uppers" of each shoe (including all materials not fully attached to the insoles) and 2 core samples from the "insoles" (including insoles *per se* and all attached in insole materials) were processed. The uppers of each shoe were cut into small pieces and separated into 3 similar specimens. The same procedure was used to make similar specimens from the insoles of each shoe. The extraction technique used in this study is a modification of a previously published protocol.[2]

Shoe samples with a total weight of 50 g were placed to cover the bottom of a 250 mL beaker. The samples were covered with 100 mL of solvent and placed in a Branson 200 ultrasonic bath for 5 minutes. For each sample, 3 extracts were made: 1 each in water, ethanol, and acetone. Each of the resulting extracts was placed in round-bottomed evaporation flasks. The extraction process was repeated on each shoe specimen with an additional 100 mL of solvent and the 2nd extract was added to the round-bottomed evaporation flask.

The resulting 200 mL of extract was evaporated to dry residue in a Buchi R-20 Rotavapor. Water baths started at 45°C and increased gradually to 100°C, ethanol baths started at 35°C and increased gradually to 75°C, and acetone bath started at 25°C and increased gradually to 50°C. The appropriate solvent was then readded to the dry residue to reconstitute the extract to a volume of 1 mL.

The methods for the quantitative and semiquantitative analyses are described in Supplementary Data S1.

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RESULTS

The results of the mass spectrometry are given in Table 1.

For the 3 thiurams (TMTDS, TMTMS, and TETDS), all shoes had concentrations <0.6347 ppm. Notably, Allbirds had the lowest concentration of these thiurams with no detectable amount of TMTDS, and rates of TMTMS and TETDS were at 11.4 and 7.4 ppb, respectively, only in the insole and only when extracted with ethanol.

DPG was detected in the upper and insole of Saucony, SeaVees, and Allbirds, and in the insole of Toms. However, the highest detectable amount was only 30.4 ppb in the top of the Saucony sample extracted with ethanol.

Sodium abietate was detected in the upper and insole of all shoes. The highest concentration, 628.7 ppm, was detected in the upper of the Saucony sampled dissolved in ethanol.

4TBP was not detected in the Saucony or SeaVees shoe, however, it was detected in the upper and insole of the Toms and Allbirds shoes. The highest concentration was 7.6 ppm in the Allbirds upper extracted with ethanol.

Suspect screening with semiquantitation analysis showed that DET was only suspected to be in 3 samples and at concentrations estimated to be at or <150 ppb (SeaVee's insole in all 3 solvents, data not shown). MBT was suspected to be present in most specimens but was estimated to be present in all at <915 ppb. DBTD was suspected to be present in 50% of samples but at concentrations <200 ppb. CBTS was suspected to be present in ~50% of specimens, with Tom's upper in acetone having the highest concentration at 1.9 ppm.

An appropriate suspect target for MOR was not identified in any specimen. IPPD was suspected to be present in some specimens, 4 of which were at levels estimated to be 1 ppm (SeaVee upper, water), 6 ppm (Allbirds upper, water), 15 ppm (Allbirds insole, ethanol), and 20 ppm (Allbirds upper, acetone). Zinc, a sum surrogate for total carbamates, was found at a concentration of 112 ppm in the Tom's insoles, 59 ppm in SeaVees insoles, 30 ppm in Saucony's insoles, but only 8 ppm in Allbirds' insoles (all in acetone extracts). The Saucony shoe had an upper with 24 ppm in water, but this was the only upper showing >10 ppm zinc in any solvent.

DISCUSSION

Our results demonstrate that the allergens tested were present in all of the shoes we analyzed, although at low concentrations. This

TABLE 1. Mass Spectrometry Results of Each Potential Allergen Alternative Shoe by Sample, Solvent, and the Presence of Each Allergen

Shoe	Location	Solvent	TETDS (ppb)	TMTDS (ppb)	TMTMS (ppb)	1,3DPG (ppb)	NAB (ppm)	4TBP (ppm)
Saucony	Upper	Acetone	X	X	X	X	X	X
Saucony	Upper	Water	X	X	X	8.2	X	X
Saucony	Upper	Ethanol	X	18.5	31.4	30.4	**628.7**	X
Saucony	Insole	Acetone	X	X	46.7	11.2	2.7	X
Saucony	Insole	Water	X	X	X	3.8	1.3	X
Saucony	Insole	Ethanol	X	X	11.2	16.7	**110.3**	X
TOMS	Upper	Acetone	X	X	541.7	X	X	X
TOMS	Upper	Water	X	X	X	X	1.8	X
TOMS	Upper	Ethanol	X	X	523	X	X	6.5
TOMS	Insole	Acetone	X	X	634.7	11.7	0.8	X
TOMS	Insole	Water	X	4.6	7.1	X	0.6	X
TOMS	Insole	Ethanol	X	12.9	175.8	2.7	**127.4**	5.7
SeaVees	Upper	Acetone	X	X	X	X	X	X
SeaVees	Upper	Water	X	8.4	X	5.1	X	X
SeaVees	Upper	Ethanol	X	X	X	X	**11.1**	X
SeaVees	Insole	Acetone	39	X	X	X	X	X
SeaVees	Insole	Water	14.7	10.7	X	12.3	0.3	X
SeaVees	Insole	Ethanol	61.7	X	X	2.3	X	X
Allbirds	Upper	Acetone	X	X	X	3.1	0.1	X
Allbirds	Upper	Water	X	X	X	4.3	0.2	X
Allbirds	Upper	Ethanol	X	X	X	4	2.9	7.6
Allbirds	Insole	Acetone	X	X	X	2.3	0.07	X
Allbirds	Insole	Water	X	X	X	25.5	0.07	X
Allbirds	Insole	Ethanol	X	11.4	7.4	16.5	4.6	5.7

X = allergen was not detected; data are shown in parts per billion (ppb) or parts per million (ppm). Concentrations >10 ppm are bolded. Conversion between ppm or ppb and concentration: 1% = 10,000 ppm; 0.01% = 100 ppm = 100,000 ppb; 0.0001% = 1 ppm = 1000 ppb.

1,3DPG, 1,3 diphenylguanidine; 4TBP, 4-tertiary butylphenol; NAB, sodium abietate; TETDS, tetraethylthiuram disulfide, TMTDS, tetramethylthiuram disulfide; TMTMS, tetramethylthiuram monosulfide.

highlights that trace amounts of allergens may be present even in products perceived to be allergen-free. Of the 4 shoes examined, all contained at least 1 thiuram and DPG. Two of the shoes, Toms and Allbirds, contained 4TBP. All 4 shoes contained sodium abietate. Suspect screening showed the presence of thioureas and benzothiazoles in some specimens but at levels estimated to be <1 ppm. Four specimens showed levels of IPPD at levels estimated between 1 and 20 ppm. Zinc was found in the insoles of all 4 shoes but at a concentration of <10 ppm in the Allbirds shoes. The uppers of all shoes except Saucony had zinc present at <10 ppm.

The concentration of an allergen is important. At low concentrations, an allergen may not elicit clinical dermatitis. The threshold for elicitation is not well understood, likely varies by individual, and has only rarely been studied. In 1 article, 4TBP at a concentration of 10 ppm was shown to elicit a reaction in 2 patients known to be sensitized to the chemical. Unfortunately, dilution below this threshold was not performed.[3] In a study on the leaching of allergens out of shoes, MBT at a concentration of 100 ppm was able to elicit an allergic reaction in 5 out of 12 patients with a known allergy.

At a concentration of 32 ppm, it did not elicit a reaction in any of the 12 subjects.[4] However, previous studies have identified the chemical ppm threshold to trigger some other contact allergens. A concentration of 100 ppm will detect in 68.2% of patients with known allergies to methylisothiazolinone/methylchloroisothiazolinone,[5] whereas 300 ppm of octylisothiazolinone elicits a reaction in 0.4% of sensitized patients.[6] For nickel sulfate, 1 ppm will elicit a reaction in 15% of sensitized patients.[7]

Although studies have investigated the potential of chemicals at ppm to elicit ACD, we were unable to find studies that investigated rates at ppb. However, as the concentration decreases, reactions in sensitized individuals usually decrease.[8] Therefore, we anticipate that as allergen concentrations drop below 1 ppm, the likelihood of an allergic reaction occurring is negligible. However, the surface area of exposure is also important. For nickel, a larger surface area exposure has been associated with a quicker time to allergy elicitation.[9]

Regarding rubber-related allergens, levels in the tested shoes were generally low. For thiurams, all specimens showed <65 ppb except for the insole of the Tom's shoes that had 634.7 ppb TMTDS. Even this specimen is <1 ppm, a level unlikely to cause contact allergy. All 4 tested shoes will likely be tolerated by patients with thiuram allergy.

For benzothiazoles, all specimens showed level <1 ppm except for the Tom's uppers, which had 1.9 ppm CBTS, a level still likely to be safe for most patients with benzothiazole allergy. The Saucony, SeaVees, and Allbird shoes (and possibly the Tom's shoes) will likely be tolerated by patients with benzothiazole allergy.

Regarding carbamates (using the presence of zinc as an assay), there was only 1 upper with >10 ppm (the Saucony shoe had 24 ppm zinc). For carbamate allergy involving the dorsum of the feet, the least likely shoes to cause reactions are the Toms, SeaVees, and Allbirds (the Saucony shoes should be avoided).

For carbamate allergy involving the soles of the feet, all of the shoes had zinc levels in the insoles >1 ppm. Therefore, for carbamate allergy and iole involvement, we advise replacement of the shoe insoles with a nonrubber insole and removal of any adhesive used to glue in the insole. The Allbirds shoes had, by far, the lowest level of zinc in the insoles (8 ppm) and would be the safest choice.

DPG and thioureas in all specimens of all shoes were far <1 ppm and should be tolerated by patients allergic to these substances.

IPPD was not detected in either the Tom's or SeaVees shoes and both of these should be safe for IPPD allergic patients. There was 1 ppm IPPD in the uppers of the Saucony shoe (Aq) and this shoe will also likely be safe for most IPPD allergic patients. The Saucony shoe had 20 ppm IPPD in the uppers (acetone) and should be avoided by IPPD allergic patients.

PTBFR (as assayed by 4TBP) was not detected in the Saucony or SeaVees shoes and should be safe for patients with this allergy. Tom's shoes had 6.5 ppm and Allbirds shoes had 7.6 ppm in the uppers (EtOH) and both should be avoided with this allergy since these levels are fairly close to 10 ppm (which has been shown to cause reactions to this allergen in a previous study).[3]

Finally, rosin (as assayed by NAB) was present at 628.7 ppm in the uppers and 110.3 ppm in the insoles (EtOH) of the Saucony shoes that should be avoided in patients with rosin allergy. The Toms shoes had 1.8 ppm in the uppers (Aq) but had 127.4 ppm in the insoles (EtOH) and are probably best also avoided with this allergy. The SeaVees shoes had 11.1 ppm in the uppers (EtOH), a level that could possibly cause reactions in some allergic patients. The best choice for this allergy is the Allbirds shoes that had 2.9 ppm uppers and 4.6 ppm insoles (both EtOH).

Besides concentration, the solvent used to detect allergens is also important. Given the hydrophobic and hydrophilic nature of individual allergens, successfully dissolving chemicals for mass spectrometry poses challenges. For example, 1 chemical may dissolve in acetone but not in ethanol. To ensure that we did not miss allergens, we used 3 distinct solvents: acetone, water, and ethanol. However, human sweat, such as what will occur from wearing a shoe, is physiologically most like water.

However, in studies of allergen leaching, variations in the pH of human sweat may alter the concentration of a particular chemical.[4] Consequently, allergen concentrations in water are a more likely approximation of real-world exposures. If only samples dissolved with water are assessed, the highest concentration of any allergen was NAB at 1.3 ppm in the Saucony insole and none of the shoes had detectable amounts of 4TBP. In practical terms, all the tested shoes could potentially be useful alternatives for patients with contact allergy to footwear allergens. However, the best choice for a shoe alternative would likely be one with low levels of allergen detected in all 3 solvents. If this is not possible, other materials such as cork or poured plastic may be acceptable alternatives.

There are several limitations to this study. Although samples from the upper and insole of 4 shoes were selected, it is plausible that if all parts of the shoes were sampled individually, some shoe parts may have contained higher concentrations of these allergens. In addition, we were not able to perform precise quantitative analysis of carbamates, due to difficulties in detecting them by mass spectrometry. We also did not investigate the presence of rubber dye or textile dye allergens, chromates, or preservatives. As such, caution is needed when recommending these 4 shoes to patients with these allergies.

We tested specific shoes and it is possible that other shoes made by these companies may not be free of the allergens we assessed despite the claims made by the manufacturer. Therefore, when recommending these shoes to patients, it is safest that the specific shoe style we have tested, not just the company's name, is communicated. The materials used by a company may also change over time. As such, older or new pairs of the shoes we analyzed may contain different concentrations of allergens.

Identification of safe alternative shoes is extremely difficult but essential to treat shoe ACD. This study, using mass spectrometry techniques, detected multiple allergens in 4 "hypoallergenic" athletic shoes, although many concentrations were likely below elicitation threshold.

SUPPLEMENTARY MATERIAL

Supplementary Data S1

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