

Patch Testing to Diphenylguanidine by the North American Contact Dermatitis Group (2013–2016)

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Background/Objectives: Carba mix (CM, 3% petrolatum) contains 1,3-diphenylguanidine (DPG, 1%), zinc diethyldithiocarbamate (1%), and zinc dibutyldithiocarbamate (1%). Because DPG is a component of CM, DPG is often not tested separately. The purpose of this study was to determine the frequency of concomitant reactions to CM and DPG.

Methods: A retrospective analysis of the 2013–2016 North American Contact Dermatitis Group data was conducted. The study group consisted of patients with final interpretation of “allergic” to either DPG or CM. Reactions coded as irritant or doubtful/macular erythema (+/– and not interpreted as allergic) were excluded.

Results: A total of 10,457 patients were patch tested to both CM and DPG, and 610 (5.8%) had allergic reactions to either CM or DPG (CM only [n = 292, 47.9%], DPG only [n = 190, 31.1%], both [n = 128, 21.0%]). A total of 39.4% of CM-allergic patients reacted to DPG, and 59.7% of DPG-allergic patients reacted to CM. Analyses found that 25% (++/+++ subgroup) to 40% (all patients) of allergic reactions to DPG would have been missed by testing to CM alone. More than 70% of reactions to CM and DPG were +/– or +.

Conclusions: Patch testing to CM will miss 25% to 40% of positive reactions to DPG. Both CM and DPG have a high frequency of +/– and + reactions.

Rubber accelerators are additives used to increase the speed and decrease the temperature needed for vulcanization. Common rubber accelerators include thiurams, benzothiazoles, carbamates, and thioureas, and all can cause allergic contact dermatitis.^{1,2} Present in most screening patch test series (Table 1), carba mix (CM) is a patch test mixture of 1,3-diphenylguanidine (DPG) and 2 dithiocarbamates: zinc diethyldithiocarbamate (ZDEC) and zinc dibutyldithiocarbamate (ZDBC; Fig. 1).³ 1,3-Diphenylguanidine is a moderate-speed accelerator, whereas both ZDEC and ZDBC are

fast accelerators. Synthesized from cyanogen chloride and aniline, DPG is used as a primary accelerator for rubber vulcanization but can also be used as a secondary accelerator for thiazole, thiuram, and sulfonamide compounds.^{4,5} 1,3-Diphenylguanidine has traditionally been used in industrial rubber production for products, such as footwear and tires, but is increasingly being used in rubber gloves.⁶

Because DPG is a component of CM, many standard patch test series do not routinely patch test for DPG alone, instead opting to test for CM or thiuram mix (TM), which commonly coreacts with

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TABLE 1. Rubber Allergens in Screening Series

Patch Test Series	CM (3% pet)	Diphenylguanidine (1% pet)	ZDEC (1% pet)	TM (1% pet)	Thioureas (1% pet)	Mercapto Mix*	Mercaptobenzothiazole*	Black Rubber Mix (and Other Paraphenylenediamine Derivatives) (0.6%)
North American Contact Dermatitis Group	X	X		X	X		X	X
American Contact Dermatitis Society Core	X	X		X	X	X	X	X
T.R.U.E. Test	X			X		X	X	X
Australian Baseline	X			X	X	X	X	X
British Standard	X			X		X	X	X#
Chinese Baseline	X			X	X	X	X	X#
International Standard	X			X		X	X	X#
Latin America Baseline	X			X	X	X	X	X#
Spanish Baseline	X			X		X	X	X#
Japanese Standard	X†			X		X	X	X
German Standard			X	X		X	X	X#
Belgian Standard				X		X	X	X#
European Baseline				X		X	X	X#
Finnish Standard				X	X	X	X	X
Hungarian Standard				X		X	X	X#
Indian Standard				X		X	X	X
Italian Standard				X		X	X	X#
Korean Standard				X		X	X	X#
Polish Baseline				X		X	X	X#
Portuguese Baseline				X		X	X	X#
Swedish Baseline				X		X	X	X

*Concentrations of mercapto mix and mercaptobenzothiazole preparations vary between series.

†The Japanese Baseline Series tests for a dithiocarbamate mix (2% pet), consisting of dimethyldithiocarbamic acid zinc, diethyldithiocarbamic acid zinc, and N-ethyl-N-phenyldithiocarbamic acid zinc (each tested at 0.5% pet).

#A different derivative of paraphenylenediamine is tested rather than black rubber mix (most often N-isopropyl-N-phenyl-4-phenylenediamine).

Information obtained from SmartPractice Canada (<http://www.smartpracticecanada.com>, accessed February 17, 2020) and Chemotechnique (<http://www.chemotechnique.se>, accessed February 17, 2020) Web sites.

CM, carba mix; TM, thiuram mix; ZDEC, zinc diethyldithiocarbamate.

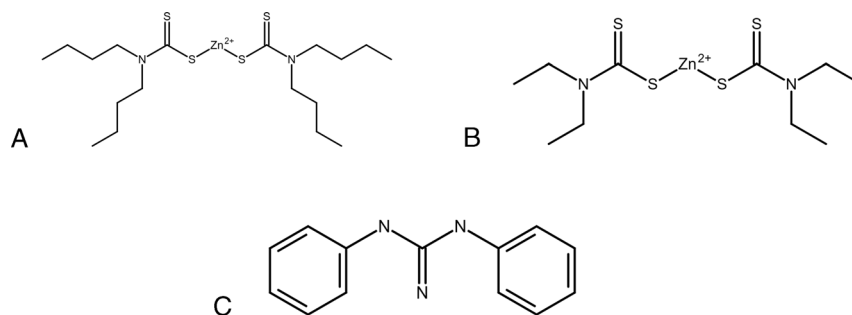


Figure 1. Chemical structures of (A) ZDBC, (B) ZDEC, and (C) diphenylguanidine. Images were created using Chem Space (<https://chem-space.com/>).

CM (Table 1). The British and International Standard Series include CM and TM, whereas the German Standard Series tests for TM and ZDEC. Many recommended series, including the European Standard, include only TM.^{7–10} Notably, the European Surveillance System on Contact Allergies has recently proposed the readdition of CM to their standard series, based on retrospective data showing an increased frequency of sensitization to CM and decreasing trend of sensitization to TM.¹¹ Others have opposed this plan, stating that CM is an “unreliable” patch test formulation and the need for confirmation by testing with individual components of CM.¹² Other members of the European Surveillance System on Contact Allergies (ESSCA) have suggested testing for ZDEC and diphenylguanidine, rather than CM.¹³ T.R.U.E. Test (SmartPractice Denmark ApS, Hillerød, Denmark), a commonly used commercially available patch test preparation, includes both CM and TM but does not test for DPG separately. The American Contact Dermatitis Society Core Series tests both DPG and CM.¹⁴

Literature on the coreactivity of DPG and CM is mixed (Table 2). Some studies only involve testing patients with known CM positivity to DPG. Mortz et al¹¹ patch tested 250 CM-allergic patients and found that 15% (n = 38 patients) also reacted to diphenylguanidine. Reaction frequencies to DPG in CM-positive patients were higher in other studies (27.8% [15/54],¹⁷ 50% [3/6],¹⁸ 86% [32/37],¹⁶ 100% [5/5]¹⁵).

It was previously estimated that patch testing to CM alone may miss approximately 10% of reactions to DPG.¹⁵ A comprehensive literature search identified 3 studies addressing this issue (Table 2). Dejonckheere et al¹⁶ tested 44 health care workers to both CM and DPG and found that 15.8% (6/38) of DPG reactions would have been missed if tested to CM alone. A retrospective analysis of 8 years of patch testing conducted by Bendewald et al¹⁷ found that 72.2% of 54 DPG-positive patients would have been missed if tested to CM alone. The frequency in a smaller study of 8 patients found that this frequency was 40.0%.¹⁸

TABLE 2. Summary of Previous Studies Examining Diphenylguanidine and CM Coreactivity

Study First Author Country Year	Population Tested	Patients Tested, n	Patients Tested to Both CM and DPG, n					% Missed DPG by Testing CM Alone
			CM+, n	DPG+, n	CM+, DPG+, n	CM−, DPG+, n		
Studies testing patients with known CM positivity to DPG								
Mortz ¹¹ Denmark 1994–2013	Patients with suspected rubber allergy	9741	250	250	38	38	–	–
Cao ¹⁵ United States 2007–2009	Patients with suspected rubber allergy	23	5	5	5	5	–	–
Studies testing sequential patients to both CM and DPG								
Dejonckheere ¹⁶ Belgium 2010–2017	Health care workers	4068	44	37	38	32	6	15.8
Bendewald ¹⁷ United States 2000–2007	Patients with suspected rubber allergy	727	727	54	54	15	39	72.2
Baeck ¹⁸ Belgium 2010–2011	Health care workers	8	8	6	5	3	2	40.0
Current study North America 2013–2016	Sequential patch-tested patients	10,457	10,457	482	318	190	128	40.3

CM, carba mix; DPG, 1,3-diphenylguanidine.

Importantly, the previous studies are relatively small. To date, investigation of concomitant reactions to DPG and CM in a large North American population has been lacking. The aim of this study was to characterize concomitant reactions between DPG and CM in this population.

METHODS

This retrospective analysis was approved by the Minneapolis Veterans Administration Medical Center's Subcommittee on Human Studies. The North American Contact Dermatitis Group (NACDG) tested a screening series of 70 allergens according to previously published standardized patch testing protocols.¹⁹ Briefly, allergens were applied to patients' skin using Finn Chambers (SmartPractice, Phoenix, AZ) and Scanpor tape (Alpharma AS, Vennessla, Norway). This study consisted of all patients tested to both DPG (1% petrolatum [pet]) and CM (3.0% pet; consisted of DPG [1.0% pet], *bis*(diethyldithiocarbamate) zinc [1.0% pet], and *bis*(dibutyldithiocarbamate) zinc [1.0% pet]; allergEAZE SmartPractice, Calgary, Alberta, Canada).

The study group was composed of all patients with a final determination of "allergic" patch test reaction to either DPG or CM; this included some doubtful/macular erythema (+/-) reactions determined by the testing dermatologist to be consistent with allergy (eg, crescendo pattern or morphology). Three-digit sources were coded for each relevant positive reaction.

Reactions with a final interpretation of "irritant" (CM: *n* = 68 C; DPG: *n* = 88) or +/- but not "allergic" (CM: *n* = 78; DPG: *n* = 76) were excluded. In addition, we excluded coding inconsistencies (eg, a reaction coded as "negative" on final read but coded "allergic," *n* = 12).

Analytical Methods

Data were compiled (Microsoft Excel 2016; Microsoft Corporation, Redmond, WA) and separated into 3 groups (CM+, CM+/DPG+, and DPG+ positive). Final counts and corresponding proportions were determined using Microsoft Excel. Statistical analyses were completed in SAS (SAS Institute, Cary, NC). Data from these groups were compared using Pearson χ^2 test, with a *P* < 0.05 considered to be statistically significant. Reaction index and positivity ratio were calculated per previous guidelines.^{20–22}

RESULTS

Concomitant Reactions

From 2013 to 2016, a total of 10,457 NACDG patients were patch tested to both CM and DPG. Six hundred ten had at least one reaction to either CM alone (*n* = 292), DPG alone (*n* = 128), or both (*n* = 190; Fig. 2A). There were 482 total reactions to CM and 318 total reactions to DPG. Overall, 39.4% of CM-allergic patients were also positive to DPG, and 59.7% of DPG-allergic patients were also

positive to CM. A total of 60.6% of reactions to CM would have been missed by testing to DPG alone, and 40.3% of DPG reactions missed by testing to CM alone in the overall category.

For the subgroup of individuals with a strong reaction (++ or +++) to either CM, DPG, or both, 48.1% of CM-allergic patients were positive to DPG and 74.8% of DPG-allergic patients were positive to CM (Fig. 2B). For this subgroup, 51.9% of CM reactions would have been missed by testing to DPG alone, and 25.2% of DPG reactions missed by testing to CM alone.

Demographics

1,3-Diphenylguanidine+ or CM+ Individuals Compared With Those not Allergic to Either (DPG-/CM-)

In pairwise comparisons, individuals with allergy to CM (CM+) or allergy to DPG (DPG+) were significantly more likely to be male (CM: relative risk [RR], 1.58; 95% confidence interval [CI], 1.42–1.75 [*P* < 0.0001]; DPG: RR, 1.71; 95% CI, 1.51–1.92 [*P* < 0.0001]), have overall occupationally related skin disease (CM: RR, 3.59; 95% CI, 3.09–4.17 [*P* < 0.0001]; DPG: RR, 2.66; 95% CI, 2.15–3.30 [*P* < 0.0001]), and/or have hand involvement (CM: RR, 1.72; 95% CI, 1.54–1.92 [*P* < 0.0001]; DPG: RR, 1.43; 95% CI, 1.23–1.67 [*P* < 0.0001]) as compared with individuals negative to both CM and DPG (non-CM/DPG allergic, CM-/DPG-; Table 3). In contrast, the CM+ and DPG+ groups were significantly less likely to have face involvement as compared with the non-CM/DPG-allergic group (CM: RR, 0.69; 95% CI, 0.56–0.85 [*P* = 0.0004]; DPG: RR, 0.54; 95% CI, 0.41–0.73 [*P* < 0.0001]). There were no significant differences for atopic markers (asthma, allergic rhinitis, atopic dermatitis) or leg involvement.

1,3-Diphenylguanidine+ Only Versus CM+ Only

In pairwise comparisons, individuals with allergy to DPG only were significantly less likely to have overall occupationally related skin disease (RR, 0.42; 95% CI, 0.26–0.68 [*P* = 0.0004]) or have hand involvement (RR, 0.64; 95% CI, 0.46–0.90 [*P* = 0.011]) compared with individuals with allergy to CM only. There were no significant differences in sex, atopic markers, hand/leg/face involvement, or proportion over 40 years (*P* > 0.05).

Final Reading Reaction Strength

Data regarding strength of final read reactions for patients positive to CM or DPG are shown in Table 4. Most reactions were weak (+/- or +; CM 71.6%, DPG 75.5%). As compared with those with weak reactions, individuals with strong (++ or +++) final readings to DPG were 1.28 times more likely to also be positive to CM (RR, 1.28; 95% CI, 1.06–1.55 [*P* = 0.0199]).

Occupational Relevance of Reactions

In addition to overall occupationally related skin disease, occupational relevance was also coded for each specific "allergic/positive" reaction. A total of 28.3% of CM reactions and 21.0% of DPG

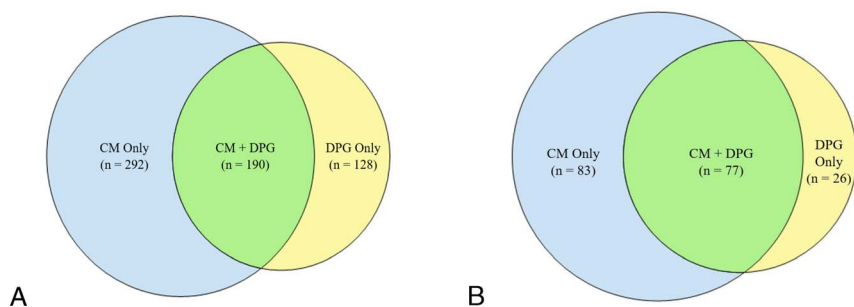


Figure 2. A, This Venn diagram includes all patients with concomitant “allergic” reactions to CM and DPG. B, This Venn diagram includes only patients with at least one strong (++ or +++) “allergic” reaction to CM and/or DPG.

reactions were coded as occupationally related (Table 5); these frequencies were not significantly different ($P = 0.1022$).

Reaction Index and Positivity Ratio

The positivity ratio (percentage of weak [+/- or +] reactions among the sum of all reactions, regardless of final interpretation of “allergic” or “not allergic”) ranges from 0% to 100%; lower numbers signify a better *quality* of patch test preparation (fewer weak reactions).²¹ In this study, the positivity ratios of CM and DPG were 68.4% and 72.5%, respectively. The reaction index (number of positive reactions minus questionable and irritant reactions divided by the sum of all 3) ranges from +1 to -1; +1 signifies a perfect patch test preparation with no macular erythema or irritant reactions.²² In this study, the reaction indices were 0.53 for CM and 0.34 for DPG.

Sources

Common sources associated with CM and DPG reactions are shown in Table 6. Gloves were the most common specifically identified source for both CM and DPG. Other common sources included undergarments/swimwear and footwear.

DISCUSSION

Few prior studies have evaluated concomitant reactions between DPG and CM. This retrospective analysis of 10,457 patch-tested individuals in North America has several key findings. In the overall population, 40.3% of DPG reactions would have been missed by testing with CM alone. In the subgroup of patients with strong (++ or +++) reactions to CM and/or DPG, 25.2% of DPG reactions would have been missed by testing to CM alone. Populations of CM+ and DPG+ individuals were demographically distinct from those not allergic to these rubber accelerators. We found gloves to be the predominant source for both groups.

Demographics

As summarized in Table 3, patients with reactions to CM, DPG, or both were more likely to be male, have overall occupationally related dermatitis, and have involvement of the hands as compared with

individuals not reacting to these 2 allergens. This is consistent with the clinical picture of allergy to rubber gloves; prior studies have also shown increased frequencies of occupational dermatitis and hand involvement.^{16,23} The link between sex and prevalence of allergic contact dermatitis to CM and DPG is less established; Warburton et al,²³ in a study of patch testing results from 12 European countries, found no correlation with sex and rubber sensitivity, including, but not limited to, CM. Our finding of a higher proportion of males may be related to a general higher proportion of occupationally related skin disease in male patch-tested patients (unpublished data, DeKoven).

Carba Mix as a Screen for Diphenylguanidine Sensitivity

In this study, we found that, overall, 40.3% (128/318) of DPG-allergic patients would have been missed by testing only to CM. It has been suggested that differences in allergy to mix constituents compared with the mix may be due to differences in concentration; in our study, DPG was tested at the same concentration standalone and as part of CM (1%).²⁴ The reason for this discrepancy may be due to inhibition by other components of the mix. In addition, DPG is known to form complexes with metal ions; it is possible that DPG may be interacting with the zinc component of ZDEC and ZDBC, creating complexes that inhibit patch test reactions.²⁵ Other studies that evaluate positivity rates of components of various mixes have found similar rates of missed allergy. Mowitz et al²⁴ found that 27% of patients with allergy to ingredients of fragrance mix (FM) I were missed by testing to FM mix I and 37% of patients with allergy to ingredients of FM II were missed by testing to FM II. In a separate study, 7 (23.3%) of 30 individuals allergic to ingredients of Compositae mix did not react to Compositae mix.²⁶ In addition, 31.6% of mercaptobenzothiazole-allergic patients were missed by testing to a mercaptobenzothiazole mix.²⁷

It is also possible that this could represent general nonreproducibility in patch testing. Several studies have evaluated the reproducibility of allergic reactions to simultaneously applied double sets of antigens, freshly prepared in Finn Chambers and applied to the right and left sides of patients' backs. Concordant reactions from such studies were 66% (n = 35),²⁸ 69.4% (n = 1285),²⁹ 88.5% (n = 383),³⁰ 90.5% (n = 220),³¹ and 93% (n = 35).³² In addition, reproducibility

TABLE 3. The Patient Demographics Index Data

	CM+ (n = 482), n (%)	DPG+ (n = 318), n (%)	CM+ and DPG+ (n = 190), n (%)	CM+ Only CM+/ DPG- (n = 292), n (%)	DPG+ Only DPG+/ CM- (n = 128), n (%)	Nonallergic DPG-/CM- (n = 9835), n (%)	CM+ (n = 482) vs Non-CM/DPG Allergic (n = 9835), RR (95% CI), P	DPG+ (n = 318) vs Non-CM/DPG Allergic (n = 9835), RR (95% CI), P	DPG+ Only (n = 128) vs CM+ Only (n = 292), RR (95% CI), P
Male	213 (44.2%)	152 (47.8)	97 (51.1)	116 (39.7)	55 (43.0)	2755 (28.0)	1.58 (1.42–1.75), <0.0001	1.71 (1.51–1.92), <0.0001	1.08 (0.85–1.38), 0.5340
Occupationally related	147 (30.7)	72 (22.8)	55 (28.9)	92 (31.8)	17 (13.5)	836 (8.5)	3.59 (3.09–4.17), <0.0001	2.66 (2.15–3.30), <0.0001	0.42 (0.26–0.68), <0.0001
Atopic disposition									
Asthma	73 (15.4)	49 (15.6)	30 (16.0)	43 (15.0)	19 (15.0)	1623 (16.6)	0.92 (0.74–1.14), 0.4325	0.93 (0.72–1.21), 0.6048	1.01 (0.61–1.66), 0.9750
Eczema	137 (28.9)	82 (26.3)	52 (27.8)	85 (29.6)	30 (24.0)	2925 (30.0)	0.96 (0.83–1.10), 0.5365	0.87 (0.72–1.05), 0.1285	0.81 (0.56–1.15), 0.2307
Hay fever	137 (28.8)	99 (31.3)	61 (32.3)	76 (26.6)	38 (29.9)	3031 (31.0)	0.92 (0.80–1.07), 0.2657	1.01 (0.86–1.19), 0.9051	1.14 (0.82–1.59), 0.4375
Hand	200 (41.5)	110 (34.6)	73 (38.4)	110 (37.7)	31 (24.2)	2377 (24.2)	1.72 (1.54–1.92), <0.0001	1.43 (1.23–1.67), <0.0001	0.64 (0.48–0.90), 0.0073
Leg	54 (11.2)	40 (12.6)	24 (12.6)	8 (2.7)	3 (2.3)	1054 (10.7)	1.04 (0.81–1.35), 0.7411	1.17 (0.97–1.58), 0.2920	0.86 (0.23–3.17), 0.8151
Face	79 (16.4)	41 (12.9)	24 (12.6)	31 (10.6)	9 (7.0)	2327 (23.7)	0.69 (0.56–0.85), 0.0002	0.54 (0.41–0.73), <0.0001	0.66 (0.32–1.35), 0.2493
Age, 40 > y	333 (69.1)	233 (73.3)	134 (70.5)	199 (68.2)	99 (77.3)	6630 (67.5)	1.02 (0.96–1.09), 0.4434	1.09 (1.02–1.16), 0.0280	1.13 (1.00–1.28), 0.0561

CI, confidence interval; CM, carba mix; DPG, 1,3-diphenylguanidine; RR, relative risk.

of patch test reactions is associated with weaker patch test reactions.³³ This may be especially relevant as CM and DPG resulted in a large proportion of doubtful and mild reactions.

Of worldwide group “standard” or screening series, only the American Contact Dermatitis Society Core Series also tests DPG alone (Table 1). Some experts have suggested that testing to CM is inconclusive and recommended confirmation testing to individual components of CM (dithiocarbamates and DPG).¹² More studies are needed to determine whether DPG should be included as a component of CM, although that has been the historical standard. Regardless of its inclusion in CM, our study strongly supports the additional testing of DPG alone.

Weak Reactions (+/- and +)

We found that more than 70% of all reactions to both CM and DPG were either doubtful/macular (+/-) or mild (+) in strength. Of note, the proportion of weak (+/- and +) reactions in the DPG-allergic patients that would have been missed by testing to CM alone was higher (79.7%) than in DPG-allergic patients also reacting to CM (72.7%), possibly indicating that reactions to DPG alone could be more irritant. However, Hamnerius et al,³⁴ in a study of 311 health care workers with hand eczema patch tested to common rubber chemicals, anecdotally reported that weak allergic reactions to DPG were often clinically relevant. In their study, symptoms of hand eczema in health care workers with weak DPG reactions improved and even resolved after switching to DPG-free gloves.³⁴

Carba mix and DPG are both well known to be problematic patch test preparations as both can cause irritation when occluded. Carba mix was removed from the European Baseline Series in 1988 because of its irritant nature.^{35,36} It has been suggested that CM's irritant nature may be due specifically to DPG. In a study of occupational dermatitis, Geier et al³⁷ tested 1987 patients to ZDEC and ZDBC and 1455 patients to DPG between 1995 and 2001. Results demonstrated 42 doubtful/macular (+/-) reactions, 27 mild (+) reactions, and only 1 strong (++) reaction to DPG. Clinical relevance was not reported.³⁷

Commonly used metrics to evaluate the quality of patch test preparations include the positivity ratio (proportion of weak [+/-, +] reactions to all positive reactions) and the reaction index (the number of allergic reactions minus questionable and irritant

reactions divided by all 3 values summed).²⁰ Previous literature has found both CM and DPG to have high positivity ratios and low reaction indexes.^{20,37,38} Prior work by our group used a cutoff for the positivity ratio of 55% to be acceptable quality. The current study demonstrated positivity ratios of 68.4% and 72.5% for CM and DPG, respectively, indicating their propensity to cause weak reactions. Reaction indexes for CM and DPG were 0.53 and 0.34, which are higher than those found in previous studies.³⁷ However, our group does not regularly record irritant reactions as such, which may cause our calculated reaction indexes to falsely appear elevated.²⁰ Aalto-Korte and Pesonen¹² and Aalto-Korte et al³⁹ proposed testing DPG at a concentration of 0.33%, compared with its current preparation of 1%, to reduce the proportion of irritant reactions. However, dose applied per square centimeter is more important, underscoring the need for careful dose application, such as with pipettes.^{12,39}

Because of the problematic nature of these allergens, it can be difficult to interpret doubtful or weak reactions to CM and DPG. In this study, of DPG-allergic patients, +/- reactions to CM were considered to be allergic in 88% of cases (compared with 25.7% of patients not allergic to DPG but +/- to CM). In other words, +/- CM reactions in DPG-allergic patients were coded as allergic more frequently than +/- CM reactions in patients not allergic to DPG. This may reflect physician comfort in coding +/- doubtful reactions as “allergy” in the presence of positive reactions to related chemicals or a stronger pretest probability of allergy to rubber accelerators based on patient history.

Allergen Sources

Although diphenylguanidine is a component of CM, it is not a dithiocarbamate. Dithiocarbamates consist of a central carbon double bonded to one sulfur and single bonded to one sulfur and one nitrogen molecule (Fig. 1). In comparison, diphenylguanidine consists of a central carbon atom with a double bond to one nitrogen atom and single bonds to 2 other nitrogen atoms (Fig. 1).⁴⁰ Because of the structural dissimilarity, cross-reactivity is unlikely. Rather, overlap between positive reactions is likely due to cosensitization from the same sources (Table 6). Although rubber accelerators, such as ZDEC, ZDBC, and DPG, can be present in a wide variety of

TABLE 4. Reaction Strength for Allergic/Positive Reactions to CM and Diphenylguanidine and DPG in 10,457 Patients

Strength of Reaction	CM+ (n = 482), n (%)	DPG+ (n = 318), n (%)	CM in CM+/ DPG+ (n = 190), n (%)	DPG in CM+/ DPG+ (n = 190), n (%)	CM+ Only (CM+/DPG-) (n = 292), n (%)	DPG+ Only (CM-/DPG+) (n = 128), n (%)
Doubtful +/-*	49 (10.2)	34 (10.7)	22 (11.6)	20 (10.5)	27 (9.2)	14 (10.9)
Mild +	296 (61.4)	206 (64.8)	114 (60.0)	118 (62.1)	182 (62.3)	88 (68.8)
Moderate ++	110 (22.8)	71 (22.3)	46 (24.2)	46 (24.2)	64 (21.9)	25 (19.5)
Strong +++	27 (5.6)	7 (2.2)	8 (4.2)	6 (3.2)	19 (6.5)	1 (0.8)

*Only doubtful reactions with a final interpretation of “allergic/positive” were included.

CM, carba mix; DPG, 1,3-diphenylguanidine.

TABLE 5. Occupational Relevance of Positive Reactions

	CM+ (n = 474), n (%)	DPG+ (n = 315), n (%)	CM+ in CM+/DPG+ (n = 186), n (%)	DPG+ in CM+/DPG+ (n = 187), n (%)	CM+ Only (n = 288), n (%)	DPG+ Only (n = 128), n (%)
Yes	134 (28.3)	66 (21.0)	51 (27.4)	51 (27.3)	83 (28.8)	15 (11.7)
Unsure/no	340 (71.7)	249 (79.0)	135 (72.6)	136 (72.7)	8 (71.2)	113 (88.3)

CM, carba mix; DPG, 1,3-diphenylguanidine.

products, allergy to these chemicals is most often due to their presence in rubber gloves.⁴¹

Although thiurams have traditionally been considered the most allergenic accelerators in rubber gloves, data suggest that sensitivity to DPG may be increasing, possibly because of the use of nonlatex gloves in health care facilities.^{6,16,18,42,43} Baeck et al¹⁸ and Crepy⁴² reported 5 cases of allergy to DPG present in synthetic rubber gloves in health care workers and, separately, cited an additional 32 cases. Most recently, Dejonckheere et al¹⁶ studied 44 health care workers with allergic contact dermatitis to synthetic rubber gloves and found that diphenylguanidine was the most commonly implicated allergen. Our study found that gloves were the top source in CM-allergic and DPG-allergic patients. However, DPG-allergic patients had a significantly lower proportion of allergy attributed to gloves compared with CM-allergic patients. This is consistent with previous reports of rubber accelerator use in gloves; Goodier et al⁴⁴ found that manufacturers reported the use of carbamates in 90.5% of gloves, as compared with DPG in 9.5%.

TABLE 6. Sources Associated With CM and Diphenylguanidine Reactions

Source	CM+ (n = 479)		DPG+ (n = 317)	
	n	%	n	%
Clothing, wearing apparel, protective equipment, textiles	277	57.8	148	46.7
Gloves	210	43.8	97	30.6
Undergarments, swimwear	26	5.4	20	6.3
Shoes, boots, sandals, slippers	16	3.3	11	3.5
Socks, stockings, belts, accessories, other	13	2.7	15	4.7
Glasses/jewelry, safety equipment	8	1.7	5	1.6
Cosmetics, beauty preparations, skin and health care products	59	12.3	24	7.6
Building and construction materials	16	3.3	8	2.5
Personal grooming devices, applicators	5	1.0	3	1.0
Machinery and vehicles	4	0.8	1	0.3
Soaps, detergents, cleansers, disinfectants, laundry aids (nonskin)	1	0.2	2	0.6
Unknown/not classified elsewhere/other	117	24.4	131	41.3

CM, carba mix; DPG, 1,3-diphenylguanidine.

Despite being reported in a few gloves, it is possible that DPG's potential for skin sensitization could be increased, depending on the type of glove and methods of sanitization. In a study of 16 patients, cetylpyridinium chloride, used in gloves for its antibacterial properties, and DPG were found to be significant occupational allergens. Pontén et al⁶ hypothesized that the presence of cetylpyridinium chloride may have an extractive effect on DPG, increasing its release from the gloves studied. In addition, Hamnerius et al⁴⁵ recently reported that the use of alcohol-based disinfectants resulted in an increased amount of DPG release from gloves known to contain DPG.

Limitations

This study is presented in the context of several limitations. This analysis was a cross-sectional, retrospective review of tertiary referral centers. Therefore, the study population is not representative of the general population or general dermatology patients. Grading of reactions can be subjective. The large proportion of doubtful (+/-) or weak (+) reactions in this study suggests the possibility of false-positive reactions. Data on the timing of the final reading (day 5, 6, 7, or 8) are not captured in the database. Pipettes for dispensing of uniform amounts of allergens are used by only some members. The criterion standard of relevance involves not only confirmation of allergen in sources but also dermatitis resolution with avoidance. Confirmation of rubber ingredients is notoriously difficult; thus, relevance is generally "possible" (source likely contains allergen). Follow-up of patients' dermatitis is not captured in the NACDG database.

CONCLUSIONS

This study demonstrates that testing for CM alone misses a significant proportion of allergic reactions to DPG (25%–40%). Both allergens are problematic allergens with a high proportion of weak reactions. More studies are needed to address the optimal patch test concentration.

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