

Positive Patch Test Reactions to Carba Mix and Iodopropynyl Butylcarbamate: Data From the North American Contact Dermatitis Group, 1998–2008

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Background: Carba mix (CM) contains 3 chemicals used as accelerators in manufacturing of rubber products and agricultural chemicals. Iodopropynyl butylcarbamate (IPBC) is a preservative used in industrial and personal care products. Potential cross-reactivity between these allergens is unclear.

Objective: This study aimed to determine concomitant reaction rates between CM (3% petrolatum [pet]) and IPBC (0.1% pet and/or 0.5% pet).

Design: A retrospective cross-sectional analysis of data from the North American Contact Dermatitis Group from 1998 to 2008 was conducted. Frequencies of positive reactions, strength of reactions, and concomitant reaction rates were calculated.

Results: A total of 25,435 patients were tested. There were 1131 allergic reactions to CM and 346 positive reactions to IPBC (either 0.1% pet and/or 0.5% pet). Fifty-two patients reacted to both allergens. Most reactions (>69%) were doubtful/weakly positive, and of those who reacted to both, most (58%) had doubtful and/or weakly positive reactions. There was a statistically significant association of concomitant reactions between CM and IPBC; formaldehyde positivity was used as control and showed statistically significant concomitant reactions.

Conclusions: Overall, concomitant reactions to CM and IPBC were low, and rates varied by strength of reaction. True cross-reactivity is unlikely; statistical association is likely due to frequent low-grade reactions to irritant patch test preparations.

Carba mix (CM) consists of diphenylguanidine, zinc dibutylthiocarbamate, and zinc diethylthiocarbamate. These 3 chemicals function as rubber accelerators and components of fungicides and other agriculture chemicals. Iodopropynyl

butylcarbamate (IPBC) is a preservative used in industrial preparations (eg, metal working fluids and paints) and personal care products and is often used in combination with formaldehyde-releasing agents.¹ Carba mix and IPBC are problematic allergen preparations; both have high positivity ratios (PRs),² indicating frequent doubtful or weakly positive patch test reactions.

Concomitant reactions can be described as cross-reactions (a reaction to an allergen occurring in a patient never exposed

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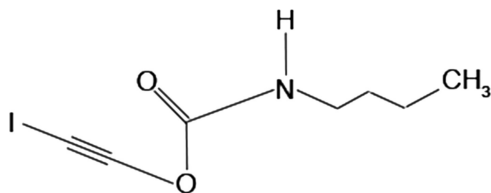


Figure 1. Chemical structure of IPBC.

to that allergen, which occurs because of original sensitization to a structurally related allergen; eg, neomycin and gentamycin), coreactions (a reaction to 2 allergens not structurally related but commonly used in the same product; eg, neomycin and bacitracin), or neither (simply coincidental). Iodopropynyl butylcarbamate (Fig. 1) and the carbamates in CM (Fig. 2) have a chemical structure consisting of carbonyl group (CO_2) with adjacent functional groups (Fig. 3). One or both of the 2 oxygen atoms in a carbamate can be replaced with a sulfur atom; a thiocarbamate is a carbamate with 1 sulfur, and a dithiocarbamate has 2 sulfur atoms (Fig. 4). Because both IPBC and carbamate share a carbonyl group in their structure, it is theoretically possible that there is structural cross-reactivity between IPBC and CM.

Although positivity rates of sensitization to CM and IPBC have been individually reported periodically by the North American Contact Dermatitis Group (NACDG) and other contact dermatitis groups, to date, data on concomitant reactions from a large population data set have been lacking. The objectives of this study were to determine concomitant patch test rates to these 2 allergens and explore the likelihood that these 2 chemicals are coreactors, cross-reactors, or simply just common borderline positive patch test reactions that, in many instances, could represent false-positive reactions.

METHODS

This analysis of deidentified data was approved by the Minneapolis Veterans Administration Medical Center's Subcommittee on Human Studies. Between July 1, 1998, and December 31, 2008, 25,435 patients were patch tested by the NACDG to a standard

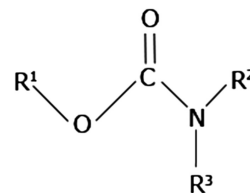


Figure 3. General chemical structure of a carbamate.

series of 50 to 70 allergens, which included IPBC (0.1% pet and/or 0.5% pet) and CM (3.0% pet). Methods for patch testing and data collection have been previously described.³⁻⁵ This analysis focused on the 25,398 individuals who were tested to CM and IPBC. Three comparison groups were defined as the following: patients allergic to CM only, patients allergic to IPBC only, and patients allergic to both CM and IPBC (0.1% pet and/or 0.5% pet). *Allergic* was defined as a positive patch test reaction with a final interpretation of allergic patch test reaction; this excluded doubtful reactions (macular erythema) not thought to be allergic in nature, negative reactions, and irritant reactions. Because this analysis focused on simple positivity, clinical relevance of reactions was not considered.

Analytical Methods

All data were manually entered into a computerized database (Access 2003; Microsoft Corporation, Redmond, Wash) and checked for quality assurance at a central location. SAS software (Statistical Analysis System Version 9.2; SAS Institute Incorporated, Cary, NC) and Access (Microsoft Corporation) were used for these analyses. Counts and proportions were determined for demographic and allergen-related data. Data from the 3 groups (CM positive, IPBC positive, and positive to both allergens) were compared using Pearson χ^2 test (Fisher exact test, 2 tailed, when appropriate). A *P* value of 0.05 or lesser was considered statistically significant.

Positivity rates for 2 other common marginal irritants on the NACDG standard series, formaldehyde (1% aqueous) and fragrance mix I (8% pet), were used as controls. For these analyses, only patients with at least 1 positive reaction to a NACDG standard allergen were included ($n = 17,181$) to avoid statistical correlation of negative reactions to both allergens.

RESULTS

Demographics

Of the 25,398 patients patch tested to both allergens in the study period, 1463 patients had a positive reaction to either CM, IPBC, or both. A total of 1131 patients had a positive allergic reaction to CM (with or without IPBC), and 332 patients reacted to IPBC (either 0.1% pet and/or 0.5% pet; with or without CM). Only 52 patients reacted to both allergens. The demographics of these patients (male, occupational dermatitis, atopic dermatitis, hand,

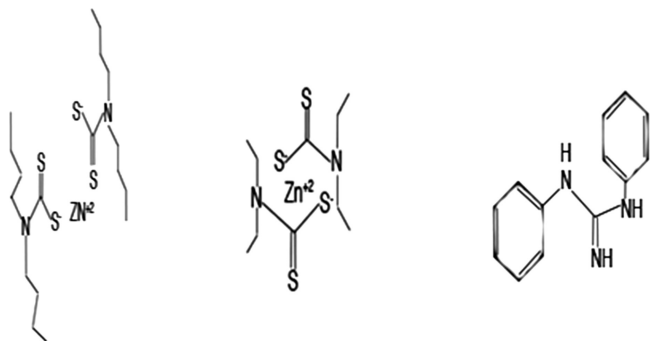


Figure 2. Chemical structures of the 3 chemicals in CM, zinc dibutyldithiocarbamate, zinc diethyldithiocarbamate, and diphenylguanidine, respectively.

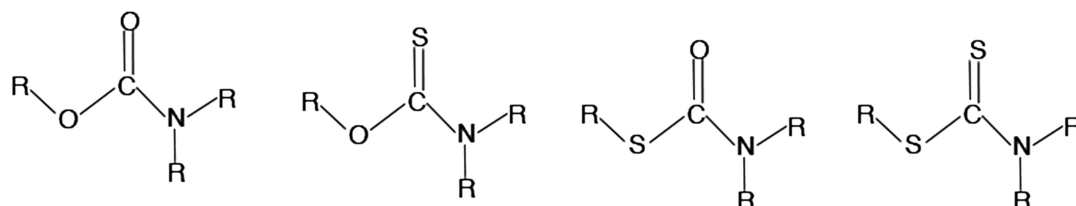


Figure 4. General chemical structures of carbamates: carbamate, O-organyl thiocarbamate, S-organyl thiocarbamate, and dithiocarbamate, respectively.

face, leg, and age >40 years [MOAHLFA]⁶) are listed in Table 1. Patients allergic to IPBC had lower rates of occupationally related skin disease (9.3%) as compared with those patients allergic to CM alone (31.8%) or both allergens (25%). The rate of dermatitis involving the hands was higher in the CM-positive group (50%) as compared with the other 2 groups (30% IPBC only and 33% both).

Reaction Strength of Final Reading

Table 2 shows the reaction strength grading of the final patch test readings. Most of the reactions to CM and IPBC were only doubtful or weakly positive (>69%). Of the 51 patients who reacted to both allergens, most (58%) had doubtful or weakly positive reactions to both allergens (Table 3).

Approximately 5% of the patients who had allergic reactions to CM also had allergic reactions to IPBC, whereas approximately 15% of the patients who had allergic reactions to IPBC also had allergic reactions to CM.

Statistical Association of Reactions to CM and IPBC

In the subgroup of patients who had at least 1 positive patch test reaction ($n = 17,181$), there was a statistically significant association between positivity to CM and IPBC ($P < 0.0001$; Table 4). Patients who had a positive reaction to CM were 2.6 times more likely to also have a positive reaction to IPBC than those who were

not positive to CM (95% CI, 1.97–3.52). The converse was also true as shown in Table 5; patients who had a positive reaction to IPBC were 2.4 times more likely to also have a positive reaction to CM than those who were not positive to IPBC (95% CI, 1.89–3.16). Because both CM and IPBC are known marginal irritants and this statistical association could be due to correlation within a patient population with a low threshold for irritant reactions, we also compared CM and IPBC positivity with 2 other known marginal irritants (fragrance mix I and formaldehyde). Although there was no statistical association between either IPBC or CM and fragrance mix I positivity, there was a statistically significant association with formaldehyde positivity.

DISCUSSION

This analysis of concomitant reactions to IPBC and CM found that there was a statistical association of positivity between these 2 allergens. We do not think that this statistical association is equivalent to clinical cross-reactivity or coreactivity; we believe that this association is due to the fact that both IPBC and CM are low-grade irritant patch test preparations. This hypothesis is supported by 3 arguments: (1) the structure of CM and IPBC differs; (2) both CM and IPBC are low-grade irritants; and (3) low-grade irritants commonly cause borderline positive patch test reactions in the same patient.

Structural Differences

Although both IPBC and CM contain the word *carbamate*, their chemical structures are very different. Carba mix contains zinc

TABLE 1. MOAHLFA Index Data

Demographic Data	CM Positive (n = 1131)	IPBC Positive (n = 332)	CM & IPBC Positive (n = 52)
Male	445 (39.4)	102 (30.7)	27 (51.9)
Occupation related	360 (31.8)	32 (9.6)	13 (25.0)
Atopic dermatitis			
Asthma*	129 (11.4)	35 (10.5)	10 (19.2)
Eczema	204 (18.0)	39 (11.7)	6 (11.5)
Hay fever*	278 (24.6)	65 (19.5)	20 (38.5)
Hand†	560 (49.5)	104 (31.3)	17 (32.7)
Leg†	146 (12.9)	29 (8.7)	6 (11.5)
Face†	68 (5.5)	14 (4.2)	4 (7.7)
Age, >40 y	795 (70.3)	231 (69.6)	46 (88.5)

Values are presented as n (%).

The total number of patients evaluated by the NACDG during study period is 25,435.

*Not part of the MOAHLFA index.

†Up to 3 anatomical sites per patient coded.

TABLE 2. Strength of CM and IPBC Reactions

Demographic Data	CM	IPBC in 0.1% pet	IPBC in 0.5% pet
Doubtful	116 (10.3)	9 (11.1)	28 (10.5)
Weak (+)	671 (59.3)	52 (64.2)	183 (69.0)
Moderate (++)	273 (24.1)	14 (17.3)	37 (14.0)
Strong (+++)	60 (5.3)	4 (4.9)	16 (6.0)
Other	11 (1.0)	2 (2.5)	1 (0.4)
Total number of reactions	1131	81*	265*
Number of patients tested	25,398	20,237	9518

Values are presented as n (%), unless otherwise specified.

*Includes 14 patients allergic to both IPBC (0.1% pet and 0.5% pet).

TABLE 3. Highest Strength of Patch Test Reactions in Patients Positive to Both Allergens*

Carba Mix	Doubtful or Weak Reaction	Moderate or Strong Reaction
Doubtful or weak reaction	30 (58.8)	5 (9.8)
Moderate or strong reaction	11 (21.6)	5 (9.8)

Values are presented as n (%).

*Excludes 1 patient who had a reaction strength of "+" for CM, and the reaction strength was "++" for the first reading and "negative" for the second reading for IPBC in 0.5% pet (n = 51).

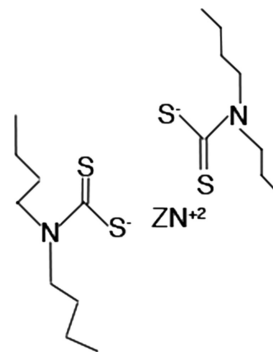
TABLE 4. Risk of Positivity for Patients With CM Allergy

Allergen Positivity	P	Risk Ratio (95% CI)
IPBC	<0.0001	2.64 (1.97–3.52)
Fragrance mix I	0.4501	0.95 (0.81–1.10)
Formaldehyde	<0.0001	1.41 (1.23–1.61)

diethyldithiocarbamate (Fig. 5), zinc diethyldithiocarbamate (Fig. 6), and diphenylguanidine (Fig. 7). As compared with these dithiocarbamates, IPBC has a very different structure (Fig. 1); IPBC contains an iodine atom but no sulfur. Given this lack of chemical structural similarity, cross-reactivity between these 2 allergens is unlikely.

Irritant Nature of IPBC and CM

Irritant patch test reactions can be impossible to clinically distinguish from weak positive patch tests. Even crescendo reactions may be irritant.^{7,8} Subsequent additional tests such as repeated open application tests, provocative use tests, and repeated patch testing with serial dilutions can help differentiate an irritant from a weak positive test. Some experts have advocated patch testing with a known irritant such as sodium lauryl sulfate.⁹ Others advocate caution when patch testing with antigens that mathematical measures have identified as problematic patch test preparations.¹⁰ The 2 commonly cited measures are the PR and the reaction index (RI). Our group previously identified a list of the most problematic patch test preparations (PR, >55 and RI, ≤ 0.46), which included IPBC in 0.1% pet, IPBC in 0.5% pet, and CM (PR, 74.7, 70.9, 69.4 and RI, 0.11, −0.06, 0.36, respectively).² The Information Network of Departments of Dermatology evaluated 4 different concentrations of IPBC (0.1%, 0.2%, 0.3%, and 0.5%) and

**Figure 5.** Chemical structure of zinc dibutyldithiocarbamate.

calculated the following: PR, 87, 100, 88.2, 85.5 and RI, −0.23, −0.21, −0.39, −0.58, respectively.¹¹

Brasch and colleagues¹¹ evaluated the association of irritant reactions to 0.5% sodium lauryl sulfate and reactions to either 0.2% or 0.3% IPBC. Approximately half of the patients with doubtful reactions to IPBC had irritant reactions to sodium lauryl sulfate, a rate which was double that of those patients with negative reactions to IPBC. In our study, 58% of the patients who reacted to both CM and IPBC had doubtful or mildly positive (+) reactions to both allergens as shown in Table 5.

Evaluation of Concomitant Reactions With Structurally Unrelated Controls

We arbitrarily chose 2 structurally unrelated common irritants, formaldehyde and fragrance mix I, as controls. Formaldehyde was originally tested at 2% aqueous but then lowered to 1% aqueous,¹² and the concentration of fragrance mix I was decreased from 16% to 8% because of high rates of irritant reactions. Some experts continue to argue that both of these lower concentration allergen preparations are still irritating.^{13,14} Our analysis found that positivity to IPBC or CM was statistically associated with formaldehyde positivity but not with fragrance mix I positivity. This could be due to the fact that formaldehyde is a problematic allergen (PR, 69.4 and RI, 0.36), whereas fragrance mix is acceptable (PR, 52.9 and RI, 0.60).² However, coreactivity could also result as both IPBC and formaldehyde/formaldehyde-releasing preservatives that may be found in the same preparations; Brasch and colleagues¹¹ reported statistical association of IPBC with formaldehyde, methyldibromoglutaronitrile/phenoxyethanol, and

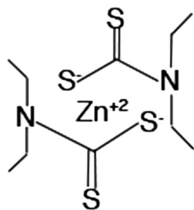
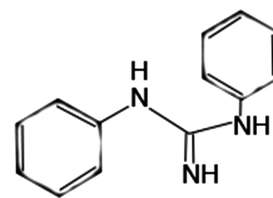
**Figure 6.** Chemical structure of zinc diethyldithiocarbamate.**Figure 7.** Chemical structure of diphenylguanidine.

TABLE 5. Risk of Positivity for Patients With IPBC Allergy

Allergen Positivity	P	Risk Ratio (95% CI)
CM	<0.0001	2.44 (1.89–3.16)
Fragrance mix I	0.2163	1.17 (0.92–1.49)
Formaldehyde	0.0047	1.44 (1.012–1.83)

methylchloroisothiazolinone/methylisothiazolinone. In contrast to our study, Brasch et al¹¹ also found that fragrance mix I positivity was statistically associated with IPBC positivity.

Different Allergen Sources Make Coreactivity Unlikely

Iodopropynyl butylcarbamate is a preservative primarily found in liquid products. Carba mix constituents are accelerators found in rubber products. Because these sources are very different, coreactivity is unlikely.

LIMITATIONS

There are several limitations to this study. The ideal study design for cross-reactivity would involve an adequately powered group of patients who are positive to CM but never exposed to IPBC who subsequently are patch tested to IPBC and several other control allergens. Similarly, the same study should be done using patients who are positive to IPBC but never exposed to CM. Our data are cross-sectional, and because of the referral case mix, in most cases, confirmatory tests for doubtful and mild reactions (repeated open application tests, provocative use tests, and testing with serial dilutions) were not feasible. Therefore, positivity was usually determined clinically based on crescendo pattern, clinical appearance, and patient history. Because borderline positive patch test reactions and irritant patch test reactions are difficult to differentiate on morphology alone, the past experience of the clinician may influence how the reaction is coded. Finally and most importantly, statistical significance is not equivalent to clinical significance.

CONCLUSIONS

In summary, although there was a statistically significant association, concomitant reaction rates of CM and IPBC were low. Only 5% of the patients who had allergic reactions to CM also had allergic reactions to IPBC. Only 15% of the patients who had allergic reactions to IPBC also had allergic reactions to CM.

Concomitant reactions to IPBC and CM are most likely due to the borderline irritant nature of both of these allergen preparations rather than true coreactivity or structural cross-reactivity.

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