

Specific IgG response to monomeric and polymeric diphenylmethane diisocyanate conjugates in subjects with respiratory reactions to isocyanates

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Background: Isocyanates are a frequent cause of occupational asthma and can also induce hypersensitivity pneumonitis.

Objectives: It is still unclear whether antibodies to diphenylmethane diisocyanate (MDI), which are elicited in some subjects with these conditions, are specific for this type of isocyanate. Moreover, preparation of conjugates to human serum albumin (HSA) with the polymeric formulation rather than monomeric MDI might result in improved detection of antibodies.

Methods: We addressed these issues by testing the sera of 13 subjects with asthma (n = 12) and hypersensitivity pneumonitis (n = 1) induced by MDI (n = 4 or 5, see below) by comparing them with sera obtained from subjects with occupational asthma caused by toluene diisocyanate (TDI; n = 5) and hexamethylene diisocyanate (HDI; n = 2). Conjugate preparations were compared by using SDS-PAGE, absorbance spectral analysis, and isoelectric focusing. Immunologic screening was done by ELISA.

Results: Specific IgG antibodies that recognize MDI-HSA conjugates were detected in all but 1 of the MDI-exposed workers and could not be found in TDI-exposed and HDI-exposed workers. The levels of specific IgG antibodies were more elevated when tested against the HSA conjugates formed with polymeric MDI compared with the HSA conjugates formed with monomeric MDI.

Conclusion: This study shows that specific IgG antibodies to MDI appear to be specific for MDI without cross-reactivity with TDI and HDI and higher by use of polymeric rather than monomeric MDI-HSA test antigens. (*J Allergy Clin Immunol* 1999;103:749-55.)

Key words: Occupational asthma, isocyanates, specific IgE, specific IgG

Abbreviations used

HDI: Hexamethylene diisocyanate
HSA: Human serum albumin
MDI: Diphenylmethane diisocyanate
OA: Occupational asthma
TDI: Toluene diisocyanate

In the early 1950s, Fuchs and Valade¹ were the first to identify subjects who reported respiratory symptoms on exposure to toluene diisocyanate (TDI). This report does not clearly establish whether the reaction was caused by a type of sensitization to isocyanates or by exposure to irritant concentrations of these compounds. Isocyanates are now the leading cause of occupational asthma (OA) caused by low molecular weight agents in most developed countries.² Isocyanates can also cause hypersensitivity pneumonitis.^{3,4} Models of sensitization to isocyanates in animals have been developed, as reviewed by Bernstein.⁵ However, the relevance of these models to OA or hypersensitivity pneumonitis induced by isocyanates in humans is uncertain. It is not clear, in particular, whether the fact of inducing the production of specific IgG or IgE antibodies is related to the development of disease at a later stage.

High levels of specific IgG antibodies have been documented in subjects with hypersensitivity pneumonitis caused by isocyanates.⁶ However, there are still controversial reports on the role of specific IgE antibodies⁷⁻¹⁰ in asthma caused by isocyanates. We previously documented a satisfactory association between isocyanate-induced asthma confirmed by specific inhalation challenges and specific IgG, but not IgE, antibodies.¹¹ Others recently reported that increased specific IgE was highly specific for the disease.¹²

Although respiratory cross-reactivity to various types of isocyanates has been documented by inhalation challenges,^{13,14} there are discrepancies on possible immunologic cross-reactivity.^{15,16}

Commercial preparations of diisocyanates exist in the form of many varied compositions.² For example, TDI can be found as the isomeric mixture of monomeric TDI

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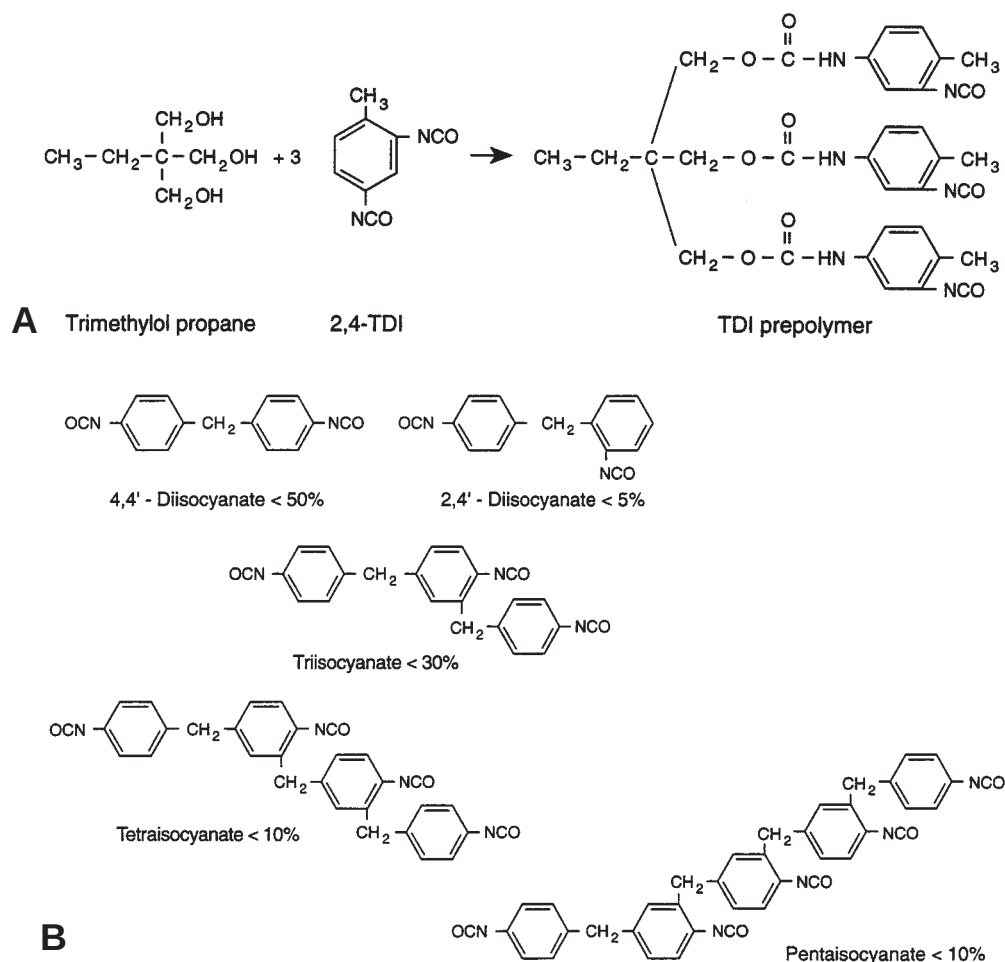


FIG 1. **A**, Structure of monomeric and prepolymeric TDI. **B**, Structure of monomeric and polymeric MDI.

or in a prepolymeric formulation composed of monomeric TDI, polyols, and their prepolymeric products (Fig 1, A). Diphenylmethane diisocyanate (MDI) can exist as the isomeric mixture of monomeric diisocyanates, but the predominant commercial formula is a mixture of monomeric and polymeric MDI (Fig 1, B) resulting from its bulk synthesis. It has been shown that prepolymers of TDI¹⁷ and polymeric MDI¹⁸ can cause OA. The presence of antibodies resulting from isocyanate exposure has been assessed until now by using conjugates to the monomers and polymers of isocyanates without specific characterization of the conjugate in terms of the proportion of monomeric and polymeric isocyanates (Fig 1, A and B). It is therefore possible that the difficulty in demonstrating specific antibodies could be related to a lack of information on the proportion of monomers and polymers.

We therefore examined the levels of specific IgG antibody responses to conjugates prepared from both monomeric and polymeric MDI in sera from subjects with asthma and hypersensitivity pneumonitis caused by MDI exposure. We used sera from subjects with OA to TDI and hexamethylene diisocyanate (HDI) as controls.

METHODS

Subjects

We assessed the sera of 13 subjects with OA or hypersensitivity pneumonitis caused by isocyanates (Table I). The sera of these subjects were not selected on the basis of the presence or absence of specific IgE antibodies to the relevant isocyanate. These sera were obtained at the time of the isocyanate challenge test that confirmed the diagnosis. The diagnosis was made within 3 months of cessation of exposure in all instances. Challenge tests were carried out by using a standardized methodology in small cubicles or with a closed-circuit apparatus^{19,20} that allowed us to determine the dose required to elicit a significant change in FEV₁. Exposure in the closed-circuit apparatus was carried out with the isocyanate generated as a vapor, thereby exposing the subject primarily to the monomer. Exposure in small cubicles was performed by exposing the subject to the isocyanate generated as an aerosol, this time liberating monomers and prepolymers, with these latter compounds existing in aerosol form but only minimally in vapor form.²¹

Chemicals

Human serum albumin (HSA) was purchased as a dry powder from Sigma Chemicals Co (St Louis, Mo). The globulin and fatty acid fraction V form was used without further purification. Monomeric diisocyanates, 2,4'-TDI and 4,4'-MDI, were obtained from Fluka Chimie AG (Buchs, Switzerland) and Bayer, Inc (Pitts-

TABLE I. Clinical and functional characteristics of the test subjects

Patient no	Sex	Age	Atopy (y)	Duration of exposure (y)	Duration of symptoms (y)	FEV ₁ (% pre-dicted)	Specific inhalation challenge		
							Type of isocyanate	Dose (ppb-min)	Reaction
161	M	32	—	14	1.5	105	TDI (mixture +)	284	Late
162	M	58	+	25	15	137	TDI (mixture +)	9	Late
163	M	37	—	12	4	98	TDI (mixture +)	2040	Late
164	M	56	—	15	2	83	TDI (polymer +, mixture +)	—	Late
167	M	35	—	3	1	105	TDI (polymer +, mixture +)	3504	Late
159	M	29	—	7	1	98	MDI (mixture +)	—	Hypersensitivity pneumonitis
160	F	32	—	0.5	0.25	91	MDI (mixture +)	22	Late
165	F	36	—	9	1	111	MDI (mixture +)	124	Late
168	F	50	+	1.5	0.9	111	MDI (polymer +, mixture +)	2220	Late
169	M	54	—	22	1	95	MDI (polymer +, mixture +)	534	Immediate
157	M	37	—	19	4	101	HDI (polymer —, mixture +)	84	Immediate
158	M	49	+	35	9	92	HDI (polymer —, mixture +)	1836	Immediate
166	M	47	+	30	7	73	IPDI (MDI) (polymer —, mixture +)	73	Dual

Atopy was present if at least 1 immediate skin reaction to 15 common inhalants was present (see text for reference values of FEV₁). Immediate and late reactions were defined as the maximum fall in FEV₁ occurring in the first or after the first hour, respectively. Hypersensitivity pneumonitis was defined as the appearance of fever and leucocytosis without significant changes in FEV₁ (less than 10%). In the case of specific inhalation challenges, reaction to the polymer means that the subject reacted or did not react when exposed to the isocyanate generated as a vapor, and reaction to the mixture means that the subject reacted on exposure to isocyanate generated as an aerosol.

burgh, Pa), respectively. Polymeric MDI (PAPI 27) was obtained from Dow Chemical Co (Midland, Mich), and a prepolymeric TDI varnish (PolyUr MC55) was obtained from Robar Inc (Montreal, Canada). Peroxidase-labeled, goat anti-human immunoglobulins were purchased from ICN (Costa Mesa, Calif). Acetone and acetonitrile were HPLC grade (J. T. Baker, Philipsburg, NJ). All other chemicals were reagent grade and were purchased from local suppliers.

Test conjugate preparation

MDI test conjugates were prepared by adding neat MDI to a stirring solution of HSA at pH 9.2. The initial concentration of HSA was 5 mg/mL, and the final ratio of MDI to protein in each reaction mixture was 400:1. All reactions were performed at room temperature. Conjugates 68 (monomeric MDI) and 78 (polymeric MDI) were allowed to react for 1 hour before quenching by dialysis against PBS and filtration to remove precipitated protein. Conjugate 82 was prepared in the same way; however, the reaction time was extended to 24 hours. Liquid-phase diisocyanate additions were performed with calibrated glass micropipettes.

The protein concentration of each test conjugate solution was determined by the Lowry method.²² Concentrations were adjusted by dilution or limited evaporation on a speed-vac system. Unmodified HSA samples were used as controls to generate the calibration curve.

Aliquots of the test conjugates were subjected to SDS-PAGE, according to the procedure of Laemmli,²³ with a 10% acrylamide resolving gel. The gels were stained with Coomassie Blue and destained in an acetic acid/isopropanol/water solution. Unmodified HSA and Sigma prestained protein molecular weight markers were used for relative molecular weight determination.

The test conjugate samples were also subjected to isoelectric focusing under denaturing conditions, according to the procedure of Robertson et al.²⁴ The gels were fixed with trichloroacetic acid, stained with Coomassie blue in methanol/acetic acid, and destained in an acetic acid/isopropanol/water solution. Unmodified HSA and Sigma isoelectric protein standards were used to determine the relative isoelectric point.

To evaluate the spectral properties of the test conjugates, we performed UV spectral scans over the wavelength from 310 to 190 nm on a sample of each conjugate with a Perkin Elmer UV-VIS spectrophotometer. Direct scans and difference spectra relative to unmodified HSA were characterized.

Aliquots of the test conjugates were placed in multiwell plates and incubated at 37°C for 1 hour and then incubated at 4°C overnight. Serial dilutions of the human serum samples were performed, and the plate development was done according to the procedure of Engrall and Perlman.²⁵ Quantification of responses was performed with an ELISA plate reader. ELISA screening was performed in quadruplicate for each conjugate/serum pair. Results were averaged, and standard deviations are indicated.

RESULTS

Baseline clinical and functional characteristics of the subjects whose sera were included in this study are given in Table I. The majority of the 13 subjects were not atopic. Duration of exposure varied from half a year to a maximum of 35 years, whereas duration of symptoms at the time of diagnosis varied from 3 months to 15 years. Except for 1 subject (no 166), baseline FEV₁ was 80% or

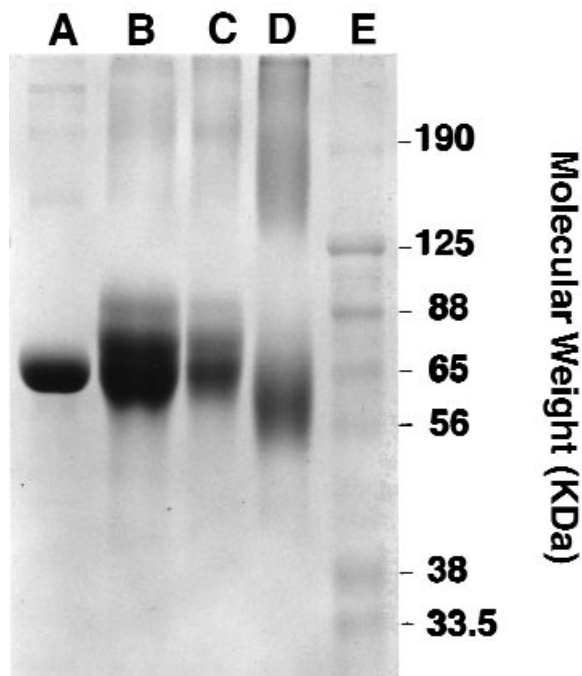


FIG 2. SDS-PAGE analysis of MDI test conjugates. Conjugates were analyzed on a 10% SDS-PAGE gel. Lane A, HSA; lane B, conjugate 68; lane C, conjugate 78; lane D, conjugate 82; and lane E, mixture of protein standards, with indicated molecular weight scale given on right margin.

greater at the time of challenge. The majority of subjects reacted to the mixture of isocyanates (containing monomers and prepolymers) generated in aerosol form. For some subjects (numbers 164, 167, 168, 169, 157, 158, and 166), we were able to know whether they were specifically reactive to the monomers or prepolymers by exposing them to the isocyanates generated as vapor. Among subjects exposed to MDI, all showed a late reaction after inhalation challenge, except for subject number 169, who had an isolated immediate reaction.

Monomeric and polymeric MDI-based materials were used to synthesize HSA conjugates for evaluation of the effect of these differential forms on immunologic response detection. Approximately 50% of the polymeric material used consisted of the monomeric 4,4'-MDI. Monomeric and polymeric conjugates were made, and the aqueous soluble fraction was characterized and used for ELISA screening. SDS-PAGE of these modified proteins illustrated both intramolecular and intermolecular structural modifications, with an enhancement of intermolecular cross-linking in the polymeric-modified sample that is further increased with extended reaction time (conjugate 78 vs 82) (Fig 2). Comparison of the absorbance profiles that were normalized for protein content relative to the absorbance at 278 nm showed variable levels of aromatic ring incorporation, as evidenced by the difference in absorbance at 254 nm. Isoelectric focusing of the monomeric conjugate provided evidence of protein

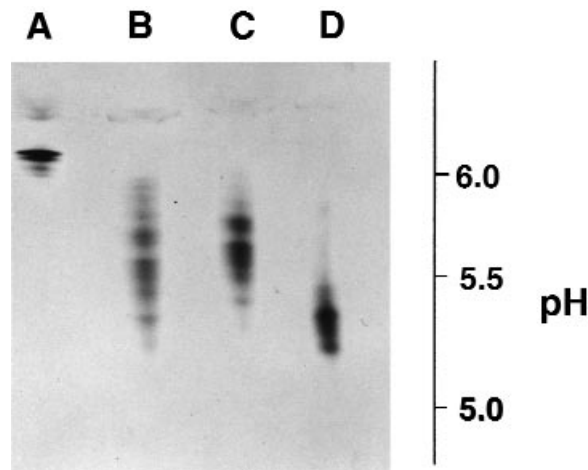


FIG 3. Isoelectric focusing analysis of MDI conjugates. Isoelectric separation of conjugates over the pH range of 5.0 to 6.5. Lane A, HSA; lane B, conjugate 68; lane C, conjugate 78; and lane D, conjugate 82. The pH scale is based on direct measurement of pH in the gel at the conclusion of separation.

modification (Fig 3). An increase in sample heterogeneity was seen in the MDI conjugate, as was an overall decrease in isoelectric point relative to unmodified HSA. The isoelectric point decrease is consistent with amino group modification, which would be a favored reaction under the pH conditions during conjugation (pH 9.2).

Immunologic screening for specific IgG for each of the representative MDI conjugates is summarized in Fig 4. MDI-HSA conjugates at various formulations shows high relationship in workers' serum with MDI-induced respiratory disease. The one exception to this finding was seen in subject number 169, who was the only one in the MDI group to show an isolated immediate reaction (Table I, see above). Minimal cross-reaction was observed when the same MDI conjugates were used to screen worker sera from TDI and HDI exposures. The one exception in this analysis is the response of subject number 167, who shows a high response to the MDI conjugates and an equally high response to control unmodified HSA. In addition, the levels of specific IgG were higher for the polymeric MDI conjugate than for the conjugates made with monomeric MDI.

DISCUSSION

This study shows that specific IgG antibodies to MDI were (1) specific for MDI without cross-reactivity with TDI and HDI and (2) higher by use of polymeric, rather than monomeric, MDI-HSA test antigens.

Few studies have examined the possibility of immunologic cross-reactivity between different types of isocyanates. Grammer et al¹⁵ examined the specificity of IgG antibodies against TDI-HSA, MDI-HSA, and HDI-HSA by inhibition studies with a variety of isocyanate hapten carriers. Complete inhibition was found when using HSA conjugated with the type of isocyanate that

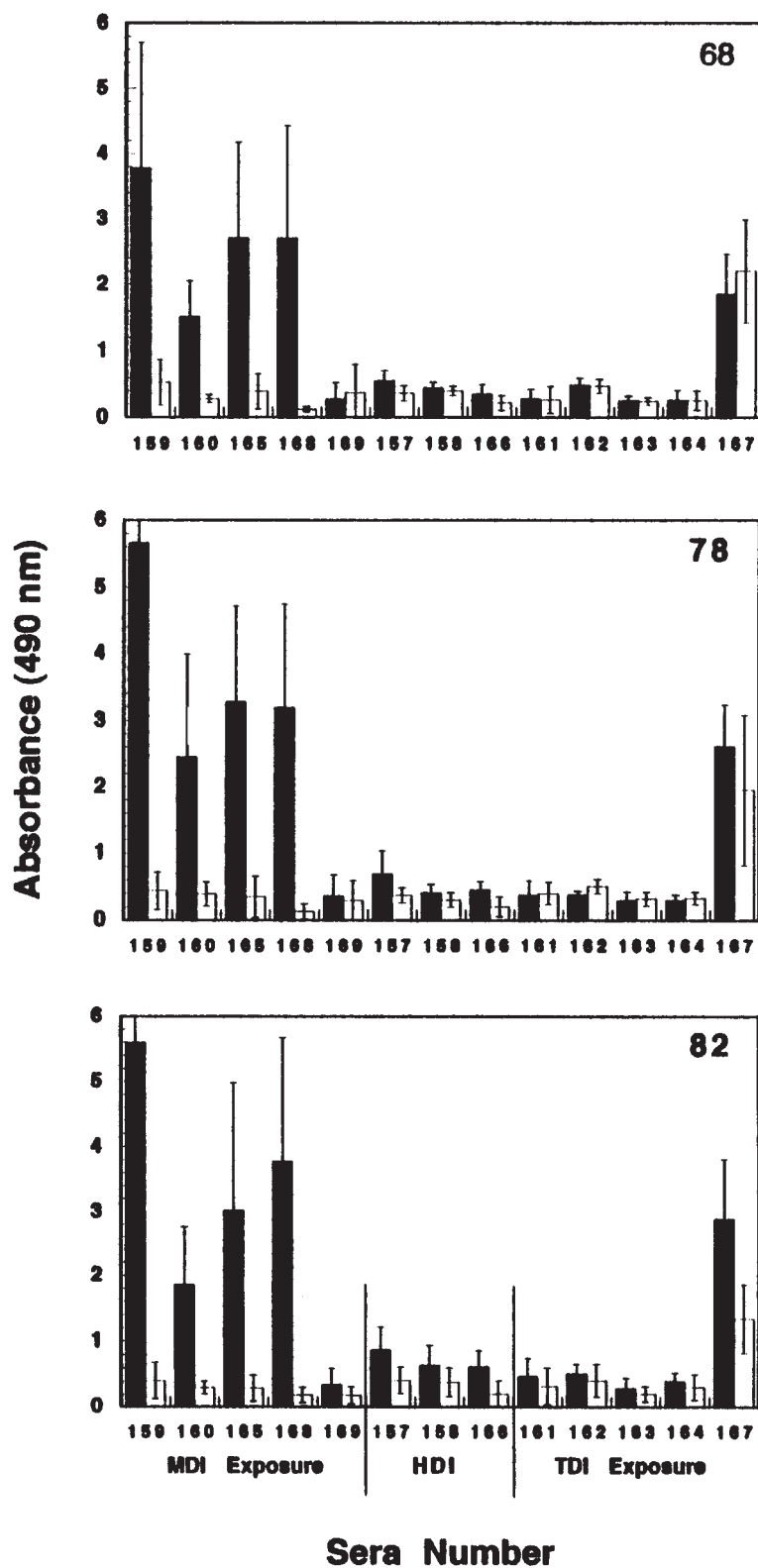


FIG 4. ELISA results of sera tests with MDI test conjugates. **A**, 4,4' monomeric MDI-HSA conjugates (number 68); **B**, 1-hour reaction time, polymeric MDI-HSA conjugate (number 78); **C**, 24-hour reaction time, polymeric MDI-HSA conjugate (number 82). *Filled bars* indicate response to test conjugates, and *open bars* indicate response to unmodified HSA.

caused asthma, whereas inhibition was absent or partial with the other types of isocyanates. More recently, Lushniak et al¹⁶ found that 6 workers who had IgG antibodies specific for one diisocyanate-HSA conjugate showed cross-reactivity to antigens prepared with other diisocyanates.

Although some authors found increased levels of specific IgE antibodies in subjects with OA caused by isocyanates,^{12,26} there is more agreement on the presence of higher levels of specific IgG antibodies, especially for MDI and HDI.^{11,27} Subjects with hypersensitivity pneumonitis generally have the highest levels.^{6,28,29} The only subject with hypersensitivity pneumonitis (number 159, Table I) had the highest levels of specific IgG. Our study was not aimed at examining the validity of assessing specific IgE or IgG in the diagnosis of OA and hypersensitivity pneumonitis. The fact that all but 1 of our subjects exposed to MDI showed increased specific IgG antibodies to MDI may not only reflect the disease they were affected with (asthma and hypersensitivity pneumonitis) but also the type of exposure.

Several models can be proposed to explain the enhanced responses when polymeric, compared with monomeric, test conjugates are used to measure the level of specific IgG antibodies in MDI-exposed individuals. First, the conjugates made by using polymeric MDI are structurally more relevant to the potential stimulating antigen because the polymeric MDI more closely mimics the commercial starting material to which the patients may have been exposed. Second, an indication of a positive correlation between the increased antibody response comparing conjugates 68, 78, and 82 in MDI-exposed individuals (Fig 4) with the degree of increased structural heterogeneity of the conjugates (Figs 2 and 3) supports a model of complex structural change resulting from greater reaction with the complex polymeric MDI as a key to antigen presentation. A third explanation for the increased antibody response to commercial polymeric MDI could be the presence of HSA conjugates formed as the result of reaction of the HSA with other components in the original crude polymeric-MDI mixture. Although the major components of the typical polymeric MDI are described (Fig 1, B), other components such as residual amounts of aniline, formaldehyde, polyamines, and phenylisocyanate used or created during polymeric-MDI synthesis³⁰ may result in modification of HSA and thus formation of unique conjugates.

This study has practical implications. First, although there are cross-reactions on bronchial challenges with different types of isocyanates, as originally reported by O'Brien et al,¹⁴ IgG antibodies seem specific for this type of isocyanate, at least in the case of MDI-induced respiratory reactions and/or exposure. We therefore suggest assessing specific IgG antibodies to MDI by using MDI-HSA conjugates rather than HDI-HSA or TDI-HSA conjugates. Second, higher levels of specific IgG antibodies are likely to be detected by using a polymeric conjugate. This could allow for better separation between diseased individuals and control subjects and would war-

rant comparisons in a larger number of individuals exposed to MDI with or without related respiratory diseases.

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The following correction applies to the practice parameter by Spector et al entitled "Parameters for the diagnosis and management of sinusitis," which appeared in volume 102, number 6, part 2, pp S107-S144, 1998, of The Journal.

On p S140, the second-to-last paragraph before the references cites reference 15 as being conducted with "nasal flunisolide." The actual drug used was "nasal budesonide."