

Antibodies and Immune Profiles of Individuals Occupationally Exposed to Formaldehyde: Six Case Reports

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Six patients with multiple subjective health complaints, which have been correlated with chronic exposure to formaldehyde during the course of their education and occupations, were tested for the existence of antibodies (IgE, IgM, and IgG) to formaldehyde (F) conjugated to human serum albumin (F-HSA). In addition, the percentage and absolute numbers of peripheral lymphocyte subpopulations as determined by surface markers were investigated. Antibody titers to F-HSA were present as follows: IgE (2 patients), IgM (3 of 4 tested patients), and IgG (5 patients). Analysis of lymphocyte subpopulations showed T-helper/suppressor (H/S) ratios ranging from 0.8 to 3.3. All 6 patients had elevated Tal cells (antigen memory cells), whereas interleukin 2 receptor positive cells were within expected values. Following formaldehyde exposure, 5 of the patients complained of an initial flulike illness from which they have not completely recovered. The sixth individual had a history of recurrent respiratory infections and surgical removal of hyperplastic ethmoid sinus tissue. The common occurrence of anti-F-HSA antibodies, flulike illness, and Tal cells are interpreted as suggestive of a chronic antigenic stimulation of the immune system in these 6 patients. Further immunological work-up of additional subjects and immune parameters with similar history of formaldehyde exposure and subjective health complaints is warranted.

Key words: formaldehyde, albumin, antibodies, Tal cells, immune activation, flulike illness

INTRODUCTION

Formaldehyde conjugates with human serum albumin (F-HSA), forming a new antigenic determinant [Horsfall, 1934; Pass and Marcus, 1970]. Subsequently, anti-F-HSA IgE, IgM, and IgG antibodies have been demonstrated in experimental animals and humans in a variety of exposures. Antibodies to F-HSA of all isotypes have been found in dogs [Patterson et al., 1985], formaldehyde anaphylaxis [Marucie et al., 1986], in hemodialysis patients [Patterson et al., 1986], in mobile home dwellers [Thrasher et al., 1987; Broughton and Thrasher, 1988], in occupational exposures [Wilhelmsson and Holmstrom, 1987] and in other environmental settings [Broughton

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and Thrasher, 1988]. In addition, modulations of cell-mediated immunity following inhalation exposure to formaldehyde have been reported. Pross et al. (1987) found increases in eosinophils, basophils, and T-suppressor cells resulting from acute formaldehyde inhalation in patients with suspected asthma from ureaformaldehyde foam insulation. Other parameters of the immune profile, such as phytohemagglutinin stimulated mitogenesis, H/S ratios, and NK cells, were unchanged. On the other hand, individuals chronically exposed to formaldehyde in mobile homes have been shown to have perturbations in peripheral T-cells effecting total numbers, H/S ratios, mitogen (PHA, ConA, and PWM) stimulation, and Tal cells [Thrasher et al., 1987; Broughton and Thrasher, 1988].

In this study we report the existence of IgE, IgM, and IgG antibodies to F-HSA as well as modulations in lymphocyte subsets in 6 individuals occupationally exposed to formaldehyde. In addition, these patients have ongoing health problems similar to those described in workers with multiple chemical sensitivities [Cullen, 1987].

MATERIALS AND METHODS

Patients

Six patients with ongoing multiple health complaints were obtained as follows: 2 (patients 1 and 2) volunteered after learning of our work from mutual colleagues and 4 (patients 3 to 6) were referred by attending physicians for diagnostic testing. Each of the patients has had numerous physical examinations and diagnostic tests (SMAC 24, urinalysis, CBC, EKG, EEG, respirometry, chest X-rays, etc.) to determine the cause of their health complaints. The etiology to their illness had not been resolved. It was felt (by physicians as well as patients) that their health problems were related to formaldehyde exposure.

Patient 1. This male, age 49, a lifetime nonsmoker, had a history of asthma since his late teens when he worked as an animal technician. He had been a mortician since the age of 27 with daily exposures to formaldehyde, reaching concentrations as high as 4 ppm. At the age of 33 he experienced an exacerbation of the asthma, followed by ethmoid sinus surgery for removal of hyperplastic tissue at age 35. His present health is marked by an aggravation of asthma, frequent respiratory infections, malaise, and an increase in olfactory acuity to a variety of odors. His medicinal regimen consists of Prednisone (10 mg/day as needed), with the following inhalators: Vanceriol, Ceclovent, and Alupent. He continues to work as a mortician. He had not used Prednisone for 2 to 3 weeks prior to diagnostic testing.

Patient 2. This male, age 33, a life-time nonsmoker, has had a history of asthma and allergies. Shortly after commencing teaching obligations in human anatomy with ambient formaldehyde reaching to about 2 ppm, he experienced a severe exacerbation of his asthma. The episode was characterized by an initial flulike illness followed by chronic malaise, from which he has not completely recovered. Additional health complaints were loss of physical stamina, nausea, loss of appetite, muscle spasms, and frequency of urination. He also stated that a marked increase in acuity of hearing and olfaction is present. Cacophony is bothersome where it used to be tolerated. Odors, such as perfume, formaldehyde, tobacco smoke, bleach, diesel exhaust, etc., once tolerated, now aggravate his health, precipitating symptoms. Initially he was prescribed Prednisone to control the asthma. Currently he uses the following medications: Terbutaline, Albuterol, Vanceriol, Cromolyn Sodium, and

Theodal. Upon recommendation by his pulmonologists, he avoided teaching human anatomy 9 months prior to testing. However, he occasionally perfused research animals with solutions of paraformaldehyde and glutaraldehyde while wearing a formaldehyde respiratory mask (3M Corp.). According to the patient, avoidance of formaldehyde has permitted some improvement in his health.

Patient 3. This male, age 41, originally smoked a pipe, but was a nonsmoker for several years prior to testing. He had practiced pathology for 15 years. As a medical student, age 22, he developed asthmatic symptoms while studying human anatomy. The asthma was exacerbated as a pathologist where breathing zone estimates of formaldehyde were 2 to 4 ppm. He eventually experienced a flulike illness, from which he has not completely recovered. Additional health complaints included eye irritation, skin rash, rhinitis, sinusitis, headaches, loss of memory, inability to complete current tasks, dizziness, gastrointestinal problems, left chest pains, and heart palpitations. He also complained of altered taste (metallic) and smell. Odors, such as diesel exhaust, perfumes, new carpeting and formaldehyde, aggravated his health, bringing on CNS symptoms and wheezing. Currently, he is on complete work disability and uses the following medications: Azma Cort, Albuterol, and Theodur.

Patient 4. This 28-year-old female is a smoker (about 6 cigarettes per day), whose only allergy history was a documented reaction to penicillin. Her first exposure to formaldehyde was while taking a course in human anatomy, at which time she began experiencing a flulike illness. Her occupation (physical therapist) required daily sterilization of spas with formaldehyde. In addition, she purchased a condominium with particle board subflooring, new carpets, draperies, and fresh paints. She was initially diagnosed as possible formaldehyde exposure because of IgG (1:128) anti-F-HSA antibodies 6 months prior to this testing. At that time she was advised to avoid formaldehyde exposure. However, she continued to have episodes that were eventually associated with a faulty gas heating system, which was shown to emit carbon monoxide and formaldehyde. Her health complaints included eye irritation, skin rash, headaches, dizziness, memory lapse, depression, G.I. disturbances with diarrhea, dysmenorrhea, vaginitis, and urinary frequency. She stated that ambient conditions containing reactive airborne chemicals (formaldehyde, perfumes, diesel exhaust, etc.) brought on CNS symptoms. She was initially prescribed Penicillin for her flulike condition and has taken only Tylenol when needed. Currently, she has returned to graduate studies, and avoids reactive environments as much as possible through recognition by olfactory stimulation.

Patient 5. This 50-year-old male and lifetime nonsmoker was an assistant professor of biology, teaching animal and human anatomy. He had no history of asthma or allergies prior to teaching. One year after initial formaldehyde exposure in the classroom (average concentration was 0.25 ppm), he was hospitalized several times for respiratory illness, which was initially diagnosed as restrictive lung disease with disability. His health complaints included an initial flulike illness accompanied with malaise, shortness of breath, joint pains, sore throat, rhinitis, sinusitis, dizziness, headaches, loss of memory, and inability to complete current tasks. One physician demonstrated a positive skin reaction to a subcutaneous injection of 5×10^{-3} M formaldehyde. The patient stated that various odors, such as new carpets, fresh paints, formaldehyde, perfumes, diesel exhaust, etc., exacerbated his health problems and brought on CNS symptoms. He is currently on complete disability and has lived for the past 3 years on the coast in Oregon, avoiding exposure to formaldehyde and

other airborne chemicals. One week prior to diagnostic testing he was exposed for several hours to new decorations that included paint, carpets, draperies, and luan paneling, which caused an immediate exacerbation of his health problems. He avoids use of medications.

Patient 6. This male, age 59, a lifetime nonsmoker, had no history of either personal or familial allergies and asthma. He worked in the following professions prior to establishing a Formica furniture manufacturing business: wholesale grocery, automobile dealership, and restaurant. Beginning at age 50 he had direct exposure to particle board and wood dust from Formica furniture. Approximately 1 year later he developed pulmonary problems, subsequently diagnosed as intrinsic asthma. Additional symptoms included rhinitis, sinusitis, headaches, malaise, and lingular pneumonia following a flulike illness from which he has not completely recovered. Currently, he is completely disabled. For the past few years he has avoided reactive airborne chemicals. Medications for the respiratory problems include Prednisone (10 mg/day alternating with 5 mg), Theodur, Berotect, Intal, and Ventolin.

Control Subjects

Control subjects consisted of 2 groups. (1) One hundred asymptomatic healthy adults were examined for antibody titers to F-HSA. These subjects were obtained as volunteers for a therapeutic drug trial. The sera, prior to the trial, were used for baseline titers. Previous exposure to formaldehyde was not determined; however, daily exposure to low concentrations of formaldehyde (<0.05 ppm) from polluted city air probably occurred. (2) Twelve healthy asymptomatic laboratory personnel were used as controls to establish baseline data on lymphocyte surface markers. One of the controls, a pathologist, age 51, had a history of exposure to formaldehyde as a medical student and pathologist. However, he had never developed formaldehyde-related symptoms.

F-HSA Conjugation and ELISA Antibody Assay

IgE, IgM, and IgG anti-F-HSA antibodies were determined by the ELISA procedure [Voller, 1979]. Formaldehyde conjugation with HSA and the ELISA antibody assays were done on sera from freshly drawn blood. The methods are published elsewhere [Broughton and Thrasher, 1988]. In brief, formaldehyde (3% in phosphate-buffered saline, PBS) was added drop-wise to 5% HSA/PBS until equimolar concentrations were obtained and then incubated at 37°C for 24 hours. The conjugate was dialyzed for 24 hours against PBS, and for an additional 24 hours against bicarbonate/carbonate buffer, pH 9.6. The conjugate (F-HSA) was stored frozen until used. If precipitation occurred during any portion of the procedure, the conjugate was discarded and started anew.

All ELISA incubations were carried out at 37°C. Microtiter plates (Falcon B.C., CA) were coated with either F-HSA (test plates) or HSA (control plates) at a dilution of 1:10 in bicarbonate buffer, pH 9.6. After 2 hours incubation, the plates were washed 3 times with PBS-Tween (0.5%, Sigma); 100 ml of appropriate dilutions of the test sera were pipetted onto the microtiter plates and incubated for 2 hours. The plates were then washed 3 times with PBS-Tween and 100 μ L of peroxidase labeled antihuman IgE, IgM, or IgG at optimum dilutions were pipetted. The plates were incubated for an additional hour, washed again in PBS-Tween and 50 μ L of substrate (orthophenyldiamine in citrate buffer, hydrogen peroxide, pH 5.0) were

added. The plates were left 15 minutes at room temperature in the dark. The enzyme reaction was stopped with 100 μ l of 4 N H₂SO₄. The resultant color was read with a microtiter reader (Dynatech) at 490 nm. The end point titer occurred when the optical density of the test (F-HSA) equalled that of the control (HSA) wells.

Lymphocyte Surface Markers

The total peripheral white cell count was performed using a Model F Coulter Counter (Coulter, FL). The total lymphocyte count was accomplished by blood smear examination. Lymphocyte surface marker procedures are published elsewhere [Broughton and Thrasher, 1988]. In brief, peripheral mononuclear cells were isolated using Ficoll Hypaque density gradient [Boyuma, 1968]. The percentages and absolute numbers of lymphocyte subsets were determined utilizing monoclonal antibodies to surface markers: LEU1 (T cells), LEU2A (T suppressor cells), LEU3A (T helper cells), and LEU10 (B cells) (Beckton-Dickinson, Los Angeles), and Tal positive and IL2 receptor cells (Coulter, FL). All surface markers, except Tal, were identified by indirect immunofluorescence [Engleman et al., 1981]. Tal cells were determined by using a direct immunofluorescent method [Fox et al., 1984].

RESULTS

The antibody titers present in the sera of the 6 patients are given in Table I. IgE titers were found in patients 3 and 4 at dilutions of 1:8 and 1:256, respectively. IgE titers were nondetectable in the other 4 subjects (1:4). IgM antibodies to F-HSA were present in 3 of the 4 patients tested as follows: patient 1 (1:64); patient 2 (1:16), and patient 5 (1:32). IgM titers were undetected in 1 subject (patient 6, 1:4) and not determined in the remaining 2 (patients 3 and 4). IgG anti-F-HSA antibodies were present in the sera of the 5 subjects as follows: patient 1 (1:64), patient 2 (1:32), patient 3 (1:32), patient 4 (1:16), and patient 5 (1:8), and nondetectable in patient 6(1:4). IgG anti-F-HSA titers were lowest in the 2 patients (5 & 6) who avoided exposure to F; IgG = 1:4 and 1:8, respectively. Anti-F-HSA isotypes were present in all 6 subjects.

Lymphocyte Surface Markers

Total peripheral white cell and lymphocyte counts as well as the percentage and absolute numbers of lymphocyte subpopulations for each of the 6 patients are given in Table II along with expected ranges for each parameter.

Patient 1 had WBC and lymphocyte counts of 18,300 and 5,124 cells per cmm. The percentage of lymphocyte subpopulations were distributed as follows: LEU1

TABLE I. IgE, IgM, and IgG Antibody Titers to Formaldehyde Conjugated to Human Serum Albumin in 6 Patients Occupationally Exposed to Formaldehyde

Antibody	Patients						Expected titers ^a
	1	2	3	4	5	6	
IgE	1:4	1:4	1:8	1:256	1:4	1:4	0.00-1:4
IgM	1:64	1:16	ND ^b	ND ^b	1:32	1:4	0.00-1:4
IgG	1:64	1:32	1:32	1:16	1:4	1:8	0.00-1.4

^aExpected titers were obtained from 100 asymptomatic adults.

^bNot determined because IgM assay was not available at the time of testing.

TABLE II. Percentage and Absolute Numbers of Peripheral Lymphocyte Subsets as Determined by Surface Markers in the 6 Patients Occupationally Exposed to Formaldehyde

Cell type	Patients												Expected ranges ^a	
	1		2		3		4		5		6		%	Abs
	%	Abs ^b	%	Abs	%	Abs	%	Abs	%	Abs	%	Abs		
Leu1	55	2,818	73	1,813	71	1,099	69	1,511	81	2094	65	1062	65-79	800-2,530
Leu3A	34	1,742	53	1,316	56	867	51	1,116	51	1318	42	686	35-55	480-1,185
Leu2A	41	2,101	29	720	17	263	36	788	31	801	27	441	20-36	220-865
Leu10	16	820	10	248	4	62	4	88	8	207	6	98	5-15	60-400
IL2	4	205	6	149	3	46	3	66	0	0	2	33	<8	<320
Tal	10	512	10	248	20	310	13	284	28	724	39	637	<4	<284
H/S	0.80		1.8		3.3		1.4		1.6		1.6		1.65-2.3	
WBCs	18,300		9,200		4,300		7,300		5,500		8,600		4,500-10,300 (Abs)	
Lymphs	5,124		2,484		1,548		2,190		2,585		1,634		1,500-4,000 (Abs)	

^aObtained from 12 asymptomatic healthy adults.

^bCells/cmm.

(55%), LEU3A (34%), LEU2A (41%), LEU10 (16%), IL2 receptor positive (4%), and Tal positive cells (10%). The absolute values for each of these cell types were 2,828, 1,742, 2101, 820, 205, and 512 cells/cmm, respectively. The H/S ratio was 0.80/1. All of the above values, except IL2 cells, were disparate (either higher or lower) to expected values.

Patient 2 had WBC and lymphocyte counts of 9,200 and 2,484 cells/cmm, respectively. The percentage of lymphocyte subpopulations were: LEU1 (73%), LEU3A (53%), LEU2A (29%), LEU10 (10%), IL2 (6%), and Tal (10%). The absolute numbers of these cell types were 1,813, 1,316, 720, 248, 149, and 248 cells/cmm, respectively. The H/S ratio was 1.8/1 because of elevated LEU2A in relation to LEU3A cells. Of these values, the absolute numbers of LEU3A and the percentage and numbers of Tal cells were above expected values.

Patient 3 had WBC and lymphocyte counts of 4,300 and 1,548 cells/cmm, respectively. The percentage of lymphocyte subpopulations were as follows: LEU1 (71%), LEU3A (56%), LEU2A (17%), LEU10 (4%), IL2 (3%), and Tal (20%). The absolute numbers of these cell types were 1099, 867, 263, 62, 46, and 320 cells/cmm, respectively. The H/S ratio was 3.3/1. These values showed a normal complement of T-cells with a reduction in the percentage of LEU2A cells, and an increase in cell types was 1,099, 867, 263, 46, and 310 cells/cmm, respectively. The H/S ratio was 3.3/1. The above values showed a normal complement of T-cells with a reduction in the percentage of LEU2A cells and an increase in the percentage of LEU3A cells, resulting in an elevated H/S ratio. Also, the percentage and absolute numbers of Tal cells were above expected values.

Patient 4 had WBC and lymphocyte counts of 7,300 and 2,190 cells/cmm, respectively. The percentage of lymphocyte subpopulations were as follows: LEU1 (69%), LEU3A (51%), LEU2A (36%), LEU10 (4%), IL2 (3%), and Tal (13%). The absolute values for these cells were 1,511, 1,116, 788, 88, 66, and 284 cells/cmm, respectively. The H/S ratio was 1.4/1. The Tal cells (percentage and numbers) were elevated above expected values. The H/S ratio was low because of an increase in LEU2A cells.

Patient 5 had WBC and lymphocyte counts of 5,500 and 2,585 cells/cmm, respectively. The percentage of lymphocyte subsets were as follows: LEU1 (81%), LEU3A (51%), LEU2A (31%), LEU10 (8%), IL2 (0%), and Tal (28%). The absolute numbers of these cell types were 2094, 1318, 801, 207, 0, and 724. The H/S ratio was 1.6/1. The Tal cells (percent and number) were elevated above expected values. In addition, the absolute number of LEU3A cells was elevated. The H/S ratio was on the low side of expected values because of an increase in LEU2A cells.

Patient 6 had WBC and lymphocyte counts of 8,600 and 1,634 cells/cmm, respectively. The percentage of lymphocyte subsets were as follows: LEU1 (65%), LEU3A (42%), LEU2A (27%), LEU10 (6%), IL2 (2%), and Tal (39%). The absolute numbers of these cells were 1,062, 686, 441, 98, 33 and 637 cells/cmm, respectively. The H/S ratio was 1.6/1. The percent and absolute numbers of Tal cells were above expected values. In addition, the percent and absolute numbers of LEU1 and LEU3A were decreased, resulting in a H/S ratio on the low side of expected.

DISCUSSION

The 6 patients in this study have expressed multiple health complaints that in certain aspects, e.g., aggravation of existing asthma, formaldehyde-asthma, rhinitis,

sinusitis, are similar to those reported for both occupational and residential formaldehyde exposure [Gupta et al., 1982; OSHA, 1987; Breyse, 1988]. Although the subjective health complaints may be attributable to the irritation and toxic effects of formaldehyde [Bardana and Montanro, 1987], several symptoms suggest that other mechanisms may be operative in these patients. These are: (1) initial flulike illness, (2) chronic malaise, (3) CNS problems (dizziness, memory less, difficulty with tasks), and (4) olfactory sensitivity with the initiation of symptoms, to ambient air-containing reactive chemicals. Multiple organ symptoms with a flulike illness and malaise are not uncommon in chemical sensitivity. Examples include TMA flu [McGrath et al., 1983], sensitivity to isocyanates [Bascom et al., 1985; Karol, 1986; Broughton et al., 1988], chronic exposure to formaldehyde [Broughton and Thrasher, 1988], as well as oral exposure to PBBs [Bekesi et al., 1985] and PCBs [Lee and Chang, 1985]. Moreover, similar health complaints have been reported for individuals suffering from multiple chemical sensitivities [Cullen, 1987]. Concomitant to these health complaints have been the presence of antibodies to haptens and/or changes in cell-mediated immunity.

Formaldehyde conjugates to HSA, producing a new antigenic determinant [Horsfall, 1934; Pass and Marcus, 1970]. Also, formaldehyde binds to proteins and nucleic acids in the nasal cavity [Casanova-Schmitz et al., 1984] and causes nasal pathology [OSHA, 1987]. Moreover, anti-F-HSA isotypes have been found in a variety of exposure conditions as mentioned earlier. In this study, the 6 cases had one or more anti-F-HSA isotypes. The presence of both IgE and IgM F-HSA antibodies is consistent with an active ongoing immunological response to current formaldehyde exposure (patients 1 to 5). Moreover, IgG antibodies in these patients indicate that immunological memory, i.e., secondary immune response, can occur with respect to formaldehyde exposure. The presence of anti-F-HSA antibodies in these patients does not necessarily indicate a sensitivity to formaldehyde, even though one did have a positive skin reaction to the chemical. At present these are interpreted as being related to formaldehyde exposure and may represent one of several immunological mechanisms giving rise to chemical sensitivities.

In addition to anti-F-HSA antibodies, the 6 patients have one other immunological observation in common, an elevation in both the percentage and absolute numbers of Tal cells. Tal expression has been shown to occur after antigenic stimulation and is considered indicative of immunological activation [Fox et al., 1984, 1985, 1986]. Also, T-cells with the Tal marker respond to recall antigens and, therefore, appear to be antigen memory cells [Hafler et al., 1986]. Moreover, Tal cells as well as the antigens have been shown to exist in elevated numbers in various autoimmune diseases [Yu et al., 1980; Fox et al., 1982; Jackson et al., 1982; Hafler et al., 1985]. Also, we have recently demonstrated the elevation of Tal cells in individuals with chronic health problems following exposure to indoor formaldehyde and isocyanates [Broughton and Thrasher, 1988; Broughton et al., 1988]. Since an increase in Tal cells occurs in individuals undergoing chronic antigenic stimulation, the elevation of these cells in these patients may be indicative of antigenic stimulation that is chronic in nature. In contrast, it is of interest to note that in these patients, and as shown in our previous communications, the IL2 cells (acute antigenic stimulation) are present in expected concentrations.

The task confronting the immune system involves encounter, recognition, activation, deployment, discrimination, and regulation. Thus investigation of the effects

of chronic chemical exposure on the immune system should include as many of these functions as possible. The observations made on these 6 patients make this apparent. First, if one examines the immune profiles with respect to the percentage and numbers of T-, T-helper, T-suppressor, and B-cells and H/S ratios, it appears that the deviations may not differ from expected values. However, the anti-F-HSA isotypes demonstrate that encounter, recognition, and discrimination have occurred with respect to formaldehyde exposure. Moreover, activation and subsequent deployment of the immune system is indicated by the elevated numbers of Tal cells. Thus it appears that the immune system may be activated rather than suppressed in some chemically sensitive individuals. Investigations into elements of immune activation and the presence of inflammatory agents may prove to be productive in the elucidation of the health problems of these individuals [Stanworth, 1985; Broughton and Thrasher, 1988].

In this vein, we have begun examining for evidence of immune activation as well as alterations in areas of immune regulation. As previously reported, evidence of autoantibodies has been found in individuals chronically exposed to formaldehyde [Broughton and Thrasher, 1988]. Similar observations have been made with other chronic chemical exposures (work in progress). In addition, the peripheral mononuclear cells from 2 of the subjects in this study and other patients have been found to have a low generation of Interleukin I and a high production of Interleukin II (work in progress). Thus investigation into other modulating agents of the immune system are warranted in order to gain insight into the systemic nature of the health complaints of chemically sensitive individuals. For example PGE₂ and thromboxane B₂ have been shown to be substantially increased in a patient sensitive to carbonless (formaldehyde-melamine copypaper) in a controlled blind study [Marks et al., 1984].

In conclusion, the effects of formaldehyde and other airborne reactive chemicals on biological systems, including humans, should include challenging with plausible antigens (e.g., conjugates) as well as analyses for evidence of immune activation. Thus the antibodies to F-HSA, the wide range of values for H/S ratios, and the increase in Tal cells found in these 6 patients are probably significant.

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