AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 33:274–281 (1998)

Airway Response to Formaldehyde Inhalation in Asthmatic Subjects With Suspected Respiratory Formaldehyde Sensitization

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The aim of the study was to characterize the mechanism of formaldehyde (FM)-induced nasal and bronchial response in asthmatic subjects with suspected FM allergy. Ten subjects purported to have FM rhinitis and asthma and 10 healthy subjects submitted to an inhalation provocation in an exposure chamber with FM at a dose of 0.5 mg/m^3 over 2 hr.

Spirometry at rest and following bronchial provocation with histamine (PC_{20}) were recorded before and after FM inhalation. In addition, FM-specific serum IgE antibodies were measured and cellular, biochemical, and mediator changes were assessed in nasal lavage before, and immediately after, provocation and at 4 hr and 24 hr later.

Provocation with FM caused only transient symptoms of rhinitis in both groups. None of the subjects supposed to have occupational asthma developed clinical symptoms of bronchial irritation. No specific IgE antibodies to FM were detected in persons with occupational exposure to FM.

No differences in the nasal response to FM were found between subjects reporting to have occupational allergic respiratory diseases and healthy subjects ($P > 0.05$).

In summary, inhaled formaldehyde at a level as low as 0.5 mg/m^3 did not induce a specific allergic response either in the upper or in the lower part of the respiratory tract. Moreover, there is no difference in nasal response to FM in asthmatic subjects occupationally exposed to FM and healthy subjects. Am. J. Ind. Med. 33:274–281, 1998. © *1998 Wiley-Liss, Inc.*

KEY WORDS: formaldehyde; occupational allergy; airway response; eosinophils

INTRODUCTION

Formaldehyde (FM) is a common indoor and outdoor pollutant. It is found in many products including particle board, plywood, floor coverings, and office furniture. Other major indoor sources are tobacco smoke and urea-formaldehyde foam insulation (UFFI). It is also used as a sterilizing agent in the health care industry and added as a preservative to cosmetics.

FM is usually described as an immunogen. Hypersensitivity to FM in the form of contact dermatitis is well documented [Hozzstald, 1934]. Ambient FM primarily affects the upper airways and the eyes [Schuch et al., 1966]. Some investigators have described bronchospastic reaction in occupationally exposed subjects [Hendrick et al., 1975]. In recent years, controversy has arisen over the possibility of IgE-dependent airway sensitization. Positive specific bronchial provocation challenge to FM or FM-containing particle board has been found in a few cases of patients with work-related asthmatic symptoms [Nordman et al., 1985]. Several reports indicate that FM-induced asthma is analo-

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Abbreviations used: FM, formaldehyde; UFFI, urea-formaldehyde foam insulation; ER, early response; LR, late response; ECP, eosinophil cationic protein; SPT, skin-prick tests; FEV_1: forced expiratory volume in 1 sec; FVC, forced vital capacity; $PC_{20}H$, provocative concentration causing a 20% fall in FEV_1; PEF, peak expiratory flow; SS, symptom score; PBS, phosphate-buffered saline solution; HSA, human serum albumin.

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Accepted 24 September 1997

gous to the occupational asthma induced by low-molecular-weight haptens. Some of these haptens, such as trimellitic anhydrate, have been shown to induce synthesis of specific IgE [Baur et al., 1995]. However, many investigators have not presented convincing data for differentiation between specific-allergic and nonspecific-irritative bronchospastic reaction in asthmatic subjects occupationally exposed to FM [Frigas et al., 1984; NIOSH, 1974]. Furthermore, immunological evaluation of workers with respiratory symptoms due to FM exposure did not reveal any correlation with specific antibodies [Dykiewicz et al., 1991; Vojdani et al., 1992]

The aim of the present study was to determine the mechanism of the airway response to provocation with a low dose of FM in order to answer the question whether FM is capable of inducing allergic inflammation in the airways of asthmatic patients occupationally exposed to FM.

MATERIALS AND METHODS

Subjects

Two groups of adults were recruited: 10 workers with bronchial asthma and 10 healthy control subjects. The characteristics of these groups is shown in the Table I. Ten subjects from the first group were occupationally exposed to gaseous FM and to formaldehyde solutions (workers of textile and shoe manufacturing, nurses). Four of them were occasionally exposed to pure gaseous FM. They were admitted to the Department of Occupational Diseases with an initial diagnosis of bronchial asthma probably due to FM. The diagnosis was made by the doctor who had been taking care of them in the workplace. It was based on the criteria of American Thoracic Society [1986]. All the patients were convinced that FM was the only chemical agent provoking the workplace asthmatic symptoms. They suffered both from rhinitis and asthmatic symptoms at the workplace as indicated by their histories. The control group consisted of volunteers who had no allergic diseases and had never been exposed to FM at the workplace (workers of the Institute of Occupational Medicine). All subjects were informed about the experiment and consented to participate in the study. The study was approved by the local medical ethical committee.

Study Protocol

The study was designed as a two-stage, single-blind examination. The aim of stage 1 was simultaneous evaluation of clinical symptoms both from the upper and the lower part of the respiratory tract with the simultaneous evaluation of morphological and biochemical changes in the nasal washings after placebo. In stage 2, all analyses were repeated during FM inhalation. One week-intervals were set between stage 1 and stage 2 of the study.

TABLE I. Dermographic Data of Subjects in Formaldehyde Study—Poland 1995–1996

	FM-exposed workers (n = 10)	Healthy controls (n = 10)
Age	23–52	19–49
Gender	7 male; 3 female	Males
Years exposed to FM	1–30	0
Smoking years (mean)	5	0
Allergic symptoms	10	0

FM, formladehyde.

Atopy Testing

All workers were tested with the skin-prick method using the set of common allergens: house dust, *Dermatophagoides pteronyssinus*, feathers, and grass pollens (Beecham-Bencard Allergy Service). A negative control was made with the allergen diluent and a positive control with histamine solution. All prick sites were examined after 20 min: the grading of the wheal (4 mm $>$ control was considered positive) and flare (5 mm $>$ control, positive) reaction was conducted following standard methods.

In all subjects, a total serum IgE level was performed and the presence of formaldehyde specific IgE antibodies was evaluated (Phadezym, Uppsala, Sweden, Pharmacia). The threshold of positivity was set at 0.35 kU/L for specific antibodies.

Nasal Lavage and FM Provocation

All procedures were performed with the use of the ''nasal pool'' method. Before the provocation, each nostril was washed twice with 6 ml of saline using the ''nasal pool'' device (5-ml syringe closely fitting the nostril). Nasal washings were collected immediately before the provocation and at 30 min, 4 hr, and 24 hr after the provocation. Briefly, saline in the volume of 6 ml was inserted into the nasal cavity for 5 min and then recovered in at least 4.5-ml vol (mean 5.2 $\pm$ 0.5 ml). All washings were always performed on the same side of the nasal cavity. Meanwhile, the patients were breathing via the other nares.

Provocational inhalation of FM was carried out in the exposure chamber with a capacity of 12 m^3 in temperature of 23 $\pm$ 0.0°C, with a dew point temperature of 11.5 $\pm$ 0.9° resulting in a relative humidity of 50%. Cooling was achieved using modulated flow of chilled water and heating by modulated steam and small electric heating elements. Room temperature was assessed by four thermocouples and the dew point for the humidity control system was measured with an automatic chilled mirror. Exposure to FM was achieved by evaporating 10 µl of an aqueous solution (10%)

of FM in the exposure chamber. The standardized procedure was calibrated to generate concentrations as close to 0.5 mg/m^3. The concentration of formaldehyde, 0.5 mg/m^3 is the newly recommended Polish exposure limit in occupational settings. The FM concentration was measured seven times annually by use of the chromatropic assay [NIOSH, 1974]. According to these measurements, evaporation of 10 µl of 10% FM solution caused concentrations of airborne FM within the range of 0.2–0.7 mg/m^3, the mean dose was 0.5 mg/m^3. Since the odor of FM at a dose level of 0.5 mg/m^3 is beyond perceptibility for most humans, we used clear air as placebo.

Clinical Symptoms from the Lower Part of the Respiratory Tract

Each patient recorded the intensity of coughing and dyspnea (shortness of breath) in a 0–3° scale: 0, lack of symptoms (asymptomatic subjects); 1, mild dyspnea; 2, medium-intensity dyspnea; and 3, the most severe dyspnea in the patient's life. Positive clinical challenge was defined as more than 1 point.

Nasal Symptom Score

The number of sneezes and the degree of mucosal edema, rhinorrhea, and itching were recorded. Total symptom scores ranged from 0 to 7 and represented the sum of the scores for sneezing (0 sneezes, 0 points; 1–4 sneezes, 1 point; >4 sneezes, 2 points), rhinorrhea (none, 0 points; mild, 1 point; abundant, 2 points), mucosal edema (none, 0 points; mild, 1 point; nasal block, 2 points), and itching (none, 0 points; itchy eyes, 1 point). Positive clinical challenge was defined as >3 points.

Nasal Washings Processing

Centrifugation (10 min at 1,000 rpm) of the nasal washings was performed to isolate the cells pellet and the supernatant. The recovered sediment was washed with sterile-phosphate-buffered saline (PBS) (Sigma, Sigma-Aldrich, Poznan, Poland) and 0.1% human serum albumin (HSA) Behringwerke A.G., Mazburg, Germany) and then suspended in 1 ml buffer with HSA. Subsequently, the cells were stained: using (1) the Turk method for leukocytes, (2) the Dunger method for eosinophils, and (3) 0.06% toluidine blue in 30% ethanol for basophils (metachromatic cells). The cells were counted in a Fuchs-Rosenthal chamber. The number of cells in 1 ml of the recovered fluid was determined. The samples were further centrifuged at 2,000 rpm for 5 min, transferred onto a slide, and air-dried. The slides were stained following the Giemsa method. On each slide first 200 cells were classified into epithelial cells, eosinophils, basophils, and mononuclear cells—a category including lymphocytes and monocytes.

The supernatant total protein content was evaluated with the Lowry method [Lowry et al., 1951]. Albumin concentration was measured using the ''rocket''—Laurell method [1966] (the assay ranged between 20 and 200 µg/ml). The permeability index (i.e., albumin-to-total protein ratio) was calculated.

Eosinophil cationic protein (ECP), and tryptase concentrations were measured with the use of radioimmunoassay (RIA) kits (Pharmacia, Sweden). The samples for these assays were obtained before provocation and at 30 min, 4 hr, and 24 hr after the challenge.

Pulmonary Function and Histamine Challenge Testing

Bronchial responses were measured by serial monitoring of forced expiratory volume in 1 sec (FEV_1) by a spirometer (Vicatest 2A, Mijnhardt, Holland), 2 hr before provocation with FM and then immediately after and at 5 hr and 24 hr after the provocation. In all participating subjects, peak expiratory flow (PEF) was measured at the beginning of the FM challenge and then every 60 min for 12 hr and also at 24 hr after the provocation with FM or placebo.

The histamine inhalation test was performed at the beginning of the provocational inhalation of FM or placebo and then at 5 min, and at 24 hr after the challenge. Prior to histamine challenge, all the patients suspected of occupational allergy to FM presented baseline FEV_1 above 60% of the forced vital capacity (FVC). Different concentrations of histamine dihydrochloride (Sigma, Sigma-Aldrich, Poznan, Poland) were prepared shortly before provocation in normal saline and delivered through the DeVilbiss nebulizer No. 646. The histamine concentrations were as follows: 0.03, 0.06, 0.125, 0.250, 0.5, 1, 2, 4, 8, and 16 mg/ml. Histamine $PC_{20}H$ FEV_1 was defined as a provocative dose causing a 20% fall in FEV_1.

Statistics

The Wilcoxon matched pairs, signed-rank test was used to determine the significance of the increase in protein concentration, cell proportion and total number of cells and mediators levels. The data were expressed as the mean ± SEM. The results obtained after the nasal challenge in occupational asthmatic subjects were compared with those in the healthy subjects using the Mann-Whitney U test. The differences were regarded as significant at $P < 0.05$.

RESULTS

Symptom Score

A 2-hr inhalation of 0.5 mg/m^3 FM in the exposure chamber caused sneezing, itching and congestion in all subjects. These symptoms were the most severe immediately after inhalation both in asthmatic subjects (4.6 ± 1.6 points) and in healthy subjects (4.3 ± 1.2 points) and less

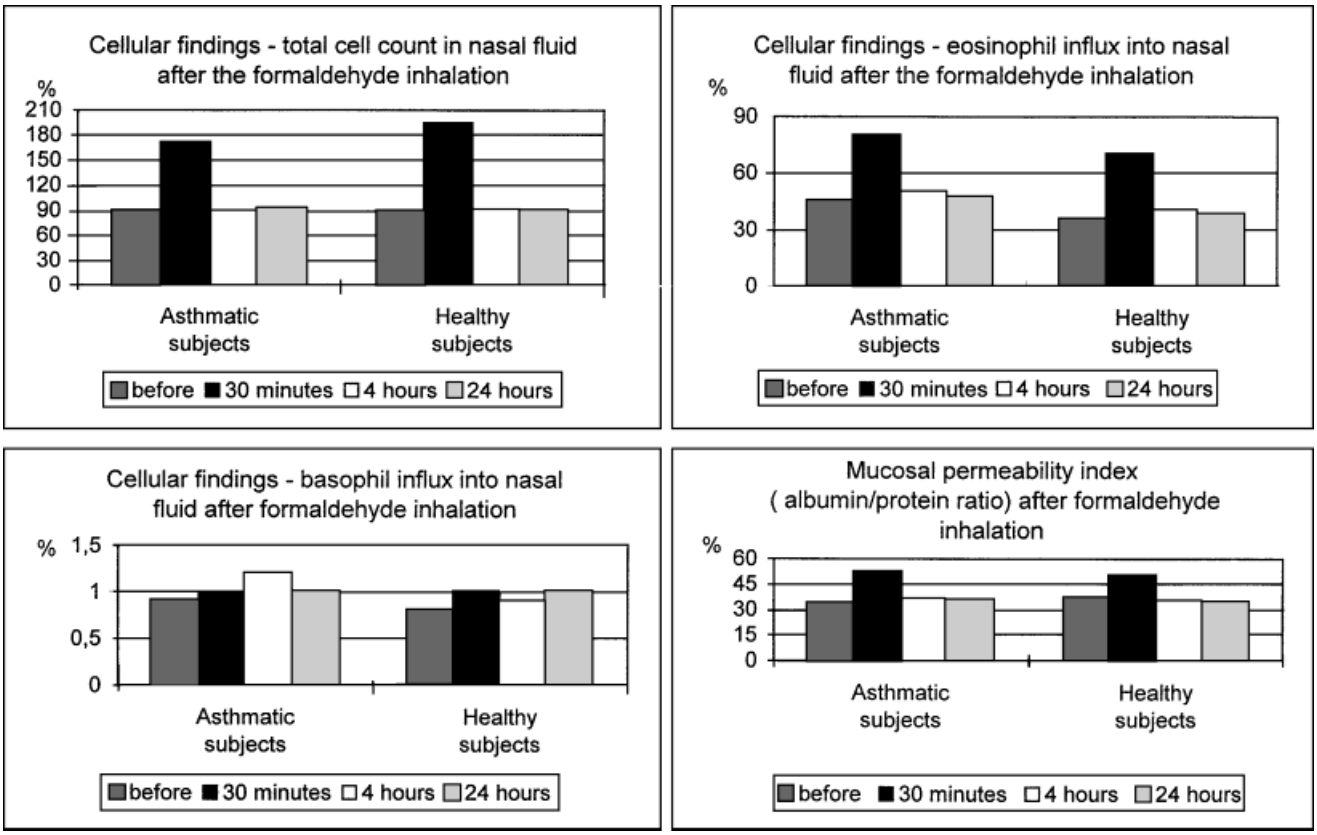

FIGURE 1. Cellular and biochemical findings (mucosal permeability index) in nasal fluid after formaldehyde inhalation in asthmatic subjects.

severe 4 hr after the FM challenge (1.8 ± 1.2 and 1,2 ± 1.3, respectively).

Cellular and Biochemical Findings

Provocation with FM resulted in an increase of the number of leukocytes recovered from nasal washings from both asthmatic and healthy subjects from 90 ± 14 × 10^3/ml to 170 ± 70 × 10^3/ml ($P < 0.05$) in healthy subjects and from 88 ± 19 × 10^3/ml to 193 ± 7 × 10^3/ml in asthmatic subjects). The influx of leukocytes, however, was observed only immediately after provocation. Furthermore, all the subjects exhibited a significant influx of eosinophils into nasal washings immediately after the inhalation of FM: the number of eosinophils in asthmatic subjects increased from 45 ± 15 x 10^3/ml to 80 ± 15 × 10^3/ml ($P < 0.05$) and in healthy subjects from 35 ± 19 × 10^3/ml to 70 ± 10 × 10^3/ml ($P < 0.05$). There was no significant difference between the number of basophils in both groups before and after the provocation.

Protein analysis of nasal washings showed an increase in the permeability index in both groups immediately after the provocation from 34% to 52% in the asthmatic subjects and from 37% to 50% in the healthy subjects. In 4 asthmatic subjects exposed to pure FM in the workplace, both nasal symptoms and changes in the nasal washings did not differ from the reaction observed in all subjects provoked with FM (Fig. 1). None of the parameters determined in the nasal washings after clear air inhalation differed as compared to the baseline levels ($P > 0.05$) and no nasal symptoms were produced in the same analyzed patients from the two groups (Fig. 2).

Mediator Levels

Both in asthmatic and in healthy subjects, the inhalation challenge with FM did not induce a significant increase in the tryptase concentration at all time points after the challenge. The occupationally exposed and healthy subjects were found to have a slightly higher postchallenge levels of ECP in the nasal secretions after the FM inhalation, but the increase was not significant (Table II). No significant changes were observed in ECP and tryptase levels at all times after the provocation with FM and placebo between asthmatic and healthy subjects (Mann-Whitney U-test).

Effect of FM and Placebo Inhalation on Pulmonary Function

None of the asthmatic subjects developed clinical symptoms of bronchial irritation during provocation with

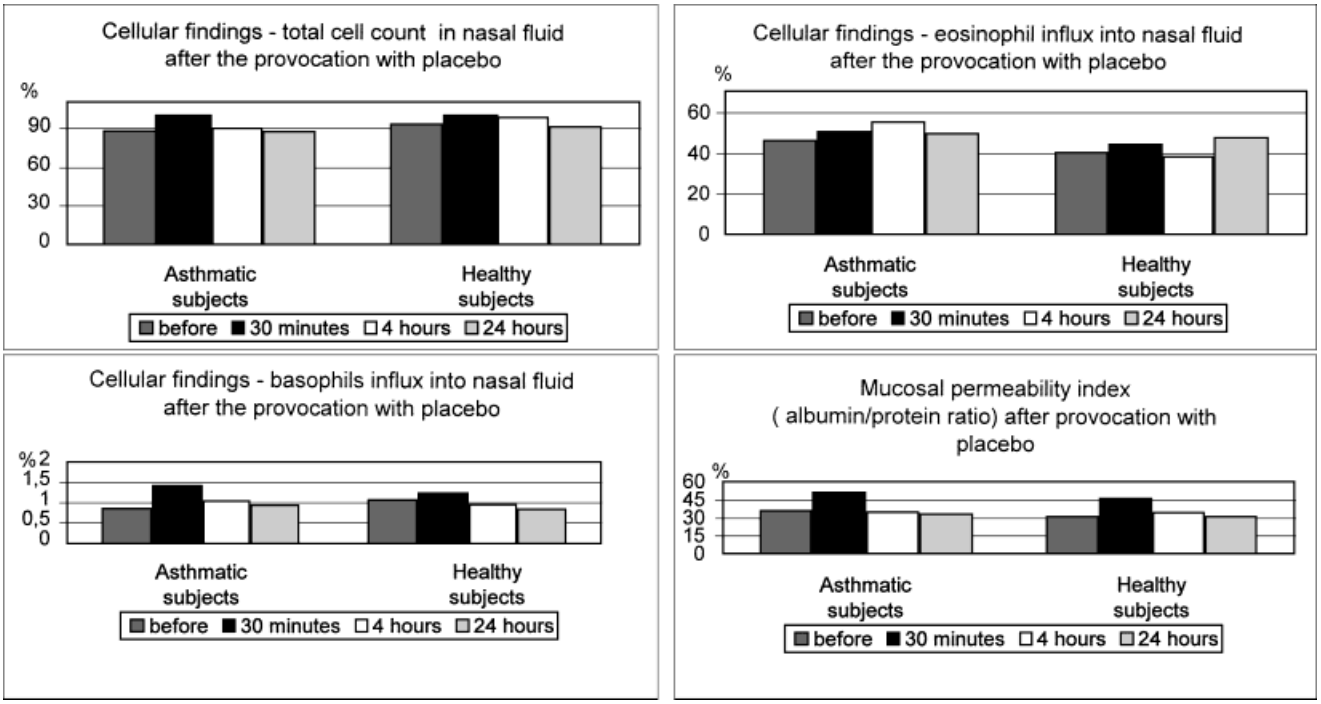

FIGURE 2. Cellular and biochemical findings (mucosal permeability index) in nasal fluid after placebo inhalation in asthmatic subjects.

TABLE II. Mast Cell Tryptase Activity (U/L) and ECP Concentrations (μg/L) in the Nasal Fluid Before and After Inhalation Provocation With Formaldhyde

Time point	Prechallenge	30 min after	4 hr after	24 hr after
		Asthmatic subjects		
Tryptase	1.3 ± 0.7	1.2 ± 0.8	1.2 ± 0.6	1.1 ± 0.5
ECP	3.9 ± 1.2	4.2 ± 0.7	4.0 ± 0.5	4.1 ± 0.5
		Healthy controls		
Trypase	1.2 ± 0.9	1.3 ± 0.5	1.1 ± 0.4	1.2 ± 0.4
ECP	3.8 ± 1.8	4.1 ± 1.2	3.9 ± 1.6	3.9 ± 0.9

ECP, eosinophil cationic protein.

FM. There was no significant change in FEV_1, PEF, and $PC_{20}H$ values at all times after the provocation with FM in the asthmatic and in healthy subjects (Fig. 3). No significant changes were observed in FEV_1 and PEF at all times after placebo provocation in both groups (Wilcoxon test). There were significant differences in baseline FEV_1 and PEF values between the asthmatic and healthy subjects (Mann-Whitney U-test). No remarkable changes were found after the provocation with placebo in either group.

The characteristics of the skin-prick response to common allergens, the value of total serum IgE, and the presence of specific IgE to FM in the two groups of the studied subjects is shown in Table III.

DISCUSSION

For many years, formaldehyde has been considered a potential cause of bronchial asthma and other allergic disorders. However, recent studies have not confirmed that FM could induce asthma and it is still doubtful that this substance is capable of being a respiratory sensitizer [Wantke et al., 1996a; Salkie, 1991]. In contrast, its capacity to cause an allergic sensitization in the skin is well known [Horrsfall, 1934]. FM, like many other low-molecular-weight toxicants may cause irritation of bronchial mucosa, inducing inflammatory reactions that lead to the development of asthma [Holmstrom et al., 1988]. These low-molecular toxicants may also facilitate sensitization to environmental high-molecular allergens, as Tarkowski and Górski [1995] revealed that FM facilitates animal sensitization to ovalbumin. Animal studies revealed that other irritants such as sulfur dioxide increase the sensitivity of animals to develop anaphylactic reaction in response to the ovalbumin [Matsumura, 1970]. To find out whether FM could act as an allergic agent, we studied the nasal and bronchial response to FM inhalation in subjects occupationally exposed to this agent.

Typically, provocation with allergen results in an influx of inflammatory cells to the site of allergic reaction, with the most predominant increase in eosinophil numbers, and a less dramatic but characteristic influx of metachromatic cells

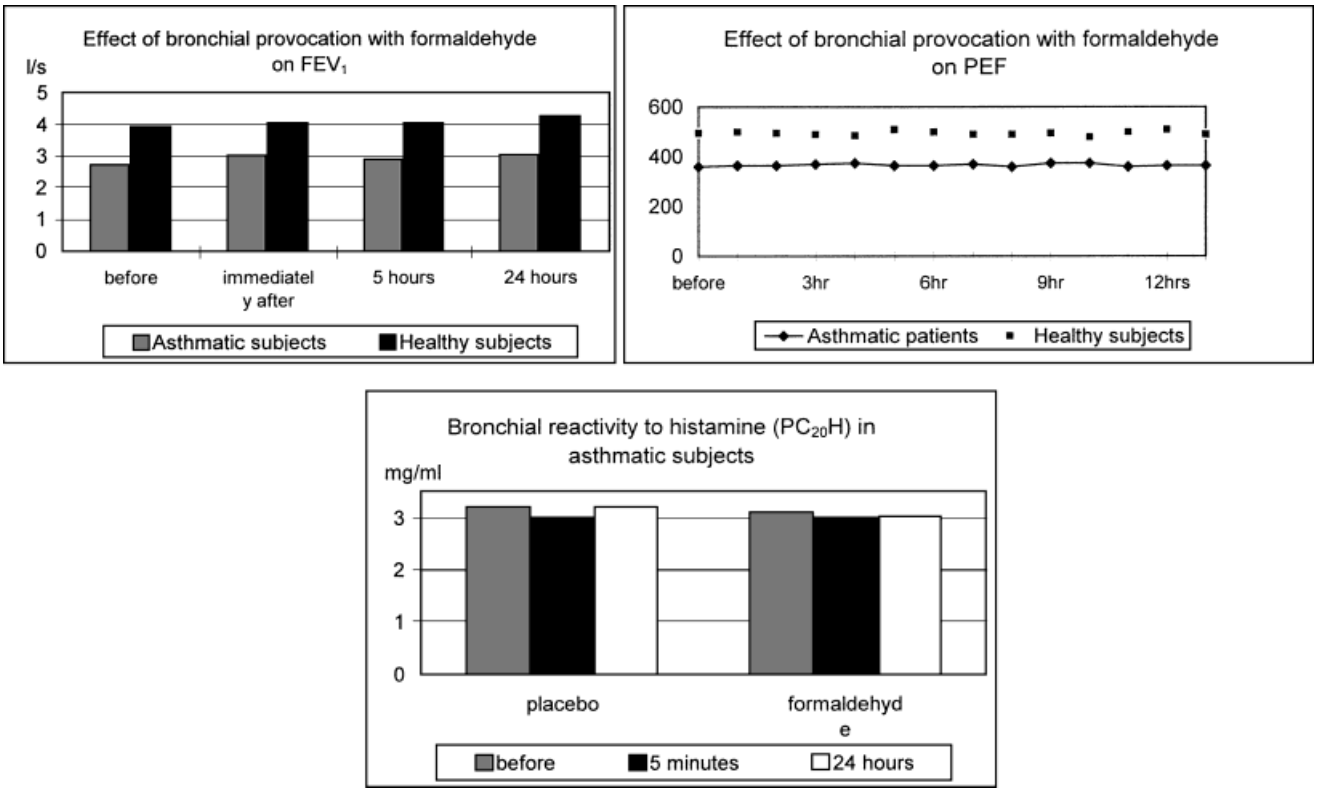

FIGURE 3. FEV_1, bronchial reactivity to histamine ($PC_{20}H$) and PEF before and after the provocation with formaldehyde and placebo.

TABLE III. Characteristics of the Skin-Prick Response to Common Allergens, Value of Total Serum IgE, and Presence of Specific IgE to FM

Studied group	Total serum IgE mean ± SD	Specific serum IgE	Positive skin-prick test
Asthmatic subjects	15 ± 30	0	0
Healthy subjects	40 ± 20	0	2

FM, formaldehyde.

[Prat et al., 1993]. Morphological changes during allergic reaction usually last hours; for example, after bronchial provocation with allergen, the eosinophil infiltration can persist for 90 hr and longer [Dupuis et al., 1992; Pin et al., 1992].

Some investigators, such as Pazdrak et al. [1993], reported influx of eosinophils to nasal washings immediately after provocation with FM. The observed increase in the number of these cells could be explained in several ways. First, it may have been associated with increased permeability; however, an increase in the numbers of the other cell, e.g. basophils was not observed. Second, cells may have been attracted by mediators released from other cells activated during inflammatory processes as the observed nasal symptoms suggest that some inflammatory mediators (among them, histamine) were released during the FM provocation. On the other hand, Zeigher et al. [1976] described FM as the agent capable of neutralizing histamine.

FM and other irritants may cause stimulation of trigeminal sensory nerves, as well as induction of axon responses [Lundberg et al., 1983]. Activation of axon responses is suggested by a release of neuropeptides, especially substance P (SP), calcitonin gene-related peptide (CGRP) and gastrin-related peptide (GRP), which may induce epithelial permeability, prolonged vascular secretion and activate inflammatory cells responses [Joos et al., 1988]. In animals SP enhanced the production of tracheal macromolecules and stimulated glycoprotein secretion, chloride secretion and mucociliary activity [Lindberg et al., 1983]. SP is known to dilate blood vessels and increases vascular permeability [Pernow, 1983]. In subjects with allergic rhinitis, an application of SP increases airflow resistance in the nasal cavities, which is accompanied by protein diffusion and infitration of polymorphonuclear cells [Devillier et al., 1988].

Some investigators suggest that prolonged (until 24 hr after the allergen challenge) increase in the albumin/protein ratio as an index of mucosal permeability is more specific than the prolonged (up till 24 hr) eosinophil influx for allergic mucosal response [Prat et al., 1993; Wihl et al., 1995]. As observed in our study, a transient increase in the

mucosal permeability shortly after the FM challenge suggests nonspecific nasal reaction. We observed similar reactions during nonspecific nasal provocation with histamine.

The typical allergen challenge triggers an acivation of mast cells and influx of eosinophils along with a pronounced increase in the concentrations of their enzymes—tryptase and eosinophil cationic protein (ECP). Wang et al. [1995] noted that the combined assesment of eossinophil count and ECP concentration in nasal fluid is a good marker of nasal inflammation in allergic patients, and that ECP levels reflect the eosinophil present. Castells and Schwartz [1988] observed that tryptase levels in nasal fluid appear promising as a useful indicator of allergic reactions and indicate that mast cell activation is the major factor in the immediate nasal allergic response. Lack of an evidence for mast cell and eosinophil degranulation and the similarity of the responses to provocation in healthy subjects in our study would indicate the occurrence of nonspecific, nonallergic inflammatory processes in the nasal mucosa.

None of 10 asthmatic subjects were found to develop an immediate, late or dual response to inhalation with FM. At a concentration of 0.5 mg/m^3, this agent did not significantly increase the bronchial response to histamine in the asthmatic subjects participating in the study.

Negative inhalation challenge tests with FM have been reported by other workers as well [Frigas et al., 1984]. This can be explained by the very low concentration of FM used for provocation and its very good solubility in the water which might result in trapping of FM in the upper airways. Perhaps one can expect bronchial response to FM at higher concentrations [Pross et al., 1987].

It has now generally been accepted that the increase in airway reactivity is usually associated with increased mucosal inflammation of the airways. The lack of airway hyperreactivity in asthmatic subjects after the provocation with FM supported our hypothesis that FM at low concentration is not capable of acting as a specific agent in a development of an allergic respiratory disease. Nordman et al. [1985] made a diagnosis of FM asthma on the basis of history and a positive 30-min inhalation test to FM at concentrations of 1.2 and 2.4 mg/m^3. The conclusions of this study were criticized as a positive response was based on a 15% decrease in PEF. However, there have been a number of reported cases of work-related asthmatic symptoms in individuals exposed to inhaled FM. However, most of these reported cases of work-related asthmatic symptoms were exposed not to gaseous FM, but to formaldehyde resin dust. Popa et al. [1969] described a worker who had been exposed to urea formaldehyde resins at a smelting furnace and who had dyspnea and other symptoms beginning after 3–4 hr of work. This patient reacted with a delayed response on provocation inhalation testing 2 hr after exposure to heated urea-formaldehyde resins.

We did not find any antibodies against FM in the serum of asthmatic subjects.

FM is a low-molecular-weight chemical that could behave as a hapten, reacting with native proteins to form an antigenic conjugate capable of stimulating the production of specific antibodies. FM-specific IgE were detected in a small proportion of exposed individuals, but this was not associated with respiratory symptoms in all cases [Dykiewicz et al., 1991]. By contrast, there were symptomatic individuals in whom specific IgE was not found [Thrasher et al., 1990; Vojdani et al., 1992]. IgE-mediated sensitization to FM is rare and a matter of debate [Liden et al., 1993; Wantke et al., 1996b]. Recently, it has been noted that schoolchildren exposed to levels of FM within a range of 0.053–0.092 mg/m^3 are more susceptible to toxic substances than are adults and that they are more susceptible to IgE-mediated sensitization [Wantke et al., 1996b], but the investigators did not find a link between symptoms and sensitization to FM. Thus, the clinical relevance of antibodies specific to FM in humans remains unclear.

In summary, inhaled formaldehyde at a level as low as 0.5 mg/m^3 did not induce a specific allergic response either in the upper or in the lower part of the respiratory tract. Moreover, there is no difference in nasal response to FM in asthmatic subjects occupationally exposed to FM and in healthy subjects.

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