Formaldehyde is a well-known airborne contaminant causing eye, nose, and throat irritation as well as airway irritation and slight neuropsychologic changes (Hester and Harrison 1998; Samet et al. 1988).

The major indoor sources of formaldehyde are off-gassing from urea–formaldehyde foam insulation, particle board, paneling, plywood, some carpets and furniture, and, to a lesser extent, tobacco smoke and indoor combustion sources. Indoor concentrations of formaldehyde can vary between different countries (Sakai et al. 2004). In a Japanese study, formaldehyde concentrations ranged between 91.25 and 290 μg/m³ (Minami et al. 2004). In a double-blind crossover study to either formaldehyde or purified air for 60 min. The order of exposure to formaldehyde and air-only was randomized, and exposures were separated by 2 weeks. We also performed an allergen inhalation challenge after each exposure. Airway responsiveness to methacholine and lower airway inflammation (induced sputum) were assessed 8 hr after allergen challenge.

**RESULTS:** The median dose of allergen producing a 15% decrease in forced expiratory volume in 1 sec (PD15FEV1) was 0.80 IR (index of reactivity) after formaldehyde exposure compared with 0.25 IR after air-only exposure (p = 0.06). Formaldehyde exposure did not affect allergen-induced increase in responsiveness to methacholine (p = 0.42). We found no formaldehyde-associated effect on the airway inflammatory response, in particular the eosinophilic inflammatory response, induced by the allergen challenge 8 hr before.

**CONCLUSION:** In this study, exposure to 500 μg/m³ formaldehyde had no significant deleterious effect on airway allergen responsiveness of patients with intermittent asthma; we found a trend toward a protective effect.

**KEYWORDS:** allergen, asthma, formaldehyde, human exposure study. *Environ Health Perspect* 115:210–214 (2007). doi:10.1289/ehp.9414 available via http://dx.doi.org/ [Online 7 November 2006]

Formaldehyde is an etiologic factor in occupational asthma. However, although formaldehyde may cause asthma in some individuals, this occurs relatively rarely (Nordman et al. 1985; Paulusenbach et al. 1997).

Whether nonoccupational exposure to formaldehyde is related to asthma is still subject to discussion (Delfino 2002; Institute of Medicine 2000). In murine models, formaldehyde exposure has been shown to enhance the allergic eosinophilic airway inflammation in sensitized mice (Sadakane et al. 2002). In a part of the European Community Respiratory Health Survey, asthma prevalence was greater for newly painted homes, consistent with greater differences in formaldehyde exposure (Wieslander et al. 1997). A relationship between physician-diagnosed asthma and indoor concentration of formaldehyde was reported even at low levels of exposure in children (Rumchev et al. 2002). Franklin et al. (2000) reported that exposure to formaldehyde in homes could produce a subclinical inflammatory response in the airways of healthy children. A possible association between exposure to formaldehyde and allergic sensitization to common aeroallergens has been suggested by another cross-sectional study in children (Garrett et al. 1999).

Human exposure studies can provide valuable data for assessing more specifically the acute effects of air pollutants, particularly the airway response to allergen (Sandström 1995). The hypothesis that formaldehyde enhances asthmatic response to allergen has not yet been investigated in controlled conditions in humans. To test this hypothesis, we carried out this controlled human study to investigate the effect of a short exposure to 500 μg/m³ formaldehyde on asthmatic response to inhaled allergen.
was at least 3 mm greater than that for the negative control and at least 50% of the diameter of the positive control. Blood samples were obtained for analysis of total IgE and eosinophils in serum. Pulmonary function tests were performed and spum was collected. All subjects were free from upper respiratory infections for at least 4 weeks before the study. Before enrollment in the study, all participants gave written informed consent. The study was approved by the ethical committee of Saint-Germain-en-Laye-Hospital (project 00019, registered on 9 May 2000).

**Study protocol.** In a crossover design study, each subject was exposed at rest to filtered air or to a concentration of 500 μg/m³ (0.4 ppm) formaldehyde for 60 min on two separate days. The exposures were performed at the same hour (0700 hours) and occurred on the same day of the week, with an interval of 2 weeks between exposure. The order of exposure to formaldehyde and air-only was double-blinded and randomized. The only member of the research team aware of the type of exposure was the engineer in charge of the injection of formaldehyde into the chamber. The nature of exposure was made known to the other members of the team only after completion of the statistical analysis.

Lung function was measured with a spirometer according to the European Community Respiratory Health Survey specifications; measurements were taken immediately before, during, and 8 hr after the end of the allergen challenge. Forced expiratory volume in 1 sec (FEV₁) and PEF were measured with a portable combined spirometer every 15 min during the exposure to formaldehyde or air-only in the chamber and every hour until the methacholine provocation test, which was performed 8 hr after the end of the allergen bronchial challenge.

**Formaldehyde/clean air exposure.** A 8.8-m³ exposure chamber was installed at the Hospital Bichat in Paris. The chamber was supplied with fresh, particle-free air at a mean temperature of 25°C and a mean relative humidity of 32%. The air supply passed through both HEPA and activated carbon filters. The formaldehyde atmosphere was created by injecting and diluting saturated vapors from a heated solution of formaldehyde at the exit of the filtration box; these vapors flowed into the ventilation diffuser located in the center of the chamber ceiling. A continuous 1-hr injection of the formaldehyde solution was sufficient to reach a steady state. The formaldehyde concentration in the chamber was monitored continuously with semiconductor gas sensor technology during the experiments to ensure that there was no fluctuation in formaldehyde levels during exposure. The air ejected from the chamber was evacuated outside the building without recirculation.

**Table 1. Characteristics of subjects.**

| Subject | Age (years) | Sex | Asthma duration (years) | Smoking (% pred) | FEV₁, at inclusion |
|---------|-------------|-----|------------------------|------------------|-------------------|
| 1       | 34          | M   | 18                     | N                | 100               |
| 2       | 33          | F   | 19                     | N                | 101               |
| 3       | 45          | M   | 10                     | N                | 109               |
| 4       | 18          | M   | 12                     | N                | 105               |
| 5       | 24          | M   | 8                      | N                | 103               |
| 6       | 28          | F   | 10                     | E                | 111               |
| 7       | 26          | F   | 20                     | N                | 95                |
| 8       | 37          | F   | 15                     | N                | 109               |
| 9       | 25          | M   | 20                     | N                | 101               |
| 10      | 26          | F   | 18                     | N                | 93                |
| 11      | 21          | M   | 6                      | N                | 108               |
| 12      | 26          | M   | 14                     | N                | 89                |

Abbreviations: E, ex-smoker; F, female; M, male; N, never smoker; % pred, percent predicted.
malignant squamous cell contamination did not differ significantly between subjects who were exposed to air-only and those who were exposed to formaldehyde.

**Results**

All 12 subjects completed the two exposures and all of the allergen and methacholine challenges. Four subjects reported minor complaints during exposure to both air-only and formaldehyde. One reported nose irritation during air-only exposure, and another subject reported having a runny nose during formaldehyde exposure but no symptoms or discomfort during air exposure. No distinct odor was reported by any subject during exposure to air-only or formaldehyde. No major clinical adverse reaction was observed.

Exposure of allergic asthmatic patients at rest to 500 μg/m³ formaldehyde for 1 hr had no direct effect on respiratory function either during or immediately after the exposure session. The FVC and FEV₁ values, measured immediately after formaldehyde exposure, were not significantly different from those obtained after air-only exposure.

**Allergen bronchial challenge.** Airway responsiveness to allergen was measured using the PD₁₅FEV₁. Formaldehyde versus air-only exposure resulted in a PD₁₅FEV₁ that was higher in five patients and unchanged in seven (Figure 1). The median PD₁₅FEV₁ was 0.80 (range, 0.15–2.0) IR after formaldehyde exposure compared with 0.25 (range, 0.1–2.0) IR after air-only exposure (p = 0.06) (Table 2). We observed no “order effect” concerning PD₁₅FEV₁: results were not significantly different between the first exposure to formaldehyde or air-only (no wash-out) and the second exposure (after a wash-out).

**Methacholine bronchial challenge.** Methacholine responsiveness was assessed 8 hr after the end of the allergen challenge. Formaldehyde versus air-only exposure resulted in a PD₂₀ methacholine that was lower in three subjects, higher in four, and unchanged (within a doubling dose) in five (Figure 1). Formaldehyde exposure did not affect the allergen-induced increase in responsiveness to methacholine (median PD₂₀, 0.17 mg after formaldehyde vs. 0.23 mg after air-only exposure; p = 0.42) (Table 2).

**Discussion**

Several epidemiologic studies (Franklin et al. 2000; Garrett et al. 1999; Rumchev et al. 2002; Wieslander et al. 1997) have suggested possible associations between formaldehyde exposure and either asthma or allergic sensitization to common aero allergens. These cross-sectional studies assessed chronic exposure to low levels of formaldehyde. Concerning the effect of acute exposures to formaldehyde on allergic response, the only data available were reported in a murine model (Sadakane et al. 2002). Several studies have been performed with air pollutants to assess interaction with allergenic response; some have shown that asthmatic response could be enhanced by a brief preexposure to air pollutants, in particular, nitrogen dioxide or ozone (Barck et al. 2005; Jórrès et al. 1996; Molfino et al. 1991; Strand et al. 1997; Tunnicliffe et al. 1994).

The hypothesis that a brief exposure to ambient levels of formaldehyde enhances asthmatic response to allergen has not yet been reported in controlled human exposure studies. The aim of this study was to examine whether a 1-hr exposure to 500 μg/m³ formaldehyde enhances the asthmatic response to inhaled pollen allergen in subjects with intermittent asthma. We chose this level of formaldehyde to remain within realistic conditions while

![Figure 1. Ratios between PD₂₀FEV₁ and PD₂₀ methacholine measurements for each subject (after formaldehyde exposure divided by after air-only exposure). The ratios between the PD₂₀FEV₁ measurements are always ≥ 1, showing an unchanged or a decreased allergen responsiveness with formaldehyde compared with air-only. The ratios between the PD₂₀ methacholine measurements after exposure to formaldehyde and air-only range from 0.15 to 18.](image)

**Table 2.** Results (median [range]) of allergen bronchial challenge performed immediately after exposure to formaldehyde or air-only and methacholine bronchial challenge performed 8 hr after exposure.

| Exposure            | Formaldehyde | Air-only    | p-Value |
|---------------------|--------------|-------------|---------|
| Allergen challenge  | 0.80 (0.15–2.0) | 0.25 (0.10–2.0) | 0.06    |
| Methacholine challenge | 0.23 (0.01–3.6) | 0.17 (0.03–4) | 0.42    |

*p-Values were determined by signed rank test.*
maximizing our chances to demonstrate an adverse effect. Mean indoor formaldehyde concentrations are usually < 500 μg/m³, although such a concentration can be found in indoor environments (Institute for Environment and Health 1996).

Formaldehyde exposure alone did not cause any change in lung function, which is in accordance with earlier reports that concluded that lung function of healthy nonsmokers and asthmatics was generally unaffected by exposure to formaldehyde at levels ≤ 3,700 μg/m³ (Sauder et al. 1987). We found no significant differences between the bronchial allergen responses after formaldehyde exposure compared with exposure to air-only. However, there was a tendency toward a lower immediate bronchial allergen response after exposure to formaldehyde compared with air-only, contrary to expectations. This result is not compatible with an adverse effect of formaldehyde on asthmatic response in the conditions tested and might suggest a protective effect. Such an effect was reported in mice exposed to low concentrations of nitrogen dioxide (Hubbard et al. 2002; Proust et al. 2002). Moreover, Fujimaki et al. (2004) showed a decreased production of IL-1β in ovalbumin in immunized mice after exposure to a low dose of formaldehyde.

We assessed the effect of formaldehyde using conditions that minimize the possibility of bias: the order of exposures to formaldehyde or purified air was both randomized and double blinded. Subjects were tested in the same controlled conditions and with a constant level of air pollutants, temperature, and humidity. The delay between exposures was consistent with the literature concerning this type of study (Strand et al. 1997). The longer the wash-out period, the higher the risk of developing respiratory infections; we considered 2 weeks a good compromise between the risk of bias because of a late reaction after the allergen challenge and the risk of exclusion because of infection. Furthermore, if the delay between exposures had had an effect, we would have found different results between the first exposure to formaldehyde or air-only (no wash-out) and the second exposure to formaldehyde or air, which was not the case (i.e., no “order effect”). Post hoc calculations showed that the power of the study was sufficient (> 80%) to show a significant difference if there was a 2-fold variation in PD15FEV1 between the two arms. We observed an increase in PD15FEV1 after formaldehyde exposure compared with air-only exposure (Figure 1). The increase was near statistical significance (two-sided, p = 0.06). The true value of the variation in PD15FEV1 may correspond to a decreased responsiveness with formaldehyde compared with air-only or to no change. However, in spite of the low number of patients, the power of the study is sufficient to conclude that the probability for an increased responsiveness with formaldehyde is very low (3%). Moreover, if there was an increased responsiveness, the increase would probably be so small that it would be impossible to demonstrate, even with a very large study.

Corren (1992) showed that a late bronchial response occurs 2 to > 12 hr after allergen exposure. In the present study, methacholine challenge and induced sputum tests were performed 8 hr after the end of allergen bronchial challenge, approximately when the maximum airway inflammatory reaction to allergen occurs. We observed no significant modification in airway responsiveness to methacholine after formaldehyde exposure at this time (8 hr after exposure). To assess airway inflammation, bronchial biopsy remains the gold standard. However, this process is invasive compared with induced sputum, which has proven to be a reproducible, sensitive, and valid method for the assessment of airway inflammation (Wilson 2002). Induced sputum has been used to detect cytokines in patients with bronchial asthma, and the up-regulation of cytokines in the Airways can be assessed using noninvasive techniques, including sputum induction (Taha et al. 2001). In the present study, we measured in induced sputum several inflammatory cytokines and mediators that are well-known to be involved in the physiopathology of asthma. Formaldehyde exposure did not significantly affect inflammatory cytokines and mediators measured in sputum 8 hr after the end of the bronchial allergen challenge. However, the total dose of allergen required to reach the expected respiratory effect was higher after formaldehyde exposure than after air-only exposure (0.8 IR vs. 0.25 IR). A potential effect of formaldehyde on the response to methacholine challenge could have been masked because of the differences in allergen exposure between the two arms. It also applies for the airway inflammatory response.

Our study included patients with intermittent asthma who were not taking any anti-inflammatory therapy; although we observed no effect in this particular group of patients, this does not necessarily mean that the results can be generalized to patients with more severe asthma. Therefore, additional research is needed to examine effects among individuals with severe asthma.

To our knowledge, this is the first controlled human study examining possible interactions between formaldehyde exposure and allergen on asthmatic response. In this study, exposure to 500 μg/m³ formaldehyde did not enhance the asthmatic response to allergen. We even observed a trend to a protective effect. Future studies assessing effects of formaldehyde at higher doses, or with repeated or longer exposures, are needed to clarify interactions between formaldehyde and allergens in airways of patients with asthma.

### Table 3. Results [median (range)] for parameters measured in sputum.

| Exposure            | Baseline | Formaldehyde | Air-only | p-Value* |
|---------------------|----------|--------------|----------|----------|
| Total no. of cells  | 244 (213–496) | 255 (215–633) | 258 (229–438) | 0.50     |
| Bronchial cells (%) | 14.4 (1.7–46) | 4.4 (30–40) | 3.5 (0.20–33) | 0.82     |
| Macrophages (%)     | 27 (3–57) | 27.4 (2.8–79) | 17.3 (2–82) | 0.57     |
| Lympocytes (%)      | 0.3 (0–2.2) | 1 (0–7) | 0.4 (0–1.7) | 0.31     |
| Neutrophils (%)     | 58 (0.3–94) | 32 (0–81) | 34 (0–92) | 0.73     |
| Eosinophils (%)     | 2.1 (0–31) | 11.3 (0.8–69) | 13.2 (2–81) | 0.91     |
| ECP (ng/ml)         | 57 (3.8–130) | 130 (3.9–200) | 105.5 (41–200) | 0.92     |
| Eotaxin (pg/ml)     | 0 (0–0) | 0 (0–14) | 0 (0–15) | 1.00     |
| GM-CSF (pg/ml)      | 0 (0–1.6) | 0 (0–0.69) | 0 (0–7.87) | 0.12     |
| IFN-γ (pg/ml)       | 0 (0–23) | 0 (0–14) | 4 (0–14) | 0.58     |
| IL-1 (pg/ml)        | 10.5 (1.9–30) | 11.5 (8–30) | 7.5 (3–30) | 0.74     |
| IL-4 (pg/ml)        | 0.19 (0.2–5) | 0.17 (0–0.85) | 0.06 (0–1.7) | 0.74     |
| IL-5 (pg/ml)        | 0 (0–13) | 4.5 (0–18) | 4 (0–16) | 0.82     |
| IL-8 (pg/ml)        | 494 (17–1312) | 675 (69–1,200) | 714.5 (81–2,500) | 0.74     |
| IL-10 (pg/ml)       | 1.7 (0–5.5) | 1.4 (0–8.6) | 3.45 (0–8.9) | 0.47     |
| MCP-1 (pg/ml)       | 0.11 (0–72) | 29 (0–108) | 26.5 (0–129) | 0.52     |
| TNF-α (pg/ml)       | 0.26 (0–5.4) | 0.16 (0–1.3) | 0.26 (0–3.6) | 0.20     |

* p-Values were determined by signed rank test and indicate comparison of formaldehyde to air-only. Significant increase between baseline and 8 hr after the end of the allergen challenge, whether the subject was exposed to air-only or to formaldehyde (p < 0.05).

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