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Review Article

Effects of formaldehyde, as an indoor air pollutant, on the airway

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Abstract

Homes are being built to be more airtight because of demands for energy conservation in recent years. At the same time, recognition of numerous sources of formaldehyde in indoor environments has increased concerns about health hazards from this pollutant. Formaldehyde has been shown to cause and exacerbate asthmatic symptoms. In addition, the effects of formaldehyde on the airway are proportional to the concentration and duration of exposure and are greater in inflamed than in healthy airways. Formaldehyde may induce features of airway inflammation associated with asthma, such as epithelial disruption, microvascular leakage and increased airway secretions. Exposure to this chemical may facilitate IgE sensitization to a variety of allergens, as well as producing IgE-mediated allergic responses to itself. Thus, avoidance of formaldehyde exposure may reduce the incidence and severity of asthma, although the ability of low concentrations of formaldehyde to trigger mechanisms contributing to asthmatic symptoms is still debated. Setting appropriate exposure limits for formaldehyde as an indoor environmental pollutant requires further quantitative and predictive evaluation of its health effects.

Key words: airway inflammation, asthma, formaldehyde, IgE, immune system, indoor environments.

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Introduction

Formaldehyde, a known cause of occupational asthma, may also adversely influence health when present in ordinary room air. Formaldehyde has been found to be related to 'sick building syndrome' (health disturbances induced by chemical contaminants in office environments), which has shown an increased rate of occurrence in Europe and North America following the first world oil crisis.[1] In recent years, the structure of housing in Japan has rapidly shifted to Western forms and people now are living in very airtight rooms during most of their daily routines. When room ventilation is inadequate, contaminants, including formaldehyde, may stagnate in rooms and adversely affect the health of inhabitants. Allergic diseases are increasing in occurrence and 'sick house syndrome' has received attention as a household counterpart of sick building syndrome.

Formaldehyde, a gaseous organic compound, is soluble in water. It has strong reducing properties and is chemically able to copolymerize various substances. Such properties have made it a popular raw material in the manufacture of urea-type or phenol-type synthetic resins, both of which are used frequently as adhesive agents in fabricating plywood, flooring, particle board and fiberboard. Urea formaldehyde resin also is used in textile synthesis for clothing, as a preservative in paper and as a foam-type heat insulator. Furthermore, formaldehyde is often added to products, such as wallpaper, adhesive agents, cosmetics and detergents, as a preservative or fungicide. When the ambient temperature is increased, the formaldehyde contained in these products is volatilized and formaldehyde compounds are decomposed to liberate formaldehyde, which is released into room air. Cigarette smoke and combustion exhaust gas also contain formaldehyde in high concentrations and indoor formaldehyde concentrations often reach

levels several-fold greater than those present in outdoor environments.[2] We often are exposed to relatively high concentrations of formaldehyde gas in newly built housing and in poorly ventilated clothing or furniture stores. The formaldehyde contained in cosmetics, detergents and sometimes wallpaper also comes into direct contact with skin. Even most vaccine preparations contain some formaldehyde, which is introduced subcutaneously.

At monthly intervals over 2 years, Kodama *et al*.[3] followed changes in formaldehyde concentration within a newly built single-family house of steel structure unit design. Measurements were made in four places (living room, bedroom, children's room and bathroom) and were averaged (Fig. 1). The average formaldehyde concentration before the occupants moved into the house was 0.712 p.p.m. (highest in the bedroom, 1.175 p.p.m.). After the family moved in, average values decreased, but they increased again in summer. Thereafter, the formaldehyde concentrations decreased only slightly and slowly. The formaldehyde concentration 1 year after moving in was more than 0.1 p.p.m., declining to less than 0.1 p.p.m. only after 2 years. A concentration of 0.08 p.p.m. is the maximum allowable indoor formaldehyde concentration, recommended by the World Health Organization (WHO). The serial measurements above indicate that formaldehyde contamination in the room air of Japanese housing is a very serious problem.

Respiratory health effects of formaldehyde

Acute health effects of formaldehyde at various concentrations

Ambient formaldehyde primarily affects the upper airway and eyes. Even in low-level exposure, people with heightened olfactory awareness may notice a foul odor, while incurring no physiologic consequences. The odor threshold for formaldehyde has been reported to vary between 0.05 and 1 p.p.m.[1] Acute upper airway and eye irritation are the most common complaints in homes and offices where materials containing formaldehyde compounds are used extensively. The degree of irritation is directly proportional to the concentration and duration of formaldehyde exposure. These symptoms appear to have a wide range of threshold concentrations (eye irritation, 0.01–2.0 p.p.m.; upper airway irritation, 0.1–25 p.p.m.).[1] The US Industrial Health Foundation panel,[4] charged with recommending occupational exposure limits, concluded from well-controlled studies of volunteers that for most people, eye irritation unequivocally due to formaldehyde does not occur below 1 p.p.m. and that for most people moderate to severe eye, nose and throat irritation does not occur until airborne concentrations exceed 2–3 p.p.m.

Uptake of formaldehyde by nasal mucous membranes has been demonstrated to be extremely high,[5] reflecting the high water solubility of formaldehyde. This suggests

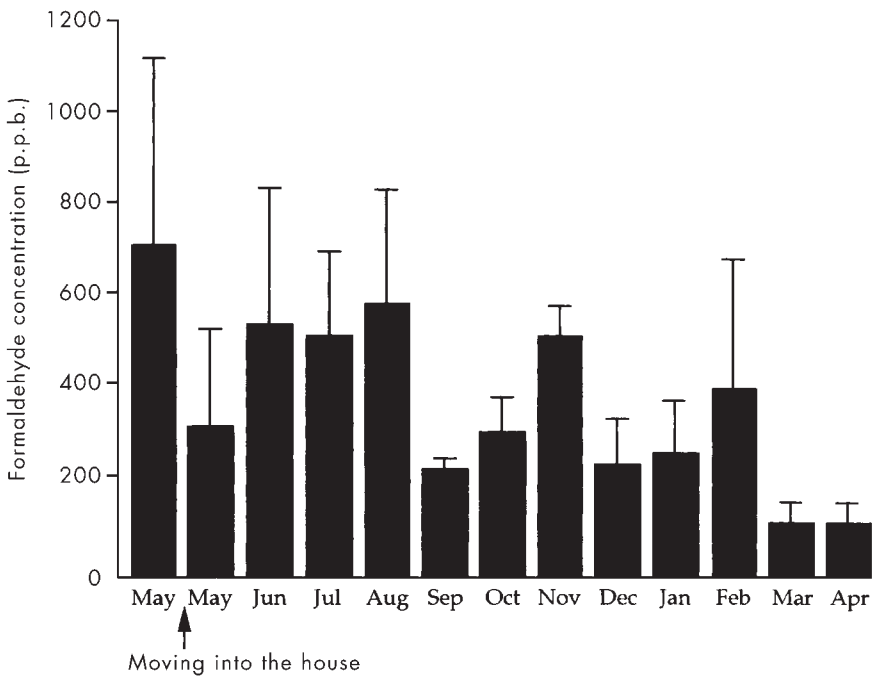

Fig. 1 Changes in formaldehyde concentration within a newly built single-family house of steel structure unit design, before and after the family has moved in. Measurements were made in four places (living room, bedroom, children's room, and bathroom) and averaged. Values are the mean ±SD.

that little formaldehyde should reach the lower airways following nasal inhalation. However, lower airway and pulmonary effects, such as cough, chest tightness and dyspnea, have been observed at concentrations between 5 and 30 p.p.m.[1] Levels of formaldehyde exceeding 50 p.p.m. can induce severe pulmonary edema and inflammation.[1] Relatively large amounts of the gas may reach the lower airways via the mouth, followed by almost complete uptake.[5]

Formaldehyde and occupational asthma

Occupational 'formalin asthma', a term referring to a volatile aqueous formaldehyde solution, has been described in a worker in a match factory[6] and in workers employed in the tanning and rubber industries.[7] The match factory report is the earliest reference to asthma attributable to formaldehyde. In the other report, 28–48 workers who had been exposed to a variety of chemicals, including formaldehyde, were suspected to have occupational asthma or asthmatic bronchitis.[7] One person showed immediate and delayed bronchoconstriction to formaldehyde in a provocative test. Unfortunately, the possible involvement of other chemicals in causing asthmatic symptoms was not investigated. In addition, the concentrations of formaldehyde used for the bronchial challenge test were not recorded.

Hendrick and Lane have found that formaldehyde caused a significant fall in the forced expiratory volume in 1 s (FEV_1) in a hemodialysis nurse with asthma 2–6 h after exposure in a provocative test.[8] The decrease in FEV_1 was abolished by pretreatment with inhaled betamethasone and the nurse's asthmatic symptoms were prevented by avoidance of unnecessary exposure to formaldehyde. Another case in this report involved an elderly pathologist with a 17 year history of working with formaldehyde, who thought that his prolonged exposure had worsened his asthmatic symptoms.[8] Unexpectedly, a formaldehyde provocative test was negative. The same authors have reported similarly mixed results in a slightly broader survey: two of five patients with asthma attributable to formaldehyde (four staff members of a hemodialysis unit and a patient undergoing hemodialysis) had positive provocative tests with formaldehyde.[9] A significant fall in peak expiratory flow (PEF) also was observed from 2 to several hours after challenge. Subsequently, Hendrick and colleagues have observed that bronchial hyperresponsiveness to formaldehyde in the previously reported hemodialysis nurse[8] persisted for 6 years, due to low levels of intermittent exposure.[10] Thus, repeatedly inhaling formaldehyde may prevent full recovery from bronchial hyperresponsiveness and asthmatic symptoms due to this agent. However, mechanisms underlying the abnormal airway responses have not been explained.

Nordman *et al*. administered a provocative test with formaldehyde (1–2 p.p.m., 30 min) to 230 workers who had been exposed to formaldehyde previously and manifested asthmatic symptoms.[11] Formaldehyde significantly reduced PEF in 12 subjects (5.2%): immediate PEF changes were observed in six cases, late PEF changes in four and both immediate and late PEF changes in two. Interestingly, these subjects with bronchial hyperresponsiveness to formaldehyde did not always show bronchial hyperresponsiveness to histamine or methacholine, in contrast to a report by Burge *et al*.,[12] which has noted a close relationship between histamine and formaldehyde bronchial reactivity. The concentrations of formaldehyde used in the provocative tests were as low as those detected in domestic settings, suggesting that domestic exposure may provoke, worsen or prolong asthmatic symptoms in patients sensitive to formaldehyde. In the study by Nordman *et al.*, challenges were unblinded and a positive response was defined as a 15% decrease in PEF, measured with a Wright peak flowmeter. Therefore, the conclusions may not be firm.

Frigas *et al*.[13] have concluded that cases of formaldehyde-induced asthma may be rare, in a study of formaldehyde bronchial challenge (0.1–3 p.p.m., 20 min) that failed to provoke bronchoconstriction in 13 selected patients with symptoms suggestive of asthma, with suspected exposure to formaldehyde as a cause. In contrast, the same workers have found that one subject with asthma had bronchial constriction as a result of exposure to urea-formaldehyde foam, but not to formaldehyde gas.[14] Airborne particles containing formaldehyde, then, may contribute more to asthma symptoms than gaseous formaldehyde. Krakowiak *et al*.[15] have found that inhaled formaldehyde at low doses (0.4 p.p.m. for 2 h) may have no bronchoconstricting effect in asthmatic patients occupationally exposed to formaldehyde or in healthy subjects, although some transient symptoms of rhinitis occurred in both groups at such doses. Moreover, no formaldehyde-specific IgE antibodies were detected in serum from any subject in that study.

Most clinical studies have found a low incidence of positive provocative tests with formaldehyde, even in patients whose asthmatic symptoms were attributable to

formaldehyde. Thus, formaldehyde may not be an important cause of asthma, because a positive provocative test is essential to this determination. Further, inhaled formaldehyde is unlikely to be potent in directly inducing bronchoconstriction, because cigarette smoke, known to contain 30–40 p.p.m. formaldehyde in side-stream sampling, is not a common cause of acute airway obstruction.[16] In a few cases, bronchial exposure to formaldehyde has produced sustained bronchoconstriction several hours later; the reaction is reduced by pretreatment with corticosteroids.[8,9,11] This means that formaldehyde can cause airway inflammation leading to airflow limitation in specific populations. As described in previous studies,[11,13,15] clinical histories suggest that chronic workplace exposure to formaldehyde is closely related to asthmatic symptoms in many cases, even though the prevalence of a positive provocative test with formaldehyde is very low. This inconsistency suggests that formaldehyde may exacerbate asthma or increase susceptibility to it, rather than typically acting as a direct cause. Importantly, standardized methods for provocative tests with formaldehyde have not been established.[17,18] Therefore, conclusive evidence determining the role of formaldehyde in development of asthma is still required.

Formaldehyde and pulmonary function in healthy subjects

Alexandersson *et al*. have shown that small exposures to formaldehyde (e.g. 0.36 p.p.m. for several hours) cause slight but significant deterioration in lung function, including a 2% decrease in the percentage FEV_1 in non-asthmatic subjects occupationally exposed to formaldehyde.[19] The deterioration was reversible and no lasting effects could be established. Both smokers and non-smokers displayed similar changes. Kriebel *et al*.[20] examined the effects on PEF change in 24 students repeatedly exposed to formaldehyde (0.49–0.93 p.p.m. for 3 h/week) during a clinical anatomy laboratory course lasting 10 weeks. Peak expiratory flow measured before each laboratory session declined over the semester by an average of 2% of baseline; the change was statistically significant. In this study, asthma was among the important predictors of PEF decrements. After 14 weeks away from the laboratory, the students' PEF had returned to pre-exposure levels. Kilburn *et al*. have studied the effects of long-term workplace exposure to low concentrations of formaldehyde on pulmonary function parameters (forced vital capacity and FEV_1), in 280 non-smoking white women working as histologic technicians.[21] Most of this cohort exposed to formaldehyde had better pulmonary function at the age of 20 than a comparison population at age of 20, but they had greater decrements with time, resulting in lower pulmonary function values than in controls at the age of 60.

Formaldehyde in non-occupational settings and symptoms of asthma

Krzyzanowski *et al*.[22] have studied relationships of chronic respiratory symptoms and pulmonary function to formaldehyde in homes in a sample of 298 children and 613 adults. In the children, medically diagnosed asthma and chronic bronchitis were more prevalent in houses with higher formaldehyde levels (0.06–0.12 p.p.m.). In addition, PEF values decreased linearly with increasing concentration of formaldehyde, an effect discernibly greater in asthmatic children than in healthy ones when the ambient formaldehyde concentrations were below 0.05 p.p.m. Such relationships were not clearly evident in adults. Smedje *et al*.[23] have studied the physical characteristics of school environments in terms of asthma, finding concentrations of formaldehyde to be significantly related to prevalence of childhood asthma.

These summarized studies suggest that, even in non-asthmatic subjects, repeated and long-term exposure to formaldehyde causes a small degree of bronchial obstruction that probably results from airway inflammation. The changes appear to be proportional to the ambient concentration and duration of exposure and are greater in inflamed than in healthy airways. Furthermore, long-term exposure to formaldehyde may cause irreversible lung dysfunction, although the decreases in pulmonary function following single or repeated formaldehyde exposures appear to be reversible.

Formaldehyde as an immunogen

Formaldehyde is a potent contact sensitizer that can elicit contact dermatitis. As mentioned earlier, formaldehyde has been demonstrated to induce bronchoconstriction immediately following its inhalation in a small subgroup of patients with asthma. The mechanisms underlying this asthmatic response may be complicated. Inhaled formaldehyde is presumed to rapidly combine with a variety of proteins, such as albumin, inducing formaldehyde-specific IgE antibodies. These IgE, in turn, could mediate bronchoconstriction.

In the past, hemodialysis frequently exposed patients to high levels of formaldehyde because of its use as a coil disinfectant. Under those conditions, a patient may have been infused with as much as 126 mg formaldehyde during a single hemodialysis session.[18] Maurice *et al*. have reported a 20-year-old woman undergoing long-term hemodialysis who developed severe anaphylactic shock, requiring resuscitation, within 20 min of beginning a session.[24] Skin prick tests with 0.1% and 1% formalin were positive in the patient but negative in control subjects. Levels of formaldehyde-specific IgE antibodies were elevated in a radioallergosorbent test (RAST) using paper discs coated with formaldehyde-conjugated human serum albumin (formaldehyde-HSA). Similarly, Ebner and Kraft[25] and Wantke *et al*.[26] have reported that four patients undergoing dental treatment with formaldehyde-containing tooth-filling material developed systemic reactions 1–10 h later. These patients had a positive RAST to formaldehyde-HSA but a negative skin test with 1% formalin, suggesting the involvement of IgE-mediated mechanisms. Patterson *et al*.[27] have reported that IgG antibodies to formaldehyde-HSA were more prevalent in subjects who had been exposed to formaldehyde intravenously during hemodialysis using formaldehyde-disinfected equipment than in 32 persons exposed to gaseous formaldehyde; only one subject with gaseous exposure had IgG antibodies to formaldehyde-HSA. Systemic exposure to significant levels of circulating formaldehyde, then, frequently results in both IgE and IgG sensitization.

Wilhelmsson and Holmstrom have reported that two of 30 formaldehyde-exposed workers with rhinitis possessed high levels of IgE antibodies to formaldehyde-HSA, as determined by RAST.[28] The two workers had severe rhinitis, strongly linked by clinical evidence to the workplace. This observation indicates that long-term inhalation of formaldehyde can sensitize atopic individuals. However, whether formaldehyde-specific IgE antibodies contributed to the symptoms of rhinitis in these workers was not determined by provocative testing. Grammer *et al*.[29] have described a worker with clinical symptoms compatible with bronchospasm induced by inhaled formaldehyde. This individual had significant levels of IgE and IgG antibodies to formaldehyde-HSA and a positive skin test to formaldehyde-HSA, although a provocative test with formaldehyde at 0.3–5 p.p.m. for 20 min was negative. Grammer *et al*. carried out a more extensive clinical and immunologic evaluation of 37 workers exposed to formaldehyde.[30] While none had IgE or IgG antibodies to formaldehyde-HSA, some complained of irritant symptoms related to workplace exposure to formaldehyde or other irritant chemicals. When Salkie examined the prevalence of atopic symptoms and hypersensitivity to formaldehyde in 63 pathologists in active practice, 29 complained of formaldehyde hypersensitivity, but formaldehyde-specific IgE antibodies were not detected.[31] Kramps *et al*. have reported a similar negative result, finding formaldehyde-specific IgE antibodies in only one of 86 sera from individuals exposed to formaldehyde.[32] Liden *et al*. have found that among 23 patients with a previous positive patch-test reaction to formaldehyde, only two had formaldehyde-specific IgE antibodies.[33] Wantke *et al*. assessed the sensitizing potency of formaldehyde exposure during 4 weeks of an anatomy dissection course in 45 medical students.[34] A 4 week exposure to low concentrations of gaseous formaldehyde (0.059–0.219 p.p.m.) did not induce production of IgE reactive to formaldehyde. However, Wantke *et al*. have reported elevated IgE levels to formaldehyde in 24 of 62 8-year-old children (39%) attending a primary school where indoor formaldehyde concentrations did not exceed 0.08 p.p.m.[35] Therefore, children may be more susceptible to IgE sensitization to formaldehyde than adults. In this study of children, however, IgE sensitization did not correlate with clinical complaints. In contrast, there was a high correlation between the prevalence of symptoms such as rhinitis, cough and epistaxis and formaldehyde concentrations in the classrooms.

Collectively, the results suggest that inhaled formaldehyde appears to have little ability to produce IgE sensitization in adults, although children may be more sensitive to formaldehyde in this respect. In addition, the presence of formaldehyde-specific IgE antibodies is not necessarily associated with clinical symptoms. To date, no definite evidence has shown that gaseous formaldehyde induces IgE-dependent bronchoconstriction.

Formaldehyde as a modulator of antibody production in animal experiments

Tarkowski and Gorski have investigated the effect of formaldehyde exposure on IgE sensitization to ovalbumin in mice.[36] Significant enhancement of IgE antibodies to ovalbumin has been observed in mice exposed to formaldehyde at 1.6 p.p.m. (6 h/day) for 10 days and sensitized to ovalbumin intranasally. However, the same treatment with formaldehyde had no facilitating effect on IgE sensitization to intraperitoneally injected ovalbumin.

In guinea-pigs, Riedel *et al*.[37] have demonstrated that short-term exposure to low concentrations of formaldehyde (e.g. 0.25 p.p.m.) significantly enhances the production of IgG1 antibodies to ovalbumin as well; the effect is dependent on formaldehyde concentrations. The results suggest that inhaled formaldehyde may facilitate IgE sensitization to a variety of inhalant allergens, thus increasing the prevalence of asthmatic symptoms. However, mechanisms underlying these immunologic effects remain unclear.

Formaldehyde as a trigger of asthma-like states in animal experiments

Asthma is a chronic inflammatory disease of the airway with immunohistopathologic features including denudation of airway epithelium, collagen deposition beneath basement membranes, edema, mast cell activation and eosinophil, neutrophil and T-lymphocyte infiltration.[38] A trigger of asthma is defined as a risk factor that exacerbates a variety of inflammatory processes in the airway, leading to recurrent bronchial obstruction. As mentioned earlier, several clinical studies have suggested that formaldehyde may trigger asthma, but the mechanisms involved are not clear.

We have investigated the effect of gaseous formaldehyde on airway microvascular leakage and bronchoconstriction in mechanically ventilated rats.[39] To examine the role of formaldehyde-induced tachykinin release, the effect of a selective inhibitor of tachykinin NK1 receptors (CP-99 994) has been studied on airway responses induced by formaldehyde. Inhalation of gaseous formaldehyde produces a concentration-dependent increase in vascular permeability in the rat trachea and main bronchi (Fig. 2), but no bronchoconstrictor effect is observed. Wei and Kiang[40] have previously found that an extremely high concentration of formalin vapor (approximately 594 p.p.m.) induces tracheal microvascular leakage in anesthetized rats, but we have noted that a much lower threshold concentration (> 2 p.p.m.) can induce some increase above baseline levels of leakage in the airways. Formaldehyde concentrations above 2 p.p.m. are sometimes detected in occupational settings. The CP-99 994 completely abolishes formaldehyde-induced airway microvascular leakage (Fig. 3), indicating that inhaled formaldehyde can release tachykinins, such as substance P, from airway sensory nerve endings in the same way as capsaicin. Because ketotifen (a selective H1 receptor antagonist) and HOE140 (a selective bradykinin B2 receptor antagonist) have no effect on airway microvascular leakage induced by formaldehyde, activation of bradykinin receptors and mast cells does not appear to participate importantly in this airway response.

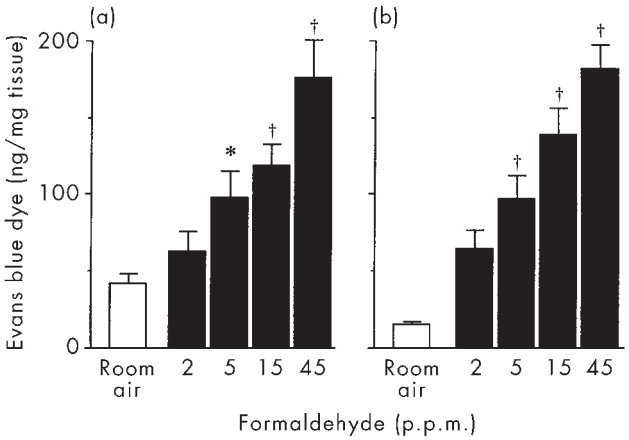

Fig. 2 Evans blue dye extravasation in the (a) trachea and (b) main bronchi induced by 10 min inhalation of gaseous formaldehyde (■) or room air (□). Values are the mean ±SEM (n = 5–7). *$P < 0.05$ and †$P < 0.01$ compared with the room air-exposed group.

In our rat model, formaldehyde significantly increases serum albumin exudation into the airway lumen in a concentration-dependent fashion, with a threshold concentration of 2–5 p.p.m. (Fig. 4). The airway response is abolished completely by the tachykinin NK1 receptor antagonist CP-99 994. Hastie *et al*. have demonstrated that formaldehyde directly inhibits ciliary activity in airway epithelium and that this effect is not mediated by altered rheologic properties of mucus.[41] The ciliary dysfunction elicited by formaldehyde was reversible. Nevertheless, temporary reduction of ciliary function would supposedly increase the dose of solubilized formaldehyde through lack of clearance and thereby increase the likelihood of locally cytotoxic levels. Cellular changes associated with exposure to formaldehyde include not only alterations of cilia, but also hypertrophy of the goblet cells.[42] Together, these changes may lead to the formation of inspissated mucus plugs. In these varied ways, airway tissue responses induced by formaldehyde may contribute to airflow limitation, resulting in asthma.

Swiecichowski *et al*. have reported that in the guinea-pig, hyperresponsiveness to intravenous acetylcholine can be induced by lower formaldehyde concentrations (> 0.3 p.p.m.) when the duration of exposure is extended from 2 to 8 h.[43] Formaldehyde has also been found to heighten airway smooth muscle responsiveness

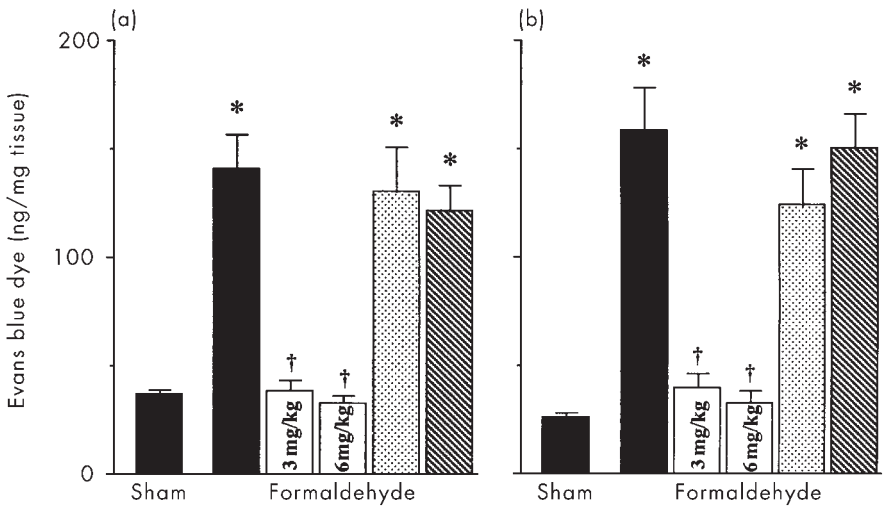

Fig. 3 Effect of CP-99 994, HOE140 and ketotifen on Evans blue dye extravasation in the (a) trachea and (b) main bronchi induced by inhalation of gaseous formaldehyde (15 p.p.m. for 10 min). Rats were treated with 3 or 6 mg/kg i.v. CP-99 994 (□), 0.65 mg/kg i.v. HOE140 (▨), 1 mg/kg i.v. ketotifen (⊡) or the vehicle only (0.5 mL/kg i.v. 0.9% saline; ■) before formaldehyde challenge. Sham, animals exposed to room air for 10 min after pretreatment with 0.9% saline (0.5 mL/kg i.v.). Data are the mean ± SEM ($n = 6$–7). *$P < 0.05$ compared with the sham treatment. †$P < 0.01$ compared with the control treatment.

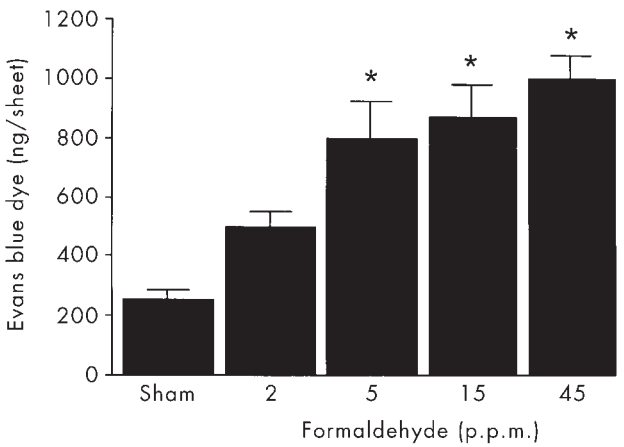

Fig. 4 Amount of Evans blue dye that exuded into the tracheo-bronchial lumen after 10 min inhalation of gaseous formaldehyde or room air. The dye in the tracheo-bronchial lumen was absorbed on filter paper (7 × 30 mm). Sham, animals exposed to room air for 10 min. Values are the mean ± SEM ($n = 6$). *$P < 0.05$ compared with sham treatment.

to acetylcholine and carbachol *ex vivo*. In the guinea-pig study, bronchoconstriction was also observed after inhalation of formaldehyde at levels above 3 p.p.m. for 2 h,[43] in contrast to our previous results in rats.[39] We have found in further studies in rats (Sakamoto *et al*., unpubl. data, 1998) that formaldehyde induces neutrophil influx into the airway and epithelial denudation within 60 min of inhalation (15 p.p.m., 10 min). The tachykinin NK1 antagonist CP-99 994 completely blocks migration of neutrophils, but has no effect on epithelial denudation. Formaldehyde may attract neutrophils into the airway by tachykinin NK1 receptor-mediated mechanisms, as capsaicin does.[44] Epithelial denudation, in contrast, may result from the non-specific cytotoxity of formaldehyde. Neutrophils can participate in inflammatory responses, including airway epithelial disruption, by releasing chemical mediators, superoxide anions or proteases. In extensively disrupted epithelium, neurogenic inflammation appears to be exaggerated;[45] the surface of intact epithelium is rich in neutral endopeptidases that degrade tachykinins and bradykinin. Such changes of epithelium may be associated with hyperresponsiveness to a wide variety of stimuli. Airway hyperresponsiveness is important to the pathogenesis of asthma and usually correlates with clinical severity.

Long-term exposure to formaldehyde may cause irreversible airflow limitation in human airways. However, no previous animal study has demonstrated toxicity from prolonged exposure to formaldehyde in the lower airway. Rusch *et al*.[46] have conducted a 26 week inhalation study in monkeys, rats and hamsters. The animals were exposed continuously to formaldehyde at concentrations of 0.19, 0.98 and 2.95 p.p.m. for 22 h/day. The results showed induction of nasal lesions only in rats and monkeys exposed to 2.95 p.p.m. formaldehyde, which induced squamous metaplasia in 62% of animals. No lower respiratory tract effects were observed, even at 2.95 p.p.m. formaldehyde. Holmstrom *et al*.[47] have examined histologic changes in the nasal mucosa of

rats following long-term exposure to formaldehyde (12.4 p.p.m.) and wood dust (25 mg/m^3). One of 16 rats had developed nasal squamous cell carcinoma at 104 weeks of exposure. In contrast, epidemiologic data regarding the human carcinogenicity of formaldehyde are variable and definitive conclusions cannot be reached.[1]

Conclusion

Previous studies of occupational asthma associated with formaldehyde have reported that the chemical exposure is chronologically related to onset or exacerbation of asthmatic symptoms in many cases; however, it is very rare that the result of provocative formaldehyde inhalation test is positive. This difference may be attributed to multiple factors. First, direct effects of formaldehyde on airway contraction are relatively slight, but formaldehyde may still have other potent effects causing dysfunction or inflammation in airways. Second, additional chemical contaminants are present in the air in workplaces and homes. Formaldehyde may be related to onset and exacerbation of asthmatic symptoms in the specific context of such composite contamination. Third, water drops or particulates containing formaldehyde entering the airway may bring about airway reactions specific to non-gaseous formaldehyde. These issues are important targets for future investigation.

Long-term and repeated exposure to formaldehyde may influence pulmonary function. Because infants spend most of their time in indoor environments, they are particularly likely to be exposed to contaminants in room air, making study of the influence of airborne formaldehyde on their airways an urgent priority. When children are exposed to cigarette smoke or SO_2 in infancy, their pulmonary function may be decreased after several years[48,49] and exposure to formaldehyde in infancy similarly may have effects on the health of children that are still unknown.

The retention ratio of formaldehyde-specific IgE antibodies has been found to be very low in patients diagnosed with occupational asthma attributable to formaldehyde. However, Wantke *et al*.[35] have detected formaldehyde-specific IgE antibody in 39% of schoolchildren, which suggests that children may have a more marked immune reaction to formaldehyde than adults. With regard to formaldehyde-specific IgE antibodies, if allergic inflammation caused by formaldehyde is superimposed on conventional asthmatic airway dysfunction, the effects of IgE sensitization by formaldehyde may be very serious. However, convincing evidence has not been found that patients with asthma who are positive for formaldehyde-specific IgE antibodies are exceptionally severely sick or refractory to treatment. Many of these issues require future study.

Formaldehyde has been hypothesized to directly produce dysfunction and inflammation in airways and also to act indirectly as a factor promoting antibody production and causing various types of inflammatory reactions. Allowable standards for formaldehyde concentration in air have been set at 0.5 p.p.m. for work environments (recommended by WHO and the Japanese Association for Industrial Hygiene) and 0.08 p.p.m. for non-occupational indoor environments (WHO); these standards may require revision as new data become available. Above all and more generally, more ventilation is needed in homes and building materials and interior furnishings should be sought that generate smaller amounts of formaldehyde and other volatile organic gases.

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