

EDITORIAL

Is formaldehyde an important cause of allergic respiratory disease?

The health effects of formaldehyde have been a matter of scientific and public interest since the 1970s. In recent years the focus of attention has shifted from the question of carcinogenicity to the effects of low-level exposure to formaldehyde, and particularly to its role as a cause of immunologically mediated respiratory disease. The paper by Wantke *et al.* [1] reports the presence of serological markers of allergy to formaldehyde in a group of children exposed to relatively low levels of formaldehyde in school-buildings. It is a timely prompt to consider the role of formaldehyde as a respiratory sensitizing agent.

Exposure to formaldehyde is ubiquitous. It is formed naturally in the troposphere, and is endogenous in plant and animal life [2]. It is widely used in industry and is well recognized as a pollutant of both indoor and outdoor air. The principal use of formaldehyde in industry is in the manufacture of urea-formaldehyde, melamine and polyacetyl resins. Consequently, it is found in many products including particle board, plywood, office furniture, floor coverings and furnishing fabrics. It is commonly used as a sterilizing agent in the health care industry, and is added as a preservative to a wide range of manufactured items, for example cosmetics, detergents and foodstuffs. The release of formaldehyde (off-gassing) from the many consumer products described above affects indoor air quality in workplaces, homes and public buildings [3–5]. Other major indoor sources are tobacco smoke and urea-formaldehyde foam insulation (UFFI). The principal determinant of exposure to formaldehyde in outdoor air is incomplete combustion of fossil fuels, particularly vehicle exhaust emissions [3–5].

The highest exposures to formaldehyde are encountered in occupational settings. For example, measured concentrations in factories engaged in resin production have mostly been in the range 1.2–12 mg/m³ [6]*. Embalmers and health care workers are typically exposed to mean levels of 0.12–1.2 mg/m³ [6]. Non-occupational exposures are generally lower. The range of outdoor levels is influenced by factors such as proximity to point sources, traffic and atmospheric conditions [5,6], but average levels are of the order of 0.005–0.01 mg/m³ in urban air, with peaks of up to 0.1 mg/m³ [3]. Indoor concentrations also vary as a result of outdoor air levels,

temperature, humidity, emission sources and ventilation [7]. However, in general, indoor levels of formaldehyde exceed those typically found in the outdoor environment. Mean levels in conventional homes without UFFI in the United States are in the range 0.025–0.06 mg/m³ [5,6] and concentrations up to 0.45 mg/m³ have been recorded in modern office buildings [4]. Formaldehyde levels in mobile homes constructed of particle board are now typically around 0.12 mg/m³, although in the past they were higher [6].

Reviews of toxicological data describe ocular and upper airway irritation with exposure to levels of gaseous formaldehyde above 0.12 mg/m³ [3,4,5,8]. Lower respiratory tract symptoms described at exposure levels above 6.15 mg/m³ are commonly attributed to irritation [5]. Exposure to much lower concentrations of formaldehyde in both occupational and domestic settings has also been associated with lower respiratory tract symptoms [9–12]. However, gaseous formaldehyde is highly water soluble, and at such low exposure levels is mainly absorbed in the upper respiratory tree [3–5]. Even in asthmatics, a group thought to be particularly susceptible to irritants, no adverse effects of pulmonary function were found with exposure to low level formaldehyde under experimental conditions [13–15]. It is therefore unlikely that irritation is the mechanism for chest symptoms associated with low level exposures. An alternative explanation is that formaldehyde can induce sensitization, and that respiratory symptoms have an immunological basis in some individuals.

An immunologically-mediated mechanism for respiratory tract symptoms is certainly biologically plausible. Formaldehyde is a low molecular weight chemical which could behave as a hapten, reacting with native protein to form an antigenic conjugate which is capable of stimulating the production of specific antibodies. Most of the literature which investigates this hypothesis relates to levels of formaldehyde typically encountered in occupational settings. There have been a number of reported cases of work-related asthmatic symptoms in individuals exposed to inhaled formaldehyde [16–19]. Positive specific bronchial provocation challenges to formaldehyde or formaldehyde-containing particle board [17], showing typical late [16,18,19] or dual [17] asthmatic responses, were found in some of these cases. However, negative specific challenge tests have been demonstrated in other cases with work related lower respiratory symptoms [16,18,20].

* Formaldehyde levels are given in mg/m³ throughout. Conversion factor: ppm $\times$ 1.23 = mg/m³.

Specific IgE antibodies to formaldehyde have been described in association with intravenous exposure during renal dialysis, and have been linked with a type 1 immediate hypersensitivity response in a small number of patients [21]. Several studies have measured specific IgE to formaldehyde-human serum albumin conjugate in small series of individuals exposed to inhaled formaldehyde at work [22–26]. Formaldehyde specific IgE was found in a small proportion of exposed individuals [22–24], but this was not associated with respiratory symptoms in all cases. Conversely, there were symptomatic individuals or groups in whom specific IgE was not found [22,23,25,27]. Anti-formaldehyde antibodies of other immunoglobulin isotypes (IgG, IgM) have been found in formaldehyde-exposed individuals [24,25,26,28], but again there is no consistent association with symptoms. The clinical relevance of antibodies to formaldehyde in humans, therefore, remains unclear.

Very few studies have measured specific antibodies in individuals exposed to low levels of formaldehyde in indoor air. Kramps *et al.* [23] found no specific antibodies among 28 adults exposed to formaldehyde in domestic and office environments, but the power of this study was too low to detect anything but a large increase in risk of sensitization. In other models of allergic respiratory disease it has been shown that the prevalence of sensitization (defined by skin-prick positivity) increases with increasing exposure intensity [29,30]. Therefore, it is likely that the risk of sensitization from exposure to formaldehyde at levels encountered in domestic and environmental situations is extremely low.

There remains a question whether the risk of immunological disease at low exposure levels is higher in susceptible groups. Wantke *et al.* express concern about the increased susceptibility of children, based upon a high prevalence (40%) of antiformaldehyde IgE in school-children exposed to levels of formaldehyde ranging from 0.053 to 0.092 mg/m³ [1]. In this study the prevalence of antibody positivity increased with increasing exposure to formaldehyde. However, as with the occupational studies mentioned above, raised specific IgE did not correlate well with clinical symptoms. Total IgE levels are known to peak in children of school age [31] and, in the absence of a relationship to symptoms, raised specific IgE may not be clinically relevant. The authors observed a decline in the highest individual specific antibody titres, which coincided temporally with both a reduction in formaldehyde exposure and in symptom prevalence. This finding does not establish a causal link between symptoms and sensitization to formaldehyde. One explanation for the observation might be that the decrement in titres merely represents regression to the mean, rather than a relationship with

exposure to the putative allergen. This phenomenon occurs when a fluctuating measure such as IgE titre or blood pressure is measured in a sample of people on two separate occasions. If nothing else has changed, the overall distribution of measurements will be similar each time. However, because of random variation, the ranking of individuals within this distribution will change. In particular, those who start near the top of the distribution will tend on average to have a lower level when measured again. To exclude this effect, it is necessary to measure the complete sample on both occasions.

In summary, it would appear that even at (relatively) high exposure levels, inhaled formaldehyde rarely induces a specific immune response; and the relationship between this response and respiratory symptoms is poor. To date, environmental exposure to formaldehyde has not been proven as an important cause of immunologically mediated respiratory disease in adults. Children may show an increased tendency to develop specific antibodies after environmental exposure to formaldehyde, but their clinical significance remains uncertain.

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