# Editorials and Annotations

## Editorial: Building Ventilation and Symptoms—Where Do We Go from Here?

In the past 2 decades, increasingly frequent episodes of symptoms (e.g., headache; lethargy; eye, nose, and throat irritation; breathing difficulties; and dry skin) among occupants of large, mechanically ventilated buildings have aroused public concern. Although explanations have sometimes been found for symptoms reported in individual buildings, in many buildings neither specific diseases nor evident causes have been identified.[1] The lack of environmental explanations, along with evident psychological distress in the workers, has to some suggested "mass psychogenic illness"; however, such illness has specific diagnostic criteria that the health complaints in these episodes rarely fit.[1] Furthermore, available studies suggest that some of these occupant symptoms involve physiological responses to environmental exposures.[2]

The role of building ventilation in this phenomenon is not well understood. Inadequate ventilation is a suspect in many symptom episodes, yet this suspicion is based on little actual knowledge about the relationship between ventilation and health. The study by Jaakkola et al.[3] reported in this issue exemplifies one kind of research necessary to provide this knowledge; however, consideration of the few relevant studies available illustrates how far we still have to go.

Building ventilation is the movement of outdoor air into a building, either mechanically or by infiltration. An important aspect of ventilation is the volumetric rate of outdoor air per person brought into a building—that is, the outdoor air ventilation rate.

Before the energy crisis of the 1970s, the minimum recommended outdoor air ventilation rate in the United States was 20 cu ft of air per minute per person (cfm/p); this rate was based primarily on the need to control odors produced by the occupants themselves.[4] In the 1970s, this recommended minimum was lowered to 5 cfm/p to reduce energy costs. Later in the decade, the phenomenon of symptom complaint episodes, sometimes referred to as sick building syndrome, first appeared. As this syndrome was thought to be related to inadequate ventilation (and thus was sometimes called tight building syndrome), the minimum ventilation guidelines were raised over time back to 20 cfm/p, the current minimum for offices.[4]

Historically, these guidelines, produced through consensus by organizations such as the American Society of Heating, Refrigerating, and Air-Conditioning Engineers, have been incorporated into building codes and other regulations as standards, setting the minimum outdoor air ventilation rate that the ventilation system in a new building must be designed to provide. In theory, a building should then actually provide and continue to provide the prescribed amount of outdoor air, but in practice, building codes have not been used for this kind of enforcement. In effect, practically enforceable standards for the delivery of outside air into occupied buildings have been rare. Only recently have proposed or established indoor air quality statutes in several states (e.g., California, New Jersey, and Washington) defined such explicit standards for outdoor air ventilation.

**Editor's Note.** See related article by Jaakkola et al. (p 422) in this issue.

## *Current Knowledge about Outdoor Air Ventilation Rates and Occupant Health*

Aside from the aforementioned study by Jaakkola et al.,[3] at least five reported experimental or cross-sectional studies (reviewed elsewhere[2]) have assessed the relationships between occupant symptoms and outside air ventilation rates in large buildings, including outside air ventilation levels ranging from well below current minimum guidelines to well above.[5–9] All previously reported comparisons in which both mean ventilation rates were *above 21 cfm/p* (or 10 L/s per person) found no significant symptom differences between ventilation rates.[2,5–7] All previously reported comparisons in which one or both of the mean ventilation rates compared were *at or below 21 cfm/p* found significantly increased symptom prevalence at the lower ventilation rate.[2,5,8,9] Jaakkola et al., however, here report no significant differences in symptom prevalence between ventilation rates of 13 and 42 cfm/p of outside air.[3]

The discrepancy between Jaakkola et al.[3] and other studies is not the result of any evident design weaknesses in the current study: Jaakkola et al.'s study involved a double-blind experiment, using a multiple crossover design and within-subject analyses to control for individual confounding factors and time effects, and a daily symptom diary to minimize recall bias.[3] One possible reason for the discrepancy may be the brief 1-week experimental periods used in this study, which would allow detection only of immediate effects. In contrast, a previous experimental study by these authors found reduced ventilation rates to be associated with significantly increased symptoms after 3 weeks but not after 3 days.[5] Nagda et al. found symptom differences between ventilation levels maintained for 2 weeks each.[8] And the cross-sectional study by Sundell et al. found symptom differences between building spaces with presumably long-term high and low ventilation rates.[9]

In interpreting epidemiologic studies, it is important to consider their limitations. Of the three studies that have found a significant relationship between lower ventilation rates and higher symptom prevalence,[5,8,9] one failed to control for the potent beneficial effects of being studied and thus may have exaggerated the relationship found.[8] Only two studies of fairly strong design[2]—one experimental[5] and one cross-sectional[9]—have found a significant relationship, and the current well-designed experimental study by Jaakkola et al. has not.[3]

On the other hand, all six reported studies had important limitations in measuring the delivery of outdoor air, with resulting misclassification errors that would reduce ability to detect actual associations of the ventilation rate with symptoms. Current measurement methods, particularly those based on air flows[5,6] or carbon dioxide concentrations,[7] are inexact in their assessment of outdoor air ventilation rates. Furthermore, the methods used in all these studies assess only buildingwide ventilation rates and do not reflect the often substantial local variations in ventilation (which cannot yet easily be measured).

Ultimately, assessment of the relationship between ventilation and health must recognize that any health effects of a low outdoor air ventilation rate would occur only because outdoor air dilutes and reduces the concentrations of indoor-generated contaminants. Indoor exposures of concern—including odors, chemical toxins, allergens, and infectious agents—come from both human and nonhuman sources, such as building materials, furnishings, cleaning products, and microbiological contaminants. Generally, the stronger or more toxic an indoor source, the more dilution required to reduce its indoor concentration to acceptable levels.

As source strengths of indoor-generated pollutants vary widely not only between buildings but also within them, so too may buildings and even locations within buildings vary markedly in their health-related outdoor air ventilation requirements. Thus, given the current limitations in our ability to measure buildingwide ventilation rates, which are no more than estimates of local ventilation rates, themselves only modifiers of each individual's diverse personal exposures, it is not surprising that studies on the relationship between the ventilation rate and health have not been consistent. Future studies should address these limitations.

## *Where Do We Go From Here?*

Since we do not yet understand the nature, distribution, or toxicity of the many sources of indoor exposures, we have a limited scientific basis for considering current buildingwide outdoor air ventilation guidelines to be health protective. Given the impracticality of collecting toxicity information on all indoor pollutants of concern (including odorants, toxicants, allergens, and infectious agents), empirical data on worker symptoms at different outdoor air ventilation rates may be useful in setting guidelines that will reduce occupant symptoms in most buildings.

Jaakkola and others have demonstrated the utility of scientific research for this purpose, but available studies are too limited for conclusions. Studies are needed in a greater variety of buildings, over longer periods of time, and with improved measurements of the outdoor air ventilation rate, various indoor exposures, and health outcomes. Measurements should assess ventilation rate variation within buildings. Experimental studies will allow the strongest inference, but observational studies of many buildings (particularly if those studies are longitudinal) can also contribute.

Research on office worker symptoms must also consider more than outdoor air ventilation, because even buildings with high levels of outdoor air ventilation can have large proportions of workers with nonspecific symptoms.[3,5,7] These symptoms are clearly of multifactorial origin: epidemiologic studies have found their substantial occurrence in every large building studied and associated with a variety of building, workspace, job, and personal/psychological factors.[2] Examples of implicated factors include air-conditioning systems, temperature, humidity, carpets, poor office cleaning, work stress, and female gender.[2] Increasing the ventilation per person may help reduce symptoms caused by indoor-generated pollutants (although pollutant source reduction would be clearly preferable); however, increased ventilation would *not* eliminate symptoms related to psychological stressors, temperature or humidity, outdoor air contaminants, or contaminants produced within ventilation systems.

Existing scientific findings suggest that standards for outdoor air ventilation rates in occupied buildings may be reasonable, particularly if bolstered by additional research. But as ventilation standards alone cannot be sufficient to guarantee adequate indoor air quality,

we must look beyond minimum ventilation requirements to consider the proper design, construction, operation, and maintenance of buildings and their ventilation systems. More research is necessary here as well; however, based on current knowledge, the US Environmental Protection Agency and the National Institute for Occupational Safety and Health have compiled some practical approaches to the prevention and resolution of health and comfort concerns related to indoor environmental quality.[10]

We should not ignore these health problems of office workers simply because they involve nonspecific symptoms and multifactorial causes and because we have generally failed to identify simple solutions. Even nonspecific symptoms, when commonly experienced in the large population of indoor workers, are of public health importance and are probably of economic importance as well.[11,12] We will be able to minimize these symptoms only when we more fully understand the requirements for truly healthy indoor environments. □

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# Annotation: How Do We Get Enough Folic Acid to Prevent Some Neural Tube Defects?

In this issue of the Journal, Duff and Cooper allude to the question of how much folate daily is enough to prevent significant numbers of neural tube defects while not exposing any group of people to too much.[1] Unfortunately, the amount of hard evidence concerning the dose of folate associated with adverse consequences (e.g., to persons with compromised intrinsic factor excretion or other groups with poor cobalamin status) is limited. In contrast, the evidence for the protective role of folic acid in the etiology of neural tube defects is very strong.

From the best inferential tool available to epidemiologists, the randomized controlled trial, we know that a daily dose of 4 mg folic acid is effective in reducing the risk of neural tube defect–affected pregnancies by 70% among women who have had a previously affected pregnancy (the so-called recurrence risk).[2] We also know that a supplement of 0.8 mg folic acid is effeetive in reducing the risk of a first occurrence.[3] By inference, because of the consistency of the effect size in these trials and in observational studies,[4–7] we conclude that 0.4 mg folic acid with a multivitamin supplement is equally effective. Only one observational study is inconsistent with this conclusion.[8] It should be noted that our strongest evidence for the protective effect is from studies of folic acid from supplements (i.e., free folate or unconjugated folate).

The simplest corollary to this evidence, in practical prevention terms, is to recommend that all women considering pregnancy take a folic acid supplement (0.4 mg). The effectiveness of this strategy is called into question on two counts: First, neural tube defects occur in pregnancy before most women even know that they are pregnant, so all unplanned pregnancies would be at risk. Second, neural tube defects occur somewhat more frequently (but by no means exclusively) among women of low socioeconomic status. This group is less likely to adopt a preventive behavior. Dietary change strategies are subject to the same objections but have some additional difficulties in that the benefits of increasing dietary folate are not well established.

*How much do dietary sources of folate contribute to the preventive potential of folic acid?* Foods naturally containing folate include orange juice (a common source at a population level[9]) and vegetables such as spinach, broccoli, and collard greens. That dietary sources of folate do confer some protection against neural tube defects may be inferred from several studies.[1,10,11] Estimating an effective level of folate from dietary sources on the basis of these studies is problematic, partly because of measurement error. Such error is associated with both dietary intake assessment and the measurement of folate in foods. Nevertheless, a reasonable inference is that approximately 0.3 mg of dietary folate daily might confer some protection. The

**Editor's Note.** See related article by Duff and Cooper (p 473) in this issue.