Clean as a Whistle, But What about that Wheeze?

Cleanliness is generally perceived as being associated with health, and maintaining a clean home by reducing asthma triggers, such as dust mites and cockroaches, has been recommended as a "critical" component of asthma management (1). However, the article by Zock and colleagues in this issue of the *Journal* (pp. 735–741) presents results showing that how you clean your house may have adverse respiratory health effects (2). Analyzing data from 22 centers from 10 European countries that have participated in the clinical part II of the European Community Respiratory Health Survey, they found a statistically significant association between new onset of wheeze, nocturnal attacks of shortness of breath, use of asthma medication, and/or physician-diagnosed asthma in adults and the use of cleaning sprays in the home. Their findings are biologically plausible with the highest risk being among individuals with the greatest potential for inhalation exposure, namely, those using sprays in their homes at least four days a week and/or using more than three different types of sprays at least one day per week (2).

Although this is the first study to demonstrate an association between the use of cleaning products in the home and the onset of asthma among adults, we should not be surprised by these results, which are consistent with previous knowledge about the adverse respiratory effects of cleaning products. First, there have been at least six previous epidemiologic studies as well as multiple case reports and case series describing increased asthma and respiratory symptoms among workers who clean homes or commercial and industrial facilities (3, 4). Second, each year cleaning agents are either the second or third most common exposure among adults who are reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System (70,000–80,000 reports/year, 9–10% of all reports/year) (5). Third, cleaning agents contain many different types of chemicals, including known irritants and allergens. Studies have shown these chemicals in the indoor air of homes (6). Fourth, a recent study found a reduction in FEV_1 and maximum mid-expiratory flow rate that was statistically associated with blood levels of 1,4-dichlorobenzene, a chemical found in air fresheners, toilet bowl deodorants, and mothballs (7). Finally, there is a previous report of increased risk of persistent wheezing in young children up to the age of 3.5 years in association with increased domestic household chemical use, and predominantly cleaning agents that were used during pregnancy (8).

The methodology used by Zock and coworkers is strong; longitudinal design, large sample size, and standardized data acquisition. However, the study design does not allow the authors to assess the biological mechanism for the association. In addition, their results are equivocal on whether the adverse respiratory outcome they found was the new onset of asthma or respiratory symptoms without asthma. They reported associations between the use of cleaning products and wheezing or whistling in the chest in the previous 12 months with the use of cleaning products and physician-diagnosed asthma. They found no increased risk with the use of cleaning products for the development of wheeze in people with a positive methacholine challenge test, and only a nonstatistically significant association in people with a physician diagnosis of asthma with a positive methacholine challenge test (2).

Four possible biological mechanisms, none of which are mutually exclusive, may explain the results of this study. First, high exposure to an irritant may cause reactive airways dysfunction syndrome (RADS) (9). Inappropriate mixture of a cleaning product containing bleach and a cleaning product containing an acid will release chlorine gas, and inappropriate mixture of bleach and ammonia will release chloramines. Second, chronic low-level exposure to the many irritants in cleaning compounds may cause inflammatory changes (10). Third, cleaning agents are known to contain sensitizers, such as amine compounds, benzylakonium chlorine, and disinfectants, such as chlorhexidine (3). There are no regulatory requirements for companies to test their products or ingredients for the ability to cause type 1 immunologically mediated reactions, such as asthma. Routine toxicological testing performed by companies that produce cleaning products includes assessing the irritant potential of the compound. Additional testing may sometimes include testing for contact dermatitis. Accordingly, the number of potential sensitizers that are present in cleaning products is unknown. Finally, although Zock and colleagues found no effect of atopy on their results, individuals who clean would be expected to have increased exposure to dust and dust mites. The ability of a chemical in a cleaning product to increase reactivity to an allergen such as dust mites has been reported in both animals and human studies (11). All four mechanisms could contribute to the epidemiologic findings of Zock and colleagues.

Despite the uncertainty of the biological mechanism of the findings reported by Zock and colleagues, clinicians should be aware of the potential for cleaning products used in the home to cause respiratory symptoms and possibly asthma. The lack of pretesting of cleaning products by industry has led to at least one recall of a miticide carpet powder and spray, marketed for individuals with asthma, after consumers reported asthma attacks and respiratory symptoms 15 to 30 minutes after use (12). As part of the settlement, the company provided funding to a nonprofit organization to purchase and staff a mobile asthma clinic. Obtaining information on the timing of symptoms and asthma exacerbations should be considered an important part of clinical management. Clinicians practicing outside of the United States, where access to specific antigen bronchial challenge testing is more readily available, will probably be able to identify new sensitizers present in cleaning products. Repeated peak flow testing by patients, as has been reported in one study of professional cleaners, may be useful in better defining both the cause and severity of symptoms (13).

The ubiquitous use and exposure to cleaning products emphasize the importance of clinicians being aware of the potential for respiratory toxicity. In addition, there is the need for researchers to conduct further studies to elucidate both the extent and mechanism of the respiratory toxicity associated with such products. Finally, the industrial producers and governmental regulators must improve the toxicological testing of these products.

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Breaking Down the "Great Wall" of COPD Care in China

China is the world's leading producer and consumer of tobacco products with more than 34.8 million cartons of cigarettes produced and 34.7 million sold each year (1). Today, there are more than 320 million smokers in China, representing 67% of the total adult male and 4% of the adult female populations in that country. Approximately one-third of all smokers in the world are Chinese (1). Not surprisingly, smoking-related lung diseases and, in particular, chronic obstructive pulmonary disease (COPD) are a major epidemic in China, costing that society billions of dollars in health care expenditures and lost productivity from premature (and perhaps unnecessary) deaths every year (2). In 2000, the total cost of COPD and other smoking-related diseases in China was more than U.S. $5 billion (2) and, in 2000, COPD was the second leading cause of mortality in China, trailing only cerebrovascular disease (3).

The morbidity and mortality from COPD in China will grow exponentially in the coming years, driven in part by the aging of the population, continued increases in smoking rates, especially in women, and the successful treatment of other common disorders, such as cardiovascular and infectious diseases (4). Despite these alarming statistics, robust prevalence estimates of COPD in China have not been available until now.

In this issue of the *AJRCCM* (pp. 753–760), Zhong and colleagues report the findings from the largest COPD prevalence study of its kind in China (5). The study was conducted in over 20,000 residents across seven different provinces and cities representing more than 230 million people (5). They found that approximately 8.2% of subjects who were 40 years and older had spirometric evidence of COPD and, of these, 75% (5.9% of the total subjects tested) demonstrated clinically relevant disease (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stages 2 or higher). These data are remarkably consistent with the published literature from other countries. A recent meta-analysis of all population-based prevalence studies across the world reported a pooled COPD prevalence of 9.2% (5.5% had GOLD stages 2 or higher COPD severity) (6).

There are, however, some interesting and notable differences between Zhong and colleagues' study and the published studies to date. First, dissimilar to the meta-analysis, Zhong and colleagues' study found that rural compared with urban residents had a higher prevalence of COPD (9 vs. 8%). The exact reasons for this discrepancy are unclear, although there are several possibilities. Although China has experienced remarkable modernization over the past two decades, in many rural areas residents continue to use wood, charcoal, or coal for fuel, leading to significant biomass exposure, especially in women, who perform most of the cooking duties. Biomass exposure is an established risk factor for obstructive airway disease and reduced lung function (7). In addition, rural compared with urban residents in Zhong and coworkers' study were older and had greater tobacco exposure, which may have further increased their risk of COPD (5). Second, nearly 9% of the cohort had a "restrictive" defect on spirometry, defined as FEV_1 less than 80% with a normal FEV_1 to FVC ratio. The underlying pathobiology of these restrictive defects is uncertain. However, such individuals are at increased risk of morbidity and mortality from COPD, similar to those with obstructive airway disease (8). If one combines both the "restrictive" and "obstructive" disorders together, the overall prevalence of "lung disease" in China may be closer to 17% (8% for obstructive disease and 9% for restrictive disease).

Although the burden of lung disease in China appears to be enormous, the tragic irony is that it is grossly underdiagnosed (and hence largely ignored). In Zhong and colleagues' study, fewer than 7% of subjects with COPD had been previously tested with spirometry, although two-thirds of them had symptoms suggestive of COPD (5). Even among subjects with GOLD stages 3 and 4 disease, fewer than 10% had ever received spirometry. These data are alarming because the assessment of airflow is absolutely essential in the proper diagnosis and management of COPD (9). The gross underutilization of spirometry represents a "Great Wall," a huge barrier to good care for patients with COPD in China. COPD is a highly preventable and treatable condition but only when it is properly diagnosed (9).

The findings by Zhong and colleagues are not only a sobering reminder of the great challenges of integrating spirometry into the day-to-day practice of clinicians but also a call to develop novel and more acceptable noninvasive intermediate biomarkers (e.g., blood) that can complement (and perhaps even supplant) spirometry in the evaluation and management of patients with COPD in China and elsewhere. Perhaps then, the "Great Wall"