Irritants and asthma

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If workplace exposures contribute to asthma, then they are too high and should not be considered low or moderate http://ow.ly/xwPuI

Asthma is a complex entity and one of the most common disorders in the world, affecting much of the workforce [1]. Asthma prevalence in children and adults has shown an increasing trend in the last decades [2, 3], which makes this disorder a major public health concern. Nevertheless, the mechanisms for the high incidence are not yet completely understood. In this regard, epidemiological studies focused on occupational asthma may contribute to unravelling the complexity of the disorder and the agents related to its onset and development.

Work-related asthma has been classified as comprising two main entities: sensitiser-induced asthma and irritant-induced asthma (IIA) [4]. The first involves a specific immunological response to a workplace sensitiser. These sensitisers are high-molecular-weight agents acting *via* the production of specific IgE antibodies or low-molecular-weight chemicals acting *via* other, hitherto less clarified immunological pathways [5–8]. The term IIA refers to asthma caused by exposure to agents that, when inhaled, act as respiratory irritants in the absence of sensitisation [9, 10]. In the 1980s, Brooks *et al.* [11] described reactive airway dysfunction syndrome. This diagnosis required very strict criteria that restricted the syndrome to the onset of asthma-like symptoms within 24 h after a single, very high exposure to an irritant agent. However, further studies suggested that repeated exposure to lower levels of irritants may also play a role in the onset of asthma after a longer latency period [10, 12–15]. Consequently, the American College of Chest Physicians guidelines recommended including in the IIA entity cases with a lag of several days before the onset of symptoms and repeated exposures over days or weeks [9]. A consensus report on IIA elaborated by a task force of the European Academy of Allergy and Clinical Immunology, in which many European Respiratory Society members took part, has recently been released [16].

This issue of the *European Respiratory Journal* contains an article by Dumas *et al.* [17], who investigated, in a cross-sectional study of a large sample of Estonian adults, the associations between asthma and occupational exposure to known asthmagens or irritants. From about 50 000 individuals recruited between 2002 and 2011 at the Estonian Genome Center of the University of Tartu, Dumas *et al.* [17] included 34 015 adults aged 18–65 years, excluding participants who had never worked, those without job codes and those with imprecise job codes. "Asthma ever" was determined by self-report using a standardised questionnaire, with more rigorous asthma definitions also being considered, such as (reported) doctor-diagnosed asthma and currently treated asthma. Potential exposure to asthmagens was assessed by an asthma-specific job–exposure matrix [18]. Of course, no study is perfect, and this cross-sectional study without firm demonstration of asthma and without documentation of exposures is no exception. Nevertheless, these limitations are compensated by the large number of subjects, the representativeness of the sample for the

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general population, the reasonably good assessment of past occupational exposures and the thorough statistical analysis.

In this study [17], 1062 individuals reported ever having asthma, with half of them reporting physician-diagnosed asthma, almost three quarters reporting current asthma and half reporting current asthma treatment. The prevalence of exposure to known asthmagens was 20%, and 17% were repeatedly exposed to low levels of irritants in their workplace. After adjustment for potential confounders, the authors showed that exposure to known asthmagens (in particular to high-molecular-weight agents) was associated with higher asthma prevalence. In addition, a significant 80% higher odds of physician-diagnosed asthma was found in individuals repeatedly exposed to low levels of irritants, when compared with individuals not exposed to any asthmagen. These associations with specific agents were further confirmed by analyses using occupation as exposure variable.

The findings in this population with a still relatively low background prevalence of asthma are in line with previous investigations, mostly conducted in western countries. They confirm previous reports on the association between occupational exposure to known asthmagens and asthma onset [19–22]. Nevertheless, the most relevant observation reported by DUMAS *et al.* [17] is the evidence of significant associations between repetitive exposures to low-to-moderate levels of irritants and asthma.

As shown by DUMAS *et al.* [17], repeated exposure to low-to-moderate levels of irritants at work is common. Almost two out of 10 workers in this Estonian study population were exposed. Nevertheless, the number of epidemiological studies investigating the associations between this type of exposure and asthma is still limited and mainly focused on the exposure to cleaning agents [23]. An interesting case–control study from Taiwan pointed to the risk of asthma in people exposed to asthmagens, both sensitisers and irritants, at work [24]. Regarding cleaning agents, a study based on data from the European Community Respiratory Health Survey reported an increased risk of asthma in professional cleaners [25]. Further studies identified the use of bleach, ammonia or sprays at work and at home as risk factors for the onset of asthma [26–28]. Moreover, beyond the effects in active users, birth-cohort studies have demonstrated harmful effects of the household use of spray-applied cleaning agents in the development of children's respiratory system [29, 30]. Admittedly, the study by DUMAS *et al.* [17] failed to detect a significant association between cleaning products and asthma. However, they observed two-fold increased odds of current physician-diagnosed asthma in professional cleaners compared with administrative and service jobs. In addition, they report a statistically significant association between physician-diagnosed asthma and low level of exposure to irritants, *i.e.* combustion particles/fumes, irritant gases/fumes or environmental tobacco smoke. The association estimates are as high as those obtained for known asthmagenic agents and higher for more specific definitions of asthma and exposure (current physician-diagnosed asthma, current treated physician-diagnosed asthma and current job).

What lessons can we learn from this important epidemiological study? For clinicians, the message from this and many other studies is that exposure at work must always be considered in individual patients with asthma [31], and the potential causes must not only be sought among the traditional sensitisers but also among irritant chemicals. For the scientific community, this study should incite researchers to investigate further the role of irritants in the pathogenesis of asthma, possibly exploring pathways beyond the traditional paradigms of allergy and adaptive immunity [32]. Finally, for public health specialists and regulators, this study adds to the mounting evidence that asthma may be caused by what many people (including the authors of this editorial) call ''low-to-moderate levels of irritants'', in reality meaning ''unmeasured levels that are common in many workplaces''. If such exposures contribute substantially to disease, then they are too high and, consequently, they should no longer be considered low or moderate. This is not only a semantic issue.

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