

## Review



# Update on the Management of Occupational Asthma and Work-Exacerbated Asthma

Ambrose Lau, Susan M. Tarlo

Respiratory Division, Department of Medicine, Toronto Western Hospital and St. Michael's Hospital, Toronto, Ontario, Canada



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### Correspondence to

Susan M. Tarlo, MB BS, FRCP(C)

Respiratory Division, Department of Medicine,  
Toronto Western Hospital and St. Michael's  
Hospital, EW7-449, 399 Bathurst St. Toronto,  
Ont M5T 2S8, Canada.

Tel: +1-416-603-5177

Fax: +1-416-603-6763

E-mail: susan.tarlo@utoronto.ca

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### ORCID iDs

Susan M. Tarlo

<https://orcid.org/0000-0002-4746-5310>

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## ABSTRACT

Work-related asthma is the most common occupational lung disease encountered in clinical practice. In adult asthmatics, work-relatedness can account for 15%–33% of cases, but delays in diagnosis remain common and lead to worse outcomes. Accurate diagnosis of asthma is the first step to managing occupational asthma, which can be sensitizer-induced or irritant-induced asthma. While latency has traditionally been recognized as a hallmark of sensitizer-induced asthma and rapid-onset a defining feature of irritant-induced asthma (as in Reactive Airway Dysfunction Syndrome), there is epidemiological evidence for irritant-induced asthma with latency from chronic moderate exposure. Diagnostic testing while the patient is still in the workplace significantly improves sensitivity. While specific inhalational challenges remain the gold-standard for the diagnosis of occupational asthma, they are not available outside of specialized centers. Commonly available tests including bronchoprovocation challenges and peak flow monitoring are important tools for practicing clinicians. Management of sensitizer-induced occupational asthma is notable for the central importance of removal from the causative agent: ideally, removal of the culprit agent; but if not feasible, this may require changes in the work process or ultimately, removal of the worker from the workplace. While workers' compensation programs may reduce income loss, these are not universal and there can be significant socio-economic impact from work-related asthma. Primary prevention remains the preferred method of reducing the burden of occupational asthma, which may include modification to work processes, better worker education and substitution of sensitizing agents from the workplace with safer compounds.

**Keywords:** Asthma; asthma, occupational; case management

## INTRODUCTION

Work-related asthma includes occupational asthma caused by conditions attributable to a particular work environment and work-exacerbated asthma which is asthma worsened, but not caused, by work exposures.<sup>1</sup>

Reviews of compensated claims for work-related asthma and clinic reviews have suggested a reduction over the past few years in rates of recognized occupational asthma in several jurisdictions, such as in Canada, France and England,<sup>2-4</sup> possibly due to preventive measures.

However, new causes of occupational asthma continue to be reported.<sup>5-8</sup> In addition, general population studies continue to suggest relatively high rates of work-related asthma accounting from 15% of adult asthmatics in a US survey,<sup>9,10</sup> up to 33% of adult asthmatics who reported work-related aggravation of asthma in a British postal survey (though the overall response rate was low at 13%).<sup>11</sup> These and previous survey findings suggest clinical under-recognition of work-related asthma. In Ontario, Canada, where work-exacerbated asthma is potentially compensable, rates of claims for work-exacerbated asthma (that was mostly transient with less than 3 days missed work), have been much more common than those for occupational asthma, accounting for 72% of accepted claims over a 5-year period.<sup>12</sup> However, in tertiary clinics the proportion of patients with occupational asthma and work-exacerbated asthma are fairly similar,<sup>13,14</sup> likely reflecting more frequent or persistent exacerbations in patients who are referred to these centres.<sup>15</sup>

Management comprises obtaining an accurate diagnosis, treatment of those with work-related asthma, and primary, secondary and tertiary preventive measures. There have been previous reviews and consensus statements on these topics,<sup>1,16-21</sup> but in this article we aim to provide an update from publications over the past 12 years.

## DIAGNOSIS

Diagnosis of work-related asthma is initiated by consideration of this possibility. It may be first suspected by the worker and the health care provider, or from employer-provided medical surveillance. Workers with respiratory symptoms may not be aware that work may be a trigger, or they may suspect a relationship but may not raise this possibility due to fear of job-loss or reduction in income if changes need to be made at work.<sup>22,23</sup> Health care providers caring for patients with asthma in primary care, emergency departments, or during acute medical admissions, may fail to question the patient about a possible work relationship.<sup>24,25</sup> Mazurek *et al.*<sup>26</sup> used a telephone call-back survey in the US among over 50,000 adult asthmatics who had ever been employed. They reported that only 14.7% had communicated with a health professional about asthma and work: 11.7% of the patients had ever told their health care provider that their asthma was related to work, and 9.1% were told this by their healthcare provider. Potentially greater education of workers about work-related asthma by web-based educational tools,<sup>27,28</sup> brochures and other means and standardized inclusion of questions in primary care regarding worsening of asthma symptoms with work and improvement off work (on weekends or holidays)<sup>29,30</sup> may lead to greater recognition of work-related asthma. Other aspects of the history include details of exposures at the onset or worsening of asthma symptoms. Changes in the work process that coincide with the onset of symptoms may help identify a culprit agent. Since there are over 300 known sensitizers<sup>31</sup> and new causes each year, the absence of a known sensitizer at work does not exclude occupational asthma. Obtaining Material Safety Data Sheets can be helpful in identifying exposure in the work place and should be made available to the worker on request. The history should also include questions about high exposure to an irritant agent at work coinciding with the initial onset of asthma symptoms that would suggest irritant-induced asthma. Work-exacerbated asthma causes symptoms worse at work, which may occur on a single occasion with an unusual exposure at work or may occur more regularly with exposure to irritants or common allergens at work. Differentiating asthma that has coincidentally started while working from occupational asthma can be challenging.

Consensus statements and reviews have been relatively consistent in the advised approach to the diagnosis of sensitizer-induced occupational asthma.<sup>1,16,18,21,32,33</sup> It has been recommended that work-related asthma be considered in all adult asthmatics and that patients should be assessed with a full history, physical examination and objective confirmation of the diagnosis of asthma. If the history suggests occupational asthma, then early investigation is advised, preferably while the patient is still employed so that at-work and off-work comparisons of asthma can be made using serial peak flow recordings and paired measures of airway responsiveness. Induced sputum to assess changes in eosinophilic or neutrophilic inflammation can also add to diagnostic certainty. Testing for specific immunoglobulin E (IgE) antibodies to a causative agent (skin tests or serum specific IgE) remains practical for only a relatively small group of the over 300 known causative agents for occupational asthma, due to a lack of commercial extracts of many occupational allergens. In addition, immunologic tests play a limited role in the diagnosis of sensitization to low-molecular weight (chemical) sensitizers. However, serum IgE antibodies to diisocyanates assayed in a research laboratory using antigens prepared from a vapor form of diisocyanates<sup>34</sup> have shown high specificity for occupational asthma, although the sensitivity is relatively low (44% for occupational asthma from toluene diisocyanate). Therefore, when available, this can add to diagnostic certainty when positive.

Specific inhalation challenge is the reference standard that is recommended for diagnosis if other investigations cannot be performed or the diagnosis remains in doubt. It is required for confirmation of diagnosis in some areas and has relatively commonly been performed in some countries such as France, Italy, Spain and Poland, but has seldom been performed in North America, with the exception of the province of Quebec, where it has been required for acceptance of a workers' compensation claim for sensitizer-induced occupational asthma. It is also often used to confirm a diagnosis of sensitizer-induced asthma from a previously unrecognized agent. However, there can potentially be false positive or false negative responses to specific challenge,<sup>35</sup> and the test requires specialized facilities available in a relatively small number of centers. Also emphasized in the European consensus statement on specific inhalation challenges<sup>35</sup> is that the test should only be performed in a specialized center with close supervision, should include a control challenge and a gradual increase in exposure to the suspected causative agent. The European group defined a positive response as at least 15% fall in FEV1 from baseline during monitoring for at least 6 hours after exposure to the suspected agent. The limited access to this specialized testing may limit its usefulness for most clinicians practicing outside of an academic center.

In comparison to the reference standard of a specific inhalation challenge, a positive test of nonspecific airway responsiveness demonstrated by a 20% drop in FEV1 ( $PC_{20FEV1}$ ) with a provocation concentration of histamine less than or equal to 16 mg/mL performed just before the specific challenge had a relatively high sensitivity (87%).<sup>36</sup> Specificity for occupational asthma (36%) was low as expected from a test that reflects all forms of asthma. Another recent study<sup>37</sup> found even higher sensitivity for methacholine challenge in comparison to specific inhalation challenge when the methacholine test was performed among 430 patients who were still working before the specific challenge, with a sensitivity of 95% and a similar specificity of 40%. Positive and negative predictive values among all subjects tested at least once while at work in that study were 44% and 98%, respectively. The conclusion was that when the methacholine test is performed in a patient who is still working with exposure to the suspect causative agent at work, a negative methacholine test makes the diagnosis of occupational asthma very unlikely. Conversely, when away from exposure an improvement in

airway responsiveness can occur in patients with occupational asthma, even into the normal range in some patients,<sup>38</sup> so that a normal response when away from work does not exclude occupational asthma. This underlies the importance of initiating investigations early while patients are still in the workplace and the increased difficulty in making a definite diagnosis of occupational asthma when the patient has been off work for a prolonged duration.

Earlier studies have shown that an increase in the severity of airway hyperresponsiveness commonly occurs after exposure to the causative workplace agent during a specific challenge.<sup>35,39</sup> A significant change in PC<sub>20</sub> with exposure to the relevant work agent *versus* without exposure performed in the same laboratory with a similar baseline FEV1 is supportive of occupational asthma.

Induced sputum eosinophils commonly also increase in patients with occupational asthma due to a sensitizer, following exposure to the causative agent at work or in the laboratory setting, and can add to the diagnosis and differentiation from work-exacerbated asthma.<sup>36</sup> A recent study using specific challenge testing showed that adding induced sputum and exhaled nitric oxide measures as well as a measure of nonspecific bronchial hyperresponsiveness increased the diagnostic sensitivity to 94% compared to a sensitivity of 87% with measurement of non-specific bronchial hyperresponsiveness alone.<sup>36</sup>

There is a less clear role for exhaled nitric oxide (FeNO) measures: a small study has suggested benefit as compared to specific challenge results,<sup>40</sup> although a previous study showed no benefit.<sup>41</sup>

Work-exacerbated asthma with daily exacerbation at work may present with a similar history as occupational asthma with improvement off work and worsening at work, and similar results on peak flow monitoring and paired methacholine challenges. In most cases, however, the onset of asthma will have preceded the work exposure, and the work exposure will be that expected to exacerbate asthma. A rise in the percentage of induced sputum eosinophils during a work week *versus* off work may also be helpful in suggesting occupational asthma, and specific challenge, if performed, can be used to make a more definitive diagnosis.

Although most descriptions of occupational asthma focus on sensitizer-induced asthma, irritant-induced asthma has also been clinically recognized and identified in epidemiological studies. Irritant-induced asthma can be diagnosed with high probability if there is objective confirmation of asthma and criteria described by Brooks *et al.*<sup>42</sup> for reactive airways dysfunction syndrome (RADS) are met. RADS (or acute-onset irritant-induced asthma) is characterized by a single high-level exposure incident with immediate-onset respiratory symptoms and evidence of bronchial hyperresponsiveness. In many cases, however, symptom onset may be delayed by days, but is still felt to represent irritant-induced asthma. When the exposure and clinical history does not meet the criteria for RADS, such as several high level exposures without immediate symptoms, or daily moderate exposures with delayed-onset of symptoms, then the diagnosis may be classified as probable or possible irritant-induced asthma as suggested in a consensus statement of the European Academy of Allergy Asthma Clinical Immunology.<sup>43</sup> In this classification, possible irritant-induced asthma can be clinically challenging to differentiate from coincidental-onset asthma with work exacerbation. While serial peak flow measurements and methacholine challenge tests are helpful in demonstrating on-and-off work worsening in asthma control, they are not specific to irritant-induced asthma. Specific inhalational challenges are possible, but irritant

substances are not well standardized and are more technically challenging to perform.<sup>35</sup> Unlike sensitizer-induced asthma, causality in these cases of possible irritant-induced asthma is inferred from epidemiological studies such as those of cleaners<sup>44</sup> where a history of chronic exposure to an irritating agent causes bronchial inflammation and subsequent asthma.

Since a diagnosis of work-related asthma can be complex, referral to specialized centers can be helpful. Within such clinics, a suggested effect of clinic structure on outcomes has been reported<sup>45</sup>; the presence of personnel with expertise in safe return to work accommodation can provide useful support,<sup>45</sup> both for temporary relocation during the diagnostic process and for the management after diagnosis. In addition to obtaining exposure information from the patient's description and material safety data sheets, access to an occupational hygienist in the clinic has been shown to increase identification of possible workplace sensitizers,<sup>46</sup> which can be important for specific challenge testing and for advice regarding relocation of the sensitized worker.

## MANAGEMENT

All patients with work-related asthma should be managed as for other asthmatics with regard to asthma education, control of exposure to environmental triggers and appropriate pharmacotherapy as per guidelines.<sup>47</sup>

Patients with occupational asthma due to a workplace sensitizer should be completely removed from further exposure to the agent for the best medical outcome as supported by a Cochrane review<sup>48</sup> and several other reviews and consensus statements.<sup>16,17</sup> The best prognosis for clearing of asthma has been associated with an early diagnosis and early removal, with milder asthma at the time of diagnosis.<sup>49</sup> Older age and causation by high-molecular weight sensitizers are also associated with worse outcome in a systematic review.<sup>49</sup> Despite these recommendations, the mean time from the onset of symptoms to diagnosis is often 2 or more years.<sup>50</sup> Although a majority of patients with occupational asthma from a sensitizer have improvement in asthma severity after removal from further exposure, and improvement can continue over several years; nevertheless, the overall rate of symptomatic clearing of asthma at a mean of 31 months has previously been reported to be 32% from a pooled estimate.<sup>51</sup> The advice to completely avoid the causative sensitizing agent at work can sometimes be achieved relatively simply by changing the material used at work (*e.g.*, natural rubber latex gloves or a quaternary ammonium cleaning product), but often this is not feasible, so that the patient needs to be moved to a different work area or to a different company or job, leading potentially to significant socio-economic impact.<sup>52-54</sup> The assistance of an effective workers' compensation system to provide economic support for lost or reduced earnings and for costs of asthma medications as well as for non-economic loss (disability) can be helpful in permitting patients to make such changes. Support from a workers' compensation system is usually dependent on having as much objective support for the diagnosis as possible, so that thorough and early investigations while the patient is still employed are important in this regard. For those who cannot stay in the same job, there may be support for retraining. Even with workers' compensation support, however, there can be significant income loss and socio-economic effects from the diagnosis.<sup>52</sup>

In cases where the diagnosis has been delayed for several years or the patient is close to retirement and does not wish to change work, there may be some benefit from reduction

of exposure as able, by means of occupational hygiene measures such as improved local ventilation and use of respiratory protective equipment, but these measures have not been demonstrated to be as effective as complete removal of exposure.<sup>48</sup> In addition, there have been a few deaths from occupational asthma associated with continued exposure at work. In the future, immune modulation might potentially allow safe ongoing exposure to the workplace agent for those with sensitizer-induced occupational asthma. Although venom immunotherapy is effective for bee-keepers with anaphylaxis to bee venom, there have been relatively few studies to provide any support for specific immunotherapy for occupational allergens. Use of a biological agent such as omalizumab has been reported only in small numbers of patients with occupational asthma,<sup>55,56</sup> so that further studies are needed to determine whether these will prevent responses to workplace sensitizers in those with occupational asthma and whether cost/benefit estimates should be considered.

Considerations for work modification for patients with irritant-induced asthma and those with work-exacerbated asthma from irritants or physical factors (such as cold air, humid air and exercise) are similar. In addition to general asthma management, exposure at work may need to be reduced to prevent further exacerbation of asthma, but usually the exposure would not need to be completely eliminated, unlike occupational asthma.<sup>16</sup> In cases of high-level exposure and acute-onset irritant-induced asthma, the exposure may have been related to an accidental spill or breakdown in process, and occupational hygiene measures may be needed in the workplace to reduce the chance of recurrence. Reduction of exposures in the work place may require better ventilation, intermittent use of respiratory protective devices or job modification. Some workers' compensation systems may provide support for those with work-exacerbated asthma to replace lost earnings from time missed due to asthma. Despite the lack of sensitization, patients with irritant-induced asthma will likely continue to have evidence of asthma long-term and may require ongoing therapy.<sup>57</sup> Due to the nature of the injury, patients may have comorbid conditions that will complicate their asthma care, including depression, post-traumatic stress disorder, occupational rhinitis, multiple chemical sensitivity syndrome and vocal cord dysfunction.

For the subset of patients with work-exacerbated asthma from common allergens at work, *e.g.*, a domestic cleaner allergic to cats or dust mites in the houses being cleaned, more stringent avoidance measures may be needed to prevent ongoing exacerbations.

## PREVENTION

Preventive measures for sensitizer-induced occupational asthma have recently been reviewed using 3 case examples of natural rubber latex, diisocyanates and cleaning products.<sup>58</sup> Systematic reviews and consensus statements have also advised primary prevention as the preferred method of prevention. Although there are genetic host factors in workers who develop occupational asthma due to sensitization to a work agent,<sup>59-62</sup> known genetic factors and other predisposing host factors are not sufficiently sensitive or specific to identify workers who should not have any exposure to a specific sensitizer, and primary prevention is focused on exposure prevention. Ideally, this consists of avoiding the use of agents that cause occupational asthma when possible and substituting safer substances for these agents, *e.g.*, substituting orthophthalaldehyde for glutaraldehyde (although ortho-phthalaldehyde has less commonly been reported to cause sensitization and asthma<sup>63</sup>). For new chemicals, a quantitative structural analysis may potentially assist in predicting the likelihood that



the agent will be a respiratory sensitizer,<sup>64,65</sup> although there can be false negative predictive values.<sup>7</sup> When complete avoidance of sensitizer use in a workplace is not possible, reduced exposure to known respiratory sensitizers can be effective, such as using encapsulated enzymes, use of robots in place of workers, improved general and local ventilation and use of effective respiratory protective equipment for short potential exposure.

Enforced exposure limits for sensitizing chemicals would be expected to reduce rates of sensitization, since rates of sensitization are generally greater with higher exposure. However, the relationship can be complex,<sup>66</sup> there is no consensus as to whether peak exposure levels may be more important than mean exposure levels, and there are no clear exposure thresholds below which all workers are protected.<sup>67,68</sup>

Primary prevention for irritant-induced asthma would consist of preventing workers' exposure to high-level irritant vapor, gases, dusts and fumes. This is included in general occupational hygiene measures and most cases of irritant-induced asthma are accidental exposures that may be difficult to predict and prevent. When accidental exposure has occurred, it is appropriate for the workplace to assess reasons for the exposure and measures that could be taken to prevent a further similar exposure at a later date.

Primary prevention of work-exacerbated asthma can include appropriate education and protection of workers who already have asthma (not induced by work exposure). Optimum control of asthma according to guidelines<sup>69</sup> will in many cases allow patients to lead a normal life, but workers who have asthma should have ready access to their reliever medication at work in case of need. In addition, they may need some accommodation to avoid exposure to respiratory irritants and other asthma triggers at work, even exposures that are within allowable levels and that do not affect nonasthmatic workers, especially if their asthma is severe or if they have a concomitant exacerbation such as at times of a respiratory viral infection or during a seasonal exacerbation.

In addition to general safety training at work as may be provided to all workers, education of asthmatic workers as to the possible effects at work on their asthma may be helpful for adherence to appropriate protective measures and knowledge as to when to request accommodation or to seek medical assistance. Such knowledge may be provided by their health care provider, a company occupational health provider or potentially by web-based information or programs on work-related asthma.<sup>27,28</sup>

Secondary prevention for occupational asthma comprises medical surveillance for early detection of affected workers so that early diagnosis and intervention can occur. Medical surveillance programs for occupational asthma usually include a pre-placement respiratory questionnaire, spirometry, and if feasible specific immunologic test(s) and possibly other tests of airway inflammation such as exhaled nitric oxide, induced sputum variables or exhaled breath condensate. The included components are then repeated at intervals during work with potential exposure to a sensitizer. Such programs may also include a component of worker-education regarding occupational asthma. As recently reviewed,<sup>70</sup> there are relatively few studies that have assessed specific effectiveness of such programs. There is no generally accepted and validated respiratory questionnaire for medical surveillance. The optimum frequency of repeat assessments during work exposure is not known; these are often administered every 6 to 12 months. Since asthma from low-molecular weight sensitizers such as diisocyanates most commonly has an onset within the first 2 or 3 years of exposure,

it may be helpful to have most intensive surveillance during that time for workers with such exposure. The inclusion of specific immunologic tests is most practical for workers exposed to high-molecular weight sensitizers, such as bakers, animal workers and workers with exposure to enzymes.

A Finnish report<sup>71</sup> indicates that only 18% of the 60 cases of occupational asthma who had been included in a medical surveillance program were diagnosed by medical surveillance and the remainder were identified at a doctor's appointment that was not related to surveillance. This suggests suboptimal sensitivity of the components of the medical surveillance that were in use. In that review, no cases were identified on the basis of abnormal spirometry alone, similar to an older review of diisocyanate workers in a medical surveillance program.<sup>72</sup> However as noted by the authors, the medical surveillance program may have increased awareness of occupational asthma symptoms and may have led to earlier medical assessment. In addition, there has been a temporal association between cases of occupational asthma from diisocyanates and introduction of a diisocyanate program in Ontario, Canada that included medical surveillance and monitoring of exposure levels. After introduction of the program, there was an initial rise consistent with increased case finding, and then a progressive fall in yearly cases, as well as earlier diagnosis with milder asthma,<sup>73</sup> similar to that described in a trial surveillance program in Quebec, Canada.<sup>74</sup>

Tertiary preventive measures comprise optimal treatment of those who have developed work-related asthma as previously discussed, in order to minimize impairment.

In summary, there have been several recent publications contributing to increased knowledge in the management of work-related asthma (**Table**). There continues to be an emphasis on the need for an early and accurate diagnosis of work-related asthma, beginning with suspicion of the diagnosis by the patient or health care provider. In addition to a supportive history, objective documentation of asthma preferably while still working, and demonstration of work-related changes in peak flows and/or airway responsiveness, immunologic tests and tests of airway inflammation may be helpful. Best prognosis is associated with early diagnosis and management, including changes in work exposure when appropriate. Preventive

**Table.** Selected recent updates in work-related asthma

Factors	Recent updates
Causes	New chemical causes of sensitizer-induced OA <sup>5-8</sup> include 3-(Bromomethyl)-2-chloro-4-(methylsulfonyl)- benzoic acid in a chemical factory producing this, <sup>5</sup> tafenoquine in the pharmaceutical industry <sup>7</sup> and triclosan in a cleaning product. <sup>8</sup>
Genetic factors	Ongoing genetic studies in OA from diisocyanates show associations but these are not sufficient to be implemented for screening of workers. <sup>59-61</sup>
Changing prevalence	Review of work-related asthma patients in a tertiary clinic over a 15-year period showed a reduction in numbers of both OA and WEA but an increase over time in the proportion attributed to cleaning products. <sup>13</sup>
Delays to diagnosis	Patients' fear of job loss and perceived inability to find a solution may contribute to delays in diagnosis <sup>24</sup> while physicians often fail to ask asthmatics for a history of possible work-related symptoms. <sup>25,26</sup>
Investigations	Sensitivity of methacholine challenge for occupational asthma is highest with recent exposure, and may increase further with the addition of induced sputum and exhaled nitric oxide as diagnostic tools. <sup>36,37,40</sup>
Specialized clinics	Addition of an occupational hygienist and return to work specialist <sup>45,46</sup> can be useful in better identifying possible causative agents, and in facilitating future work.
Outcome	Health care utilization is reduced for WEA and OA after diagnosis and management <sup>50</sup> but there are significant socio-economic impacts even with compensation support. <sup>52</sup>
Treatment	Omalizumab may have benefit in treating severe OA in patients with persistent symptoms despite maximum conventional therapy. <sup>55,56</sup>

OA, occupational asthma; WEA, work-exacerbated asthma.



measures have temporally been related to declining rates of occupational asthma, although the relative importance of each component has been difficult to determine.

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