Workplace Safety and Insurance
Appeals Tribunal

Tribunal d'appel de la sécurité professionnelle
et de l'assurance contre les accidents du travail

Work-related Asthma

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This medical discussion paper will be useful to those seeking general information about the medical issue involved. It is intended to provide a broad and general overview of a medical topic that is frequently considered in Tribunal appeals.

Each medical discussion paper is written by a recognized expert in the field, who has been recommended by the Tribunal's medical counsellors. Each author is asked to present a balanced view of the current medical knowledge on the topic. Discussion papers are not peer reviewed. They are written to be understood by lay individuals.

Discussion papers do not necessarily represent the views of the Tribunal. A vice-chair or panel may consider and rely on the medical information provided in the discussion paper, but the Tribunal is not bound by an opinion expressed in a discussion paper in any particular case.

Every Tribunal decision must be based on the facts of the particular appeal. Tribunal adjudicators recognize that it is always open to the parties to an appeal to rely on or to distinguish a medical discussion paper, and to challenge it with alternative evidence : see *Kamara v. Ontario (Workplace Safety and Insurance Appeals Tribunal)* [2009] O.J. No. 2080 (Ont Div Court). For more information about these papers, please consult the *WSIAT Guide to Medical Information and Medical Assessors*.

Introduction

Asthma is a common condition that can start at any age. It usually has no known cause, although there is a genetic component (i.e. it often occurs in other family members) and it often is associated with allergy (it has been estimated that up to 80% of children who develop asthma have an allergic component, and up to 50% of adults with asthma). The association with allergy is often manifest by a personal and/or family history of allergic rhinitis (hayfever-like symptoms) or eczema. Allergic responses in asthma are associated with production by the affected individual of IgE antibodies that are directed at specific proteins or glyco-proteins that are foreign to the body, and usually are inhaled, e.g., cat proteins, dust mite proteins, fungal proteins. These proteins and glyco-proteins are termed allergens.

Work-related Asthma

Work-related asthma is the term used to describe asthma that is either caused or aggravated by exposures at work (Figure 1).

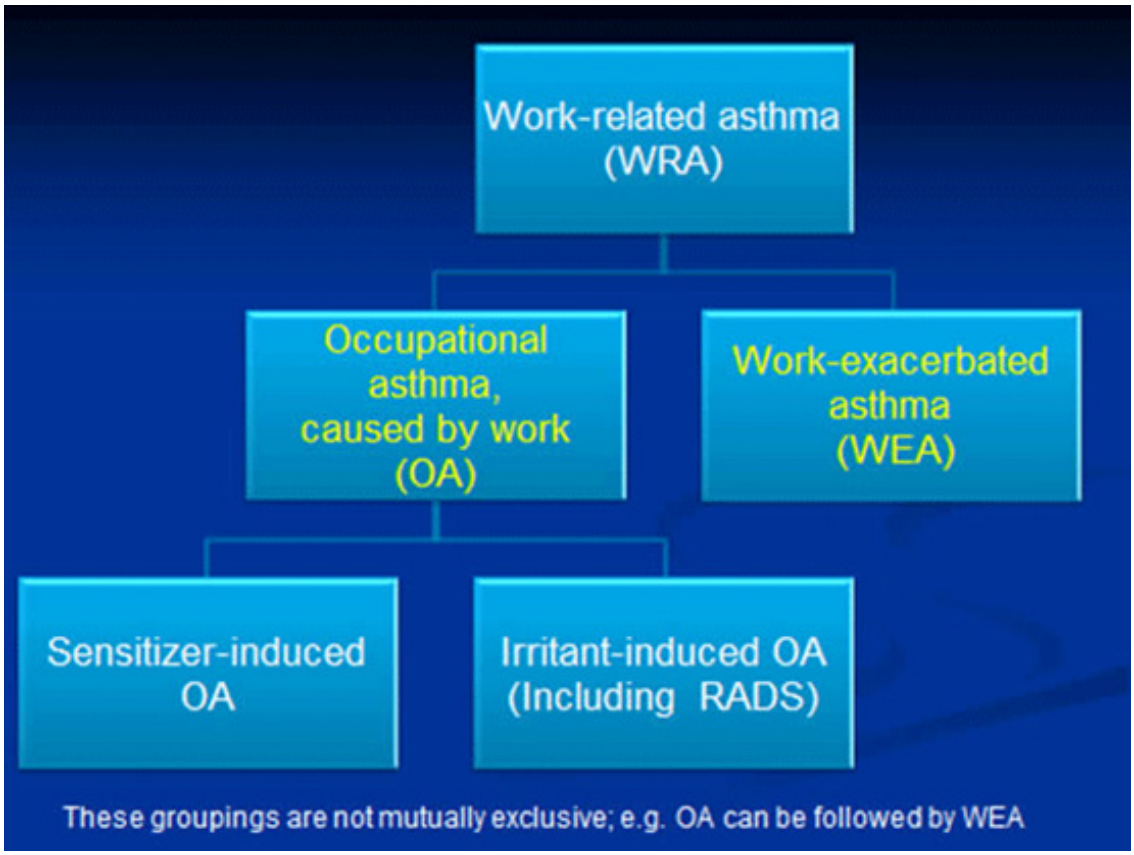

Figure 1 – Sub-types of work-related asthma

Among adults who develop asthma for the first time (termed adult-onset asthma), it has been estimated that 10-15% may have asthma that is **caused** by work, and this is termed **occupational asthma** (OA). When this occurs it is usually due to an **allergic** response or sometimes a response that behaves in a similar way to an allergic response but for which the mechanism is unclear (these responses that behave like an allergic response are also termed **sensitization**). Less commonly workplace high level irritant exposures can cause **irritant-induced OA**. The other subgroup of work-related asthma, besides OA, is **work-exacerbated asthma**, as will be discussed later.

Occupational Asthma (OA)

The clearest mechanism for OA is an allergic response to an inhaled protein or glyco-protein in the workplace, such as animal proteins (e.g. in animal care workers or veterinarians or in farmers), or food or plant proteins (such as wheat or other proteins in bakers, bell pepper proteins in greenhouse workers, natural rubber latex proteins in healthcare workers using powdered latex gloves, or glyco-proteins from fungi). Other examples include inhaled proteins from insects or enzymes. There are numerous inhaled proteins or glyco-proteins that have caused OA by an allergic mechanism and it seems likely that almost any inhaled foreign protein might cause such a response in a susceptible worker. However, among those who are exposed, only a minority will develop this response (10% or less), and the reasons to explain this susceptibility in some individuals are not fully understood. There is some association with the extent of exposure i.e. lower exposures are associated with asthma in a smaller proportion of workers than higher exposures. However, even at very low exposure levels, some workers can become “sensitized” (i.e. develop specific IgE antibodies) and can then develop OA, likely associated with genetic susceptibility. Workers who develop specific IgE antibodies to a work agent can also develop allergic nasal symptoms (allergic rhinitis) that often precede or coincide with the development of OA.

Important additional aspects of the allergic response causing OA are:

a) that there is a “latent period” of exposure before sensitization: i.e. the worker has exposure to the causative agent for weeks or even years before the first onset of symptoms – since this is an immunologic response, when that exposure triggers the production of specific IgE antibodies, it cannot cause symptoms on the very first day of exposure;

b) once specific IgE antibodies have formed, then subsequent exposures cause an allergic reaction in some people, resulting in symptoms of allergic rhinitis or asthma. However, this does not happen in everyone who develops these antibodies.

c) once OA has developed with sensitization, then exposure, even to low levels of the causative agent will trigger asthma symptoms – unless symptoms are suppressed by asthma medications;

d) the asthmatic response in a patient with OA can start within minutes of each exposure (an immediate response), or may be most noticeable 4-6 hours after the onset of exposure (a late response), or there can be a combined immediate and late response.

Some chemicals can also cause OA through a demonstrable allergic response, such as complex platinum salts and other metal salts, acid anhydrides (used to make plastics), persulphates (in hairdressers) and penicillin (e.g. in pharmaceutical workers).

Other chemicals can also cause occupational asthma and have similar features as with sensitization associated with IgE antibodies, but through mechanisms that are not fully understood, and usually without demonstrated specific IgE antibodies.

These chemicals causing sensitization by unclear mechanisms include diisocyanates and western red cedar dust: specific IgE antibodies can be identified in only a minority of those with well-documented OA caused by these agents, and they most commonly cause an isolated late response in those who have OA caused by them. Other chemicals that can cause OA by unclear mechanisms include acrylic compounds, quaternary ammonium compounds, and aldehydes such as glutaraldehyde and formaldehyde. Most chemicals that have caused occupational asthma have highly reactive molecular side-chains.

Lists have been compiled of the reported causes of OA with or without specific IgE antibodies. These are often divided into high-molecular-weight sensitizers (typically the proteins and glycoproteins) and low-molecular-weight sensitizers (typically the chemicals). Over 300 agents have been reported, some described in just a few case reports, and others in large groups of workers (and no list is completely comprehensive as new additional causes are described each year). Among the chemical sensitizers, diisocyanates and plicatic acid (in western red cedar) have been most thoroughly investigated.

Diisocyanates are very reactive chemicals used to make polyurethane products, such as in 2-part polyurethane spray paint systems, spray foam insulation for homes, urethane coatings, polyurethane foam for furnishings, used in cars (seating, headrests, bumpers etc.). They are also used in moulds in foundries, and as adhesives in particle board and oriented strand board. These chemicals have been the most common single cause of OA in many industrialized regions including Ontario, for several years. Due to this, there is a medical surveillance system in Ontario that was developed by the Ontario Ministry of Labour. This limits allowable exposure levels and requires regular questionnaires and breathing tests among those who have this exposure, in order to detect OA early.

Diagnosis of OA Caused by a Sensitizer

Since asthma can begin at any age and can occur without a cause from work, the new onset of asthma in a worker is not always due to the work exposure but may have started coincidental to the workplace for unknown reasons. Although OA should be suspected in any working adult who develops asthma, it has been recommended and should be emphasized that objective tests be performed in such patients since the diagnosis of OA cannot be reliably made solely on the basis of identified exposure to a known sensitizing agent and the history of new-onset of asthma and worsened symptoms at work.

Several consensus documents or guidelines have been developed for the diagnosis of OA from several different countries, with a similar recommended approach. The medical history should document details of respiratory symptoms, and the timing of symptoms in relation to work exposures and days or holidays off work. A history of worse asthma during a working period and improvement on weekends or holidays away from work will increase suspicion of occupational asthma, but is not sufficient for the diagnosis.

Objective Diagnosis of Asthma

It is very important to have an objective diagnosis of asthma confirmed since there are several other conditions that can cause similar symptoms to asthma. The objective tests to confirm a diagnosis of asthma require demonstration of a significant bronchodilator response on spirometry (this has been defined as at least 12% **and** 180ml increase in FEV1 after a bronchodilator) and/or a positive methacholine challenge (PC20 8mg/ml or less) after holding asthma medications for an appropriate time. However, although these tests can confirm a diagnosis of asthma in a worker with asthma symptoms, they do not prove causation from work. In addition, if the tests are performed during a period that the patient is away from work, then normal findings do not exclude the possibility of OA, since patients with OA can sometimes have complete clearing of asthma when off work. Conversely, if these tests are completely normal during a period of time that the patient is working and has symptoms (especially within 24 hours of the implicated work exposure) then it is very unlikely that the patient's symptoms are due to asthma, and another diagnosis should be considered (as detailed later).

Although spirometry and methacholine challenge tests are considered to be the gold standard for diagnosis of asthma, if spirometry is normal and methacholine challenge is normal or borderline, another test that has been considered for a diagnosis of asthma is the demonstration of variable airflow limitation on serial peak flow monitoring. However, this test is effort-dependent and there is no generally accepted cut-off value of this test for the diagnosis of asthma. In the setting of possible work-related asthma, serial peak flow readings are most useful to compare variability at work versus off work (as detailed below).

Support for an Occupational Cause of Asthma

In a worker with asthma, and a history suggesting OA, additional tests may support a work causation, such as demonstration of specific IgE antibodies to the work sensitizer (when these tests are available), although these tests can be positive even in some workers with no symptoms. These antibodies may be detected by allergy skin tests or blood tests for specific IgE antibodies using a solution containing the suspected causative protein (allergen) from work (e.g. wheat in bakers or animal extracts in those working in laboratories with animals). Although several extracts are available for assessing specific IgE to work proteins, there also are numerous work sensitizers for which there are no reliable skin tests or blood tests, especially the chemical sensitizers. In addition, the presence of specific IgE antibodies without other objective tests that confirm asthma does not prove the diagnosis of OA, since the IgE tests can be positive in some exposed workers who have no symptoms.

Other tests that show changes in asthma during working periods compared with periods off work are useful (such as serial peak flow readings and serial methacholine challenges and/or induced sputum cytology).

Peak flow readings are obtained by asking the worker to use a small hand-held machine to measure a breathing test several times a day, while at work and while off work, over several weeks and to record the result in addition to keeping a record of symptoms, asthma medication use and location and/or work exposures. This can allow an estimate of changes in asthma during periods at work and off work (preferably including at least 10 days away from the work exposure), and help to determine the probability of work-related asthma. However, most often these charts are self-recorded and therefore are considered somewhat less objective than the other tests for work-related asthma. The peak flow result is also affected by worker-effort, and potentially may be falsely low at the end of a working day when the patient may be tired. There may be other factors that can affect results such as absence of exposure to the work sensitizer during the recording period, or an intercurrent respiratory viral infection. Use of an electronic peak flow meter or portable spirometer can be helpful to provide a more objective record of results, but these are expensive and not commonly used in practice.

Methacholine challenge testing is often used as a diagnostic test for asthma, especially if the baseline FEV1 on spirometry is normal and there is no significant bronchodilator response. The test provides a measure of airway reactivity, and is typically increased in asthma (recorded as a PC20 or PD20, with lower values representing greater airway hyperresponsiveness). The test can be performed towards the end of a typical work week with symptoms (when the airways hyperresponsiveness would be expected to be worst for those with OA), and can also be performed after a period of 10 days or longer away from work (when there may be some improvement in airway hyperresponsiveness). An improvement in PC20 of three-fold or greater when away from the work exposure is very suggestive of OA. However, this test may not show significant improvement off work in all

patients with OA, so absence of significant improvement in PC20 off work does not exclude the diagnosis of OA. In addition, there can be other factors besides the work exposure that can affect the result of a methacholine challenge test and such factors need to be considered in the interpretation of results, including a recent cold, exposure to relevant common environmental allergens (e.g., cat), and use of asthma medications before the test.

Another feature of asthma with an allergic response is the finding of inflammation in the airways typically with increased eosinophils (a type of white blood cell that is common in allergic responses). This can be assessed by performing an induced sputum test (currently performed in only a few centres in Ontario). If the test is repeated at the end of a work period and again when away from the implicated work exposure (similar to the paired measures of methacholine challenge), then the finding of a significant reduction in sputum eosinophils when off work vs. during work periods suggests an allergic airway response at work. This can occur as a feature of OA, and less commonly can occur as a more isolated finding of eosinophilic bronchitis (see further detail below). As with the other tests above, there can be false positive and negative results. The test can be affected by recent use of inhaled steroid medications for asthma, and by exposure to non-work-related allergic triggers. In addition, some patients with OA from a sensitizer do not have significant sputum eosinophils but instead have an increase in neutrophils (that also can be seen in chronic bronchitis or in infective bronchitis).

Measurement of exhaled breath nitric oxide during a work period and after a period off work has also been assessed as a marker of asthma. Higher measured levels can reflect increased airway inflammation in asthma, and potentially could reflect a change in asthma related to work. A few reports have indicated benefit from use of this test for OA diagnosis. However, the test can be affected by many other factors, including diet, and it is not widely used on a clinical basis.

Specific laboratory challenge tests, reproducing the work exposure in a laboratory setting while monitoring changes in lung function, are considered a “gold standard” for diagnosis, but carry some risk, are very time-consuming and are not always a practical option. For these reasons they are seldom currently performed in Ontario.

Combinations of Tests, and Estimating Probability of Occupational Asthma

A combination of tests has been recommended for diagnosis when feasible since each individual test can be falsely negative or positive. In addition some tests may not be feasible (such as antibody tests for most chemical sensitizers, and serial tests at work and off work in a patient who has already left work and cannot return).

The course of asthma in a worker who has left work and is not able to undergo objective testing may allow some estimate of probability of OA. If there was an objective assessment that confirmed asthma while working and if there is comparative evidence showing significant improvement since leaving work where

there was a known sensitizer (and the improvement cannot be explained on the basis of asthma medications or other exposures), then this provides some support for OA. Lack of improvement does not rule out OA but makes it somewhat less likely. A history of previous childhood asthma or aspirin sensitivity and nasal polyps also does not rule out OA, but without other supporting information, the diagnosis becomes less likely.

Irritant-induced OA

This typically refers to OA induced by a high level irritant exposure, usually from an accident or fire at work. Unlike OA from a sensitizer there is usually no latency period – asthma symptoms generally start within 24 hours after the accidental exposure. The exposure may be high levels of irritating gases, fumes, smoke or dusts, and typically asthma symptoms are severe enough to lead to an unscheduled visit to the emergency department or health care provider within 24 hours. Typically symptoms persist for at least 3 months, with no preceding respiratory disease, and pulmonary function changes of asthma are documented (a significant bronchodilator response and/or positive methacholine challenge as detailed earlier).

When all the above features are present, a diagnosis of Irritant-induced OA can be made with confidence (this was initially termed Reactive Airways Dysfunction Syndrome, RADS). Difficulty in diagnosis arises when these typical findings are not all present: e.g. symptoms start several days after the exposure, or do not lead to a physician visit initially, or symptoms last for less than 3 months, or have cleared before pulmonary function tests were performed and were then normal, or if the worker had a significant smoking history and possible preceding Chronic Obstructive Pulmonary Disease (COPD). No additional tests can be performed to clarify the diagnosis and decisions may have to be reached on the balance of probabilities with the information available.

Some information suggests that there is an increased risk of developing asthma from exposures to workplace irritants that are not massive, e.g. to cleaning products, but currently this cannot be clearly determined for an individual worker and cannot be distinguished from the coincidental onset of asthma.

Work-exacerbated Asthma

In addition to OA, work exposures can aggravate or exacerbate (transiently worsen) asthma in workers who have asthma that is not caused by work. Individuals with asthma have more reactive airways than normal and it is common for asthma symptoms to be worsened with exposure to cold dry air, by exercise, by exposure to dusts, smoke, fumes or sprays or by exposure to common environmental allergens to which the patient has an allergic response. Respiratory viral infections are also a common cause of asthma exacerbations. Even without an allergic response, these

exposures are likely to lead to worsening of asthma symptoms and transient airway narrowing, especially if asthma is severe or not well controlled. If such exposure occurs at work and worsens asthma symptoms, this is termed **work-exacerbated asthma**.

It has been estimated that work-exacerbated asthma occurs in up to 25% of workers with asthma. It can commonly cause a short-term worsening of symptoms that may lead to no time off work or a few days off work. Less often, especially if the triggering exposure occurs on a daily basis at work, it may lead to more prolonged worsening of asthma and greater time off work. If the worker developed their asthma coincidentally while working and then has daily worsening of symptoms at work, then there may be suspicion of OA, especially if there is also a known exposure to a sensitizer. The worker should then be investigated as thoroughly as possible as indicated above, to try to identify whether the diagnosis is truly OA as described earlier or work-exacerbated asthma. Some of the tests used to diagnose OA may also be positive in patients with daily or frequent work-exacerbated asthma, e.g., peak flow readings, symptom scores and medication needs may worsen at work, and in a few patients there can be an improvement in methacholine PC20 when away from work. Specific IgE antibodies to a specific work agent would not be expected in work-exacerbated asthma from irritant exposures, and an improvement in induced sputum eosinophils when away from exposure would not be expected in work-exacerbated asthma from irritant exposures. However, if the exacerbation at work was from an allergen exposure to which the worker is allergic, e.g., an animal or fungal spores, then specific IgE antibodies would be expected and an improvement in sputum eosinophils would likely occur when away from the exposure.

It has generally been considered likely that work-exacerbated asthma results in temporary worsening of asthma. It is not known whether work-exacerbated asthma can cause permanent worsening of asthma severity. This is difficult to determine since asthma is a variable condition and studies over a prolonged time have suggested that unrelated to the workplace, about one third of those with asthma will worsen, one third improve and one third stay the same. Therefore, for an individual with asthma (that has not been caused by work), it is difficult to determine whether an aggravation at work has changed the long-term course of their asthma or whether any worsening over time is coincidental.

Other Difficulties in Diagnosis

A definite diagnosis of asthma requires pulmonary function tests showing the changes as described under OA. Asthma-like symptoms are more common than true asthma, and can have other causes, e.g., both rhinitis (nasal symptoms), or gastro-oesophageal reflux can result in a cough that may mimic asthma, and bronchitis or other lung disease (such as bronchiectasis) may cause similar symptoms of cough and wheezing.

There are many conditions that can mimic each of the symptoms of asthma (cough, wheeze, chest tightness and shortness of breath), emphasizing the need for an objective diagnosis as indicated above.

Some examples of conditions that may mimic asthma by causing similar symptoms, are given below:

- A dry (non-productive) cough is a frequent symptom of asthma but is also commonly caused by respiratory viral infections, an upper airway cough syndrome (associated with rhinosinusitis and a post-nasal drip), gastro-esophageal reflux (usually associated with heartburn), cardiac failure, and pulmonary fibrosis or other diffuse lung diseases.
- A cough with clear (uncolored) sputum can be present in asthma but can also occur with eosinophilic bronchitis, acute or chronic bronchitis or bronchiectasis. In addition, a post-nasal drip can result in throat-clearing and the patient may not be able to determine if the mucus produced is from the chest or from a post-nasal drip. Chest tightness can also occur from gastro-esophageal reflux (usually associated with heartburn), cardiac failure, and from anxiety/stress (causing chest wall muscle tension).
- Wheezing can also occur in acute or chronic bronchitis, or in heart failure. It can also occur from a laryngeal cause leading to an inspiratory wheeze and difficulty breathing, with hoarseness, with or without cough, that is often triggered by odors, irritant exposures, or exercise, that may mimic asthma, as detailed below.
- Shortness of breath can also be caused by numerous lung diseases, including COPD and emphysema and also by cardiac disease, or anaemia, as well as by stress/anxiety. Shortness of breath on exertion may also be due to excessive body weight, neuromuscular disease or deconditioning.
- Some patients develop laryngeal symptoms that may mimic asthma but have a different mechanism. This is termed “irritable larynx syndrome” or “inducible laryngeal obstruction” and in some patients may include “vocal cord dysfunction syndrome or paradoxical vocal cord syndrome”. It may occur as the sole cause of symptoms or may coexist with asthma and can then be a reason for an apparent poor response to asthma management. It typically causes symptoms of neck tightness, hoarseness, difficulty breathing in and wheezing when breathing in. It is important to recognize since it is different from asthma, and requires different treatment. This diagnosis is usually confirmed by assessment of the upper airway by an ear-nose-and- throat specialist with expertise in this disorder.

Another condition that is uncommon but can cause asthma-like symptoms and can be caused by sensitization to a work agent is eosinophilic bronchitis. This term refers to an inflammation of the airways, that can be caused by a sensitizer at work and

can cause cough and chest tightness but the breathing tests for asthma are typically normal in this condition. This can be diagnosed by induced sputum cytology testing if available, ideally repeated both at the end of a working week and after a period off work to identify any work-related changes. If caused by work, the management is similar to that of OA.

Management of Work-related Asthma

This discussion paper is focused mainly on diagnosis. Management of work-related asthma differs depending on the type of work-related asthma. The key management of OA due to a sensitizer is to completely avoid further exposure to that substance. This will usually require a change in work to a different area or different workplace where there is no airborne exposure to the agent (use of a respirator is not an adequate alternative). In addition medications are used as for other asthma, and exposure to other asthma triggers should be controlled. Asthma does not always clear after removal from exposure, but usually improves. However, patients with OA who move to a different work area or different workplace could then develop work-exacerbated asthma if exposed to asthma triggers at work.

Patients with OA from an irritant exposure and those with work-exacerbated asthma may be able to continue the same work but may require modifications to reduce potential exposure to irritant agents that may exacerbate their asthma (short term use of respirators may be appropriate to prevent asthma symptoms associated with transient exposures). Asthma medications should be optimized and exposures to relevant asthma triggers outside the work environment should be minimized.

Specific Questions and Answers

1. What is the significance of a delay between exposure and symptoms, and can symptoms initially occur after the worker has left the job?

Response: In a worker with occupational asthma (OA) from a sensitizer at work, the symptoms caused by this would always first start while working, or within a few hours after leaving the triggering exposure, and would not start days/weeks/months after the worker has left the job. However, the temporal relationship of the asthma symptoms, with worsening during work periods and improvement during periods away from work, may not be recognized by the worker for a period of time after the onset of symptoms, perhaps only with improvement at the time of an annual holiday. In addition, the worker may not initially report their symptoms to their healthcare provider, for fear of losing their job or losing income, and the healthcare provider may not directly question the worker about the relationship of symptoms to work. Therefore, suspicion of the diagnosis may not be raised for several months or years after onset of OA symptoms, and it can be several years before a diagnosis is fully investigated. Some studies have reported a gap of 4 years or more before the onset of symptoms and the diagnosis. Therefore, the diagnosis may not be reached until after the worker has left the workplace exposure. In addition, if the worker has already left the job, it is more difficult to then perform tests to investigate the relationship with work and confirm or refute the diagnosis.

2. Is there a maximum time to the first onset of OA symptoms after exposures at work?

Response: The time period between the first exposure to a work sensitizer, and the development of OA has been termed the “latency period”. Since OA from a sensitizer is an immunologic response, there is a period of time after first exposure until antibodies are developed to the work agent and an allergic respiratory response can occur. This can be as short as 7-10 days but more commonly workers are exposed for months to years (with no maximum time) before developing allergic nasal symptoms (allergic rhinitis) or asthma when exposed to the work agent. This has been assessed in apprentices exposed to flour or animals or latex, and has also been assessed in workers who develop OA from diisocyanates. Among bakery apprentices, a study (Herxheimer et al., 1973) showed rates of sensitization (i.e., an immunologic response) as demonstrated by skin tests, increased progressively over 5 years, up to 30% in the fifth year. Symptoms of allergic rhinitis or asthma increased up to the third year, but then fell, possibly from self-selection among those with symptoms, and loss to follow-up. For diisocyanates, most commonly the latency period is within 1-2 years from the start of exposure, but can be as long as 20 years or more. Therefore, a long latency period, in itself, is not necessarily a basis for concluding that the condition is not OA, if symptoms initially occur while the worker is still exposed to the work sensitizer. As indicated above, in a patient with OA, symptoms of asthma would not start for the first time after leaving the workplace exposure.

3. How important are medical tests in making the diagnosis?

Response: Medical tests are extremely important in the diagnosis of OA from a sensitizer, both to diagnose asthma and to show any work relationship. Tests for an objective diagnosis of asthma should be readily available by spirometry, but there can be normal test results if workers have mild asthma or have not had recent symptoms. For other tests to diagnose OA, there can be practical difficulties in arranging these tests and they need to be initiated before the worker leaves their work. Some difficulties include a lack of ready access to methacholine tests for patients living at a distance from major centres, and the need to travel for tests. Allergy skin tests can be arranged but the range of skin test solutions for workplace sensitizers is limited: there are skin test solutions for many foods, including grains and many plants and animals, but very few well characterized skin test solutions for sensitizers such as fungal exposures or enzymes, or for chemical sensitizers. Serial peak flow readings can be arranged, but are effort-dependent and therefore are less objective than the other tests. There is very limited availability of induced sputum tests, and specific inhalation challenges with a work agent.

Despite these difficulties, most patients can undergo objective tests, at least to confirm or exclude asthma at a time that they are symptomatic, and most can undergo at least one additional test to confirm or exclude an association of asthma to the work exposure(s). The certainty of confirming or excluding OA increases when more than one work-related medical test has been performed.

4. Once the worker has been sensitized and has developed OA from a work agent what time period of delay in symptoms might be expected after each exposure?

Response: As noted above, there can be a long latency from the initial exposure before the first onset of symptoms, and this can be up to 20 years or more. However, once the worker has been sensitized and has developed asthma from a work agent, then it is expected that each subsequent time they are exposed they will have symptoms, unless they are taking asthma medications that may suppress the response. Once a worker has OA from a sensitizer, the time between an exposure and the start of worsening of symptoms can be almost “immediate”, starting within a few minutes to 30 minutes, especially for high molecular weight sensitizers, or there can be a “late response” starting up to 4-8 hours after each exposure (especially for chemical/low molecular weight sensitizers), or there can be both an immediate and late response.

5. Can a worker with underlying asthma develop OA?

Response: OA has usually been defined as the NEW onset of asthma from a work exposure. However, workers with unrelated asthma can develop new sensitization to an agent that is specific to the workplace, e.g., to diisocyanates. Their asthma would

then be exacerbated at work but the effects would be similar to the effects of OA and would lead to a need to completely avoid that exposure.

6. Can work exposures cause permanent worsening of asthma in a worker who has work-related exacerbation of pre-existing asthma?

Response: As indicated in the previous response, a worker who has underlying asthma and then becomes sensitized to a work agent, such as flour in a baker, or diisocyanates, can have effects that are the same as OA and even with removal from further exposure to that work agent, may have permanent worsening of asthma.

For workers with other causes of work-related exacerbation of asthma there is unfortunately, not a clear answer to this question from published studies. The outcome of asthma exacerbated by an irritant exposure would likely relate in part to the severity of the exposure. If a worker had pre-existing asthma and then had an exposure similar to the exposures reported to cause RADS or irritant-induced asthma, then it would be more likely that the exacerbation would result in worsened asthma for months or even years, in a similar mechanism as can occur in RADS. Conversely, if there is an exacerbation of asthma from a moderate or low irritant exposure it would be expected that there would be an earlier recovery back to baseline. As an example, a single exposure to second-hand cigarette smoke or to gasoline fumes in traffic may worsen asthma for a few minutes to an hour, and a moderate irritant exposure may be expected to cause an exacerbation for a few days.

If there is recurrent and frequent exposure to varying levels of irritant agents in a workplace, such as for pig farmers, wood workers, welders, or cleaners, then there is some evidence that there is an increased risk of developing asthma, that may persist even after leaving the exposure. In some cases this may be due to a co-existing sensitizing agent e.g. enzymes, amines, or aldehydes in cleaning products, metals in welding fumes or wood dusts, but in many cases the triggering agent cannot be identified and it is from assumed irritant exposures. It is often not possible to determine objectively whether the asthma started coincidentally and was then exacerbated by irritant exposures, or whether irritant exposures caused the new onset of asthma. In the example of cleaners, one systematic review and meta-analysis showed a 35% increase in relative risk of asthma in healthcare workers with exposure to cleaning and disinfecting agents (Dang, 2021) and another showed a 50% increase in risk of asthma for occupational cleaners (Archangelo, 2020). Although there is an increased risk of developing asthma in these exposed workers as a group, these studies indicate that it is not possible to say, for an individual worker who develops asthma with these exposures, that it is more likely than not due to the exposures unless further information is available. Epidemiologic studies of chronic exposures to irritants in occupational settings have often shown a relative risk of new-onset asthma that may be statistically significant but is less than 2. Therefore those studies would generally not be sufficient to establish that an exposure is the likely cause of a worker's asthma based on a mathematical analysis of what might be "more probable than not".

If the exacerbating exposure is an allergen/sensitizer in a worker who is already sensitized, that can increase airway reactivity and worsen asthma for up to several weeks after even a single exposure, and if the exposure has been recurrent over weeks to months or more, then there may not be a return to baseline.

If the exacerbation of asthma is due to a respiratory viral infection contracted at the workplace, then airway reactivity and asthma severity is commonly worsened for up to 6 weeks after the infection, and occasionally for longer periods, such as with severe infections that may have caused respiratory bronchiolitis or pneumonia.

Assessment of a possible long-term effect of an irritant-related or allergen-related exacerbation of asthma is easier if there are objective changes that have been documented in pulmonary function and asthma medication requirements after the exposure compared with before exposure, in addition to reported symptoms. If these do show persistent worsening that continued from the time of the work-related exacerbation, and if there is no other explanation for this (e.g., a new pet in the environment) then on some facts it might be reasonable to conclude that the ongoing worsening is likely to have resulted from the work exposure, based on an assessment of the totality of the circumstances.

7. Can low level irritant exposures cause RADS or irritant-induced asthma and result in permanent impairment?

Response: The initial description of RADS in 10 patients used very strict diagnostic criteria, and none had any preceding respiratory disease (Brooks, Chest 1985). Asthma was objectively confirmed after a presumed high level accidental irritant exposure with symptoms of asthma starting within 24 hours of the exposure, and it persisted at least 12 weeks, in most cases for over a year, and in a few patients persisted for several years. Therefore, high level irritant-induced asthma can be persistent and can likely result in permanent impairment in some patients, but not necessarily in all. The persistence of impairment can most clearly be demonstrated in patients who clearly had no pre-existing lung disease.

Following the initial description of RADS, the term “Irritant-induced asthma” was used to describe a similar condition that did not fully meet the criteria for RADS, e.g., the patient may have had a smoking history or a history of childhood asthma, so that pre-existing airway disease could not be excluded, or symptoms began 2-7 days after the exposure, or there was more than one exposure and it may not have been a massive exposure, or symptoms lasted less than 12 weeks. With each modification of the initial criteria, the certainty of the relationship to the exposure(s) becomes less certain, but in some circumstances the relationship to the exposure(s) might still be found to be likely based on a consideration of all the circumstances, and especially if the exposure was high.

There is even less evidence on the causation and outcome of asthma after recurrent lower exposures to irritants. The possibility of this occurrence is raised by epidemiologic studies, e.g., of workers exposed to wood dust, pig farming, pesticides and cleaning agents, as discussed in a consensus document (Vandenplas et al 2014). These epidemiologic studies indicate an increased risk of developing asthma in those workers. However, for an individual worker exposed to relatively low levels of irritants, the attribution of causation from that exposure is difficult to determine and there are no objective tests to prove an irritant-induced causation versus the development of coincidental asthma. Some assistance in determining likelihood of causation may be obtained by review of the published epidemiologic studies for a particular type of exposure, such as for workers exposed to cleaning agents, and identification of the relative risks of asthma compared with a control population.

There is little evidence on the outcome of asthma that may be attributed to presumed lower irritant exposures (Tarlo, 2014). A consensus opinion document from the European Academy of Allergy Asthma and Clinical Immunology (Vandenplas 2014) summarized the evidence available to that date. Significant increased risks of new asthma have been reported with high level exposures to bleach, chlorine, ozone and sulphur dioxide. Among subjects with asthma induced by multiple chlorine puffs of gas in a pulp mill, over half had ongoing changes when assessed at 10-24 months after the exposure. However, in a separate study of chlorine “gassings”, airway obstruction, as reflected on spirometry, tended to persist but there was a significant improvement in methacholine response in a third of the subset of patients followed for an additional year after diagnosis, and a few had resolution of asthma on testing (Malo, 1994). A recent study (Lantto, 2023), assessed outcome for patients with acute and subacute irritant induced asthma, and at 6 months found a worse asthma outcome compared to sensitizer-induced OA. One difficulty with interpretation of these studies is to know whether asthma was caused by these exposures, or whether asthma occurred coincidentally and was then exacerbated by the exposures.

8. What is the distinction between a diagnosis of asthma and a diagnosis of COPD?

Response: COPD refers to disease(s) where the patient has fixed or irreversible airway narrowing causing fixed airflow limitation on pulmonary function tests, demonstrated after an inhaled bronchodilator is administered. In contrast, asthma requires demonstration of a reversible component to airflow limitation, as detailed previously. COPD is most commonly caused by tobacco smoking but also can result from occupational exposures to vapor/gas/dusts/fumes, or by exposure to biomass smoke, or air pollution, as has been addressed in a WSIAT Discussion Paper on COPD. In addition, patients who have long-standing asthma may develop a fixed component to their airflow limitation that meets criteria for COPD and is presumed to be due to remodeling of the airways (termed “asthma-COPD overlap”, [ACO]).

In many patients the distinction is clear on pulmonary function tests. If there is baseline airflow limitation on spirometry that significantly reverses with a bronchodilator (FEV1 improving at least 12% and 180ml), then that is diagnostic of asthma. If there is airflow limitation and there is significant limitation in airflow after a bronchodilator (usually defined as an FEV1/FVC ratio after a bronchodilator that is below the predicted reference value, or simplified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), as an FEV1/FVC ratio below 70%), then that is consistent with COPD.

If there is overlap with both diagnoses, that has been termed ACO (asthma-COPD overlap syndrome):

- Patients who have asthma may have a significant bronchodilator response but still have some “fixed” airflow limitation after a bronchodilator or after full asthma treatment indicating a component of COPD. This may result from longstanding asthma and remodeling of the airways or may be due to COPD as an additional disease.
- Patients who have COPD as their primary diagnosis may have a partial response to a bronchodilator that may or may not fit criteria for asthma, and a subset of patients with COPD may have increased blood eosinophils, suggesting a likely component of eosinophilic inflammation in airways that may be responsive to asthma treatment.
- In addition, asthma can vary over time and with medications and exposures, so the reversible component of asthma may be demonstrated on some occasions and not on others. However, the pulmonary function changes of COPD continue to be present over time, even with treatment and changes in exposures.
- In one study patients with occupational ACO were older, needed higher doses of inhaled steroids and were less likely to be allergic compared with other OA patients (Ojanguren, 2015).

9. Are there relevant effects of COVID-19 infection on work-related asthma?

Response: The COVID-19 pandemic caused more infections in some workers, such as healthcare workers and those in essential services who could not work from home (Carlsten 2021). Among workers who had asthma, infection with COVID-19 was reported to cause more severe illness in those who had underlying severe asthma or fixed airway obstruction (Lee, 2022, Uruma 2022). Any respiratory viral infection can exacerbate asthma for up to about 6 weeks. However, for those with mild to moderate underlying asthma, COVID-19 infections have been reported to have a similar risk of hospital admission or mortality as in those who did not have asthma (Sunjaya, 2022). As noted above, if the infection was severe, e.g., leading to hospital admission, then there may be persisting or permanent impairment from that.

Further resources

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