

Critical Analysis of Studies Concerning Reports of Respiratory Sensitization to Certain Wood Dusts

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ABSTRACT

Studies have been published reporting that exposures to certain wood dusts are sensitizing, resulting in respiratory symptoms in susceptible individuals. Many of the publications in this field are case reports that collectively have a number of important shortcomings. Illuminating these should further our understanding of whether respiratory sensitization results from occupational exposure to particular wood dusts. The aim of this study was to critically review and understand the evidence to date regarding reported respiratory sensitization in connection with wood dusts from oak, beech, pine, ash, and western red cedar. Publications dealing with these commercially important woods in North America have been selected from the Pubmed/Medline database (1966 to the present) using the key word, wood dust. These articles, along with supporting references on procedures and techniques, are reviewed according to the strengths and weaknesses of evidence and conclusions presented. Evidence from skin testing, specific immunoglobulin E measurements, and basophil histamine release tests suggests that reported symptoms are not likely to be immunologically derived. Because of methodological problems, challenge tests with specific wood dusts do not support the conclusion that reactions to certain wood dusts are specific. Experiments with nonspecific bronchoconstrictive agents indicate that a number of study subjects possess hyperresponsive airways. Thus, select individ-

uals can demonstrate various respiratory symptoms in the woodworking industry, but any specificity or direct cause is currently unproved. Current studies do not support that exposure to wood dusts from a number of common North American wood species causes immunologic sensitization in woodworkers. Rather, symptoms reported in some studies of exposed workers seem to follow the paradigm for nonspecific respiratory responses in individuals with hyperresponsive airways. (Allergy and Asthma Proc 26:262–267, 2005)

A number of studies have reported work-related respiratory symptoms in workers employed in the wood industries. Affected individuals report having symptoms when exposed to particular woods and their dusts. Because exposure to only certain woods have been reported in different cases, a level of specificity may seem to be present. This has led investigators to postulate specific immunologic sensitizations to particular woods or their constituents and has directed efforts to define immunologic mechanisms similar to those seen in atopic asthma and perhaps hypersensitivity pneumonitis. Many of these studies have been published as case reports. With the aim of improving our understanding of these symptoms and directing research toward practical solutions, a number of studies on specific wood dusts of commercial importance in North America, including oak, beech, pine, ash, and western red cedar, are considered in this review.

INITIAL OBSERVATIONS

The first step in identifying patients with work-related symptoms is to provide evidence of their association with the workplace. Suspicions usually are raised by the history but these can be confused with other stimuli encountered within and outside the workplace. One means that has

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been used to verify workplace-associated respiratory problems is to employ serial measurements of pulmonary functions over time (cross-shift measurements) to provide evidence of temporal relationships.¹ For example, decreases in peak expiratory flow rate (PEFR) or 1-second forced expiratory volumes (FEV₁) can be used to show evolving problems. Typically, these measurements are taken every 2 hours while at work and similarly while on leave and visually inspected for fluctuations. Because different patterns can develop, these measurements should be taken continuously for periods up to 3 weeks or until reliable patterns can be established. For example, Cartier *et al.* described a patient whose symptoms took 2 weeks to recur after returning to work.² This patient consistently exhibited isolated late asthmatic-like reactions that consisted mainly of nocturnal awakening. Often, these plots of pulmonary function over time are difficult to interpret. For example, Malo *et al.* published a case report of a worker whose PEFRs were monitored during and while off work.³ The PEFR plots showed similar magnitudes of breathing changes while on leave or at work but the changes were more common at work and were associated with increased medication usage. Although PEFR measurements are effort dependent and certainly nonspecific as to cause, the data generated from these measurements can be used successfully to indicate changes in pulmonary functions over time with various exposures. Complicating factors include extrinsic exposures, considerations of physical exertion, infections, effects of concurrent medications, and possible psychological factors associated with the workplace.

EXPLORING IMMUNOLOGIC MECHANISMS

Some of the reported work-related respiratory symptoms share many characteristics with immunoglobulin E (IgE)-mediated asthma. Both have similar clinical presentations, responses to antiasthma drugs, implications that specific exposures are responsible, and similar pathological changes.⁴ However, there are differences between asthma and the non-immune-mediated respiratory symptoms, including for the latter the relatively long lag periods observed on reexposure needed to redevelop symptoms and the fact that atopy does not seem to be a risk factor.^{4,5} Nevertheless, in the case of symptoms reported in association with wood dusts, investigators have searched for possible IgE-mediated mechanisms using skin testing, specific IgE measurements, and basophil histamine release and for possible IgG-mediated mechanisms using immunodiffusion.

Skin Testing

Positive skin tests often are used as evidence for specific IgE mechanisms. With respect to suspected respiratory symptoms in woodworkers, skin test results have been largely negative with some notable exceptions. In a study of three well-characterized patients suspected of being sensitive to oak dust, skin-prick testing with a 1:10 wt/vol extract

of oak dust was uniformly negative.⁶ Similarly, Sosman *et al.* reported several patients with suspected respiratory disease caused by wood dusts and found no positive skin tests to common inhalants or wood-dust extracts (oak, cedar, mahogany, or pine).⁷ Skovsted *et al.* made extracts of pine, beech, and oak that were concentrated 100-fold.⁸ Using a 3-mm wheal size cutoff, they reported in a single patient negative skin tests for oak but positive skin tests for pine and beech. The size of these positive tests was not reported. Subsequent studies on these patients with basophil histamine release indicated a questionable low level positive for pine extract only.⁸ Three different publications on suspected respiratory symptoms caused by dust from ash wood also reported negative skin-prick tests to ash wood extracts.⁹⁻¹¹ Curiously, Szmidt *et al.* noted a positive skin-prick test to a boiled extract but not to an unboiled extract of ash wood dust.⁹ Fernandez *et al.* reported positive titrated intradermal skin tests in one patient but no dose response was seen.¹⁰ Chan-Yeung *et al.* found that skin tests with crude extracts to western red cedar and with its constituent plicatic acid were negative in patients with suspected respiratory symptoms caused by western red cedar wood dust.¹² In most of these studies the skin testing data often are difficult to interpret. This is because the extracts are in-house and prepared with little characterization, there are patient and operator variables, and false positives are difficult to rule out. Taken together, the skin test data have not provided any substantial evidence that specific IgE mechanisms are involved in woodworkers' reported respiratory symptoms.

Specific IgE and IgG Measurements

Several publications have indicated that certain respiratory symptoms from particular wood dusts might be caused by specific IgE antibodies. The first of these publications studied 18 patients who had bronchopositive challenges with plicatic acid, a proposed cause of asthma due to western red cedar dust exposure.¹³ These authors conjugated a crude extract of western red cedar or plicatic acid attached to human serum albumin to sepharose as a solid phase. Using these conjugates and a very low cutoff for positivity, they reported that 8 of the 18 selected patients had abnormal radioallergosorbent test (RAST) values.¹³ The validity of these results can be questioned by noting that the values reported as abnormal were very low-level results with standard deviations well into the control range. In addition, the possibility that their results were caused by nonspecific IgE binding was not ruled out.

In a cross-sectional survey of 477 workers in a western red cedar sawmill, it was found, using the same assay, that 7% (35/477) of the workers had a reportedly elevated RAST to the plicatic acid human serum albumin sepharose conjugate.¹⁴ In this study only 16 of these workers with positive RASTs to plicatic acid had nonspecific bronchial hyperresponsiveness. These data do not support a relationship between the positive RASTs and bronchial hyperresponsiveness in western cedar

workers.¹⁴ However, it is important to point out that in these workers the total IgE levels were strongly associated with the positive RASTs. For example, only 1% of the workers with total IgE values <150 IU/mL had a positive RAST whereas 82% with total IgE >500 IU/mL had an elevated RAST. This strongly suggests the possibility that the positive RAST results could be caused by nonspecific binding. In addition, the data from Schmidt *et al.*, establishing a linear relationship between total IgE levels and hyperresponsive airways, suggest that the proposed relationship between positive RASTs and hyperresponsiveness proposed in this study would be expected.¹⁵

In a 4-year longitudinal follow-up of 227 red cedar workers there were no differences in positive RAST results whether the subjects were asymptomatic or symptomatic or whether they continued their exposure or not.⁵ This study notwithstanding, the previous questions about this assay suggest that specific IgE is not involved in the pathogenesis seen. In a more recent study on respiratory symptoms suspected to be caused by western red cedar–dust exposure, the authors found no significant elevated plicatic acid–specific IgE in patients as compared with controls.¹⁶ Interestingly, they reported that levels of plicatic acid–specific IgE were slightly higher in an atopic control group. Again, this suggests that the original assay used for all of these studies had a nonspecific binding problem because atopics generally have higher total IgEs than normals. The authors of this study agreed that specific IgE was unlikely to be involved in asthma associated with western red cedar wood exposures.

In a longitudinal study, RAST levels to plicatic acid were remarkably constant over a 2-year span. Similar results would be expected if nonspecific binding were a problem with this assay because total IgE levels are generally stable. In addition, this study reported no difference in RAST scores between patients who were better or worse during follow-up.¹⁴

Two case reports citing evidence for specific IgE have been reported for beech and ash wood dusts.^{10,17} In the case of beech dust using an in-house developed enzyme-linked immunosorbent assay with an arbitrary positive cutoff of >0.100 O.D. units, a result of 0.108 was reported as positive.¹⁷ The patient had a total IgE of 140 IU/mL and one might again expect this result to be caused by nonspecific binding or simply variability in spectrophotometer readings between assay wells. This very low result should not be taken as positive evidence for specific IgE. In the ash wood–dust case report a RAST of 0.57 Pharmacia RAST units was reported as positive (cutoff = 0.35 Pharmacia RAST units).¹⁰ This patient had a total IgE of 349 IU/mL, again making it likely that nonspecific binding could be responsible for this result. Supporting this is the fact that the patient had a negative skin-prick test to a 1:10 wt/vol extract of ash dust. In addition, these authors used an abnormally high amount of ash-dust extract for coupling to activated paper disks, which raises further questions regarding the validity of this test.

Recently, a large study of pine woodworkers was conducted.¹⁸ This study found evidence for specific IgE to pine wood extracts by an *in vitro* assay and immunoblotting in a very

small number of workers. They also found the same incidence of these IgE antibodies in nonexposed subjects and concluded that pine-specific IgE is not likely to be involved in respiratory symptoms in pine woodworkers. Although specific inhibitions were not performed, the authors speculated that the IgE found was likely because of cross-reactive IgE as found with proteins like profilin and certain carbohydrates.¹⁸

In addition, one group of investigators looked for precipitating antibodies as found in hypersensitivity pneumonitis.⁷ In a patient with negative skin tests to an oak-dust extract they found positive precipitins by immunodiffusion to an alcoholic extract of oak dust. Unfortunately, normal serum as a control was not similarly tested, raising the possibility that the precipitin lines were nonspecific perhaps because of tannins or other substances known to precipitate proteins that might be present in an alcoholic extract of oak dust.

Basophil Histamine Release

Basophil histamine release tests have sometimes been used to investigate whether specific IgE is involved mechanistically. In one study, it was noted that plicatic acid could induce (at 100 μ g/mL) histamine release from asthmatic patients who worked with western red cedar.¹⁶ However, it also was shown to cause histamine release from some normal subjects.¹⁶ This histamine release was shown not to involve specific IgE because no IgE antibodies to plicatic acid were found in these patients and also because lactate stripped basophils were still responsive to plicatic acid. In a follow-up study, these authors also found that tyrosine kinases were not likely to be involved in the histamine release with plicatic acid in asthmatic patients working with western red cedar.¹⁹ Because these kinases are involved in specific IgE activation, their findings are consistent with the view that histamine release caused by plicatic acid is IgE independent. In summary, there is very little evidence to support the idea that wood dusts or their components are sensitizers and that respiratory symptoms noted in some woodworkers derive from IgE- or IgG-mediated mechanisms.

SPECIFIC INHALATION CHALLENGES

One approach to associating specific workplace exposures with the production of symptoms is to perform specific inhalation challenges. Although these tests are not without their problems, they do provide the advantage of being performed without the influence of numerous other exposures typically found in the workplace that might confuse issues.²⁰ With respect to wood dusts and their components, this usually entails exposing the patient to various wood dusts or aqueous extracts of the same in the laboratory and observing subsequent pulmonary functional changes. In performing these tests it is important that the challenge test mimic actual exposures as close as possible, that nonspecific factors are excluded, and, most importantly, that variables such as the timing of the challenge with respect to the

patient's hyperresponsive state be noted. In addition, relevant controls are needed to rule out irritant effects.

Although specific inhalation challenges have been considered the gold standard for confirmation of occupational asthma, it is important to consider how these challenges are actually done. For example, Malo *et al.* challenged three nonatopic workers believed to be sensitized to oak dust.⁶ Their first challenge required a worker to saw different woods for 3 hours. In this patient this induced an early FEV₁ decrease (21%) and a late reaction 7 hours postchallenge (18% decrease in FEV₁). On the next day the same subject was exposed to aerosolized oak dust by pouring dust back and forth on a tray for 3 hours. Twenty minutes after this 3-hour challenge a maximum fall of FEV₁ of 20% was noted, with the appearance of a late reaction 7 hours after the exposure ended (FEV₁, 18% decrease). These tests were not blinded and similar challenges with other wood dusts performed 2 weeks later were negative. A single control asthmatic subject also was challenged in a similar fashion with no response. The results of these challenges were interpreted as the subject being specifically sensitized to oak dust.

In the same study, two subjects suspected to be sensitive to oak dust were first challenged with fir dust by pour test with negative results. On the following day, both subjects were challenged with oak dust for 2 hours and developed symptoms shortly thereafter. Both of these latter subjects had hyperresponsive airways that increased by ~10-fold after these challenges. These cases illustrate a major problem with the interpretation of challenge tests; *i.e.*, hyperresponsiveness in these subjects can increase after challenges.^{21,22} Thus, it is considerably more likely that the patients would have a positive inhalation challenge test regardless of what they were challenged to when their hyperresponsiveness was increased. For example, by performing control challenges first, one could speculate that this heightened the patient's responsiveness and the likelihood of giving a positive result to the next challenge. This consideration also questions the meaning of performing control exposures (other wood dusts) after a period of recuperation (3 days) at times when the patient may be less responsive.

Malo *et al.* also reported challenging a patient suspected of being sensitized to ash wood dust.³ Again, this patient's positive challenge was preceded on the previous day with challenge testing to various other wood dusts. Szmidt reported a positive challenge in a subject to ash wood dust (by breathing air from a bag full of ash wood dust) but used as a control for specificity a challenge with pine wood dust 4 days after the recuperation from the previous challenges.⁹ Cartier *et al.* described a case report of a patient with hyperresponsive airways that developed at work in a sawmill that processed eastern white cedar.² This patient had the typical workup expressing more variable FEV₁s while at work than on leave and expressed only isolated delayed asthmatic reactions. They then performed a pour test with eastern white cedar for 2 hours, which produced a nonsig-

nificant FEV₁ change of 12%. The patient was then returned to work and showed more significant changes in her PEFs. During this time this patient was challenged with western red cedar by pour test for 2 hours and showed a 25% FEV₁ 4 hours after the end of the challenge. Because these woods contain plicatic acid, she was also challenged to a nebulized solution of plicatic acid (5 mg/mL at 0.18 mL/minute). A challenge for 7 minutes produced a late asthmatic reaction represented by an FEV₁ decrease of 38% 14 hours after the challenge. During these challenges and at work her PC20 dosage also was noted to decrease. These findings are difficult to relate specifically to cedar woods because, again, the patient was in a hyperresponsive state when challenged. The inhalation of plicatic acid also could be interpreted as a nonspecific reaction to an irritant in an individual with hyperreactive airways. Interestingly, plicatic acid has been shown to activate complement by the classic pathway and this also could have produced her inflammation and reactivity.²³ This idea is reinforced in that practically all of her reactions were delayed.

In a longitudinal study of 227 workers in a western cedar sawmill it was noted that bronchial responsiveness to plicatic acid inhalation was present in 18% of the workers.⁵ For comparison, in a study of animal laboratory workers, bronchial hyperresponsiveness was present in 24% of the workers.²⁴ Thus, in considering occupational respiratory symptoms and challenge testing it is important to note that hyperresponsiveness is a rather prevalent finding in some industries.²⁵

A WORD ON PREVALENCE

Given similar workplace exposures, only a very small number of workers exhibit respiratory symptoms when working with various woods. Chan-Yeung *et al.* reported that 1.7% of the 350 workers in a cedar sawmill had positive inhalation challenge tests to plicatic acid.²⁶ During the subsequent 6 years, six new workers became positive giving an incidence of 0.3% per year. This study again confirmed that atopy was not a predisposing factor in acquiring symptoms. Although point prevalences and cumulative prevalences are difficult to establish in a disease such as asthma (because of diverse criteria), new asthma has been shown to develop in 1.4% of normal subjects in a longitudinal study.²⁷ In a large cohort (3860 subjects) the point prevalence of asthma was 6.6% and these prevalence rates were shown to increase with age.²⁷ Thus, the frequency of specific workplace respiratory symptoms does not seem to be significantly different from that found in general population studies. In addition, when considering the incidence of respiratory problems in various occupations, the subjects' ages should be taken into account.²⁸

DISCUSSION

Occupationally associated respiratory symptoms have been documented and mechanisms have been defined for a number of different types of specific occupa-

tional exposures. These include exposures to highly sensitizing substances such as platinum salts and a number of chemicals such as isocyanates where evidence for specific IgE immunologic mechanisms have been documented.^{29,30} In contrast to these reports, similar studies attempting to implicate immunologic mechanisms as being responsible for symptoms believed to be caused by exposures to various wood dusts have not been convincing.

Evidence for specific IgE directed toward extracts of various woods by skin testing, basophil histamine release, and specific IgE tests have largely been negative. A few publications exist that have reported positive findings in this regard, yet on critical examination their validity can be questioned because of procedural or improper controls. For example, it is difficult to interpret the meaning of skin test results (positive or negative) when so little is known about the composition of the extracts used. With respect to serological measurements for specific IgE, those reported as positive were at very low levels and likely because of nonspecific binding problems. In fact, the same authors in later studies on red cedar workers have largely refuted their original findings for IgE antibody involvement.^{4,31,32} A possible caveat here is that the local production of specific IgE has not been ruled out. Thus, to date, there is very little evidence that wood dusts or their components are sensitizing and that the symptoms seen in some woodworkers are caused by specific IgE mechanisms. These conclusions also support the supposition that purported reactions to various wood dusts are likely to be nonspecific.

One commonly used means to provide evidence of specific causal relationships is to challenge subjects with defined substances in an attempt to reproduce symptoms. Ideally, challenge tests should provide dose-response information, mimic actual exposures as close as possible, exclude nonspecific factors, include relevant controls (to rule out irritant effects), and take into consideration patient variables such as timing of challenge with respect to the patient's hyperresponsive status. Unfortunately, with respect to studies on woodworkers, many of these details have been neglected. For example, to incriminate specific exposures to various wood dusts, individuals have been subjected to pour tests, breathing from a bag containing wood dust, and asked to inhale uncharacterized nebulized extracts. Relating these exposures to natural exposures is difficult at best. A few studies have measured workplace exposures by gravimetric measurements.^{3,33} Here, the actual weight of inhalable particulate per volume of air has been determined. However, attempts to use this information in specific challenge testing by the techniques listed previously have not been used. Thus, it is very difficult to determine how challenge testing relates to actual work exposures.

For proper interpretation, challenge tests should rule out the presence of other antigens and bioactive contaminants before testing. For example, Cohen *et al.* identified antibodies to mold antigens in studies on sequoiosis.³⁴ This includes important substances such as endotoxins and glucans

that can produce inflammation through stimulation of the innate immune system. In addition, the physiological effects of inhaling particulate and chemically active substances such as acids (*i.e.*, plicatic acid) should be considered. These considerations are particularly important in individuals with preexisting hyperresponsive airways.

To be interpreted correctly, challenge tests should be accompanied with appropriate controls. These should include challenges in individuals with similar problems but not commonly exposed to the same substances. For example, in woodworkers, appropriate controls would include challenges of other asthmatic individuals as well as normal individuals. Several studies have attempted to do this. However, asthmatic controls should be matched for similar exhibition of symptoms both qualitatively and quantitatively. This is difficult and it should be recognized that just because a control does not respond to a particular challenge is not always strong evidence for specificity in the patient who does.

Another important control often used in these studies has been to challenge the patient in a similar fashion to the dust of a wood that is not included in the patient's work. Here, *e.g.*, inactivity to a challenge with pine wood dust in the same patient who has reacted to oak wood dust has been used as proof that the patient was specifically sensitized to oak wood dust. Problems with this interpretation arise when one considers the likely differences in particle sizes between hard- and softwoods and the fact that different woods have compositional differences that might contribute nonspecifically to a positive or negative challenge.

Reproducibility of challenge tests (both negatives and positives) usually has not been addressed in these studies. Actually, this might be because the tests themselves are not particularly reproducible or that some patients' reactivities are not stable. Regardless, if one is to use challenge testing to implicate specific wood dusts with specific symptoms, some proof of reproducibility should be evidenced.

Perhaps the most severe limitation in the interpretation of challenge testing is the fact that many of these patients seem to require a period of priming before exhibiting symptoms. Thus, the timing of the challenge test with respect to the patient's reactive status is an important variable to be considered. Because in practically every challenge study patients were primed the day before challenge with either control dusts or by work exposure, this may invalidate many of their conclusions. This is because a positive challenge after a day of priming might be expected from most patients regardless of the nature of the challenge. Indeed, hyperresponsiveness has been shown to increase following challenges.²¹ Supporting this criticism is the observation that a number of once positive challenges were negative when performed after a reasonable period of leave from work. Thus, to provide evidence of specificity using challenges, it may be necessary to perform a number of challenges (preferably blinded) at different time points relative to each other and the controls. Ideally, these also should be repeated to give evidence of reproducibility. Thus, challenge tests with various wood dusts are not simple nor is their

interpretation. To date, these tests do not provide strong evidence of specificity and need to be done in a more careful manner before hard conclusions can be drawn.

CONCLUSIONS

A critical assessment of studies and case reports of workers exposed to wood dust of species common to North America does not support that these dusts are respiratory sensitizers. Evidence from skin testing, specific IgE measurements, and basophil histamine release tests do not suggest that any of the reported symptoms is immunologically derived. Challenge tests with specific dusts have suffered from methodological problems, including tests performed without adequate controls, the failure to blind the tests, and the lack of evidence of reproducibility. Challenge tests with nonspecific bronchoconstrictive agents showed hyperresponsive airways in a number of these subjects. Thus, select individuals can present respiratory symptoms without any evidence of specificity or direct cause. It is suggested that to more fully understand these symptoms and their origins, studies use better controls and more quantitative procedures and focus on mechanisms of nonspecific hyperresponsiveness.

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