Investigation of occupational asthma: Do clinicians fail to identify relevant occupational exposures?

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BACKGROUND: Specific inhalation challenges (SIC) enable the identification of the agent responsible of occupational asthma (OA). A clinician may fail to identify a specific agent in the workplace, which may potentially lead to a misdiagnosis. The expert assessment method performed by an occupational hygienist has been used to evaluate occupational exposures in epidemiological studies.

OBJECTIVE: The broad aim of the present study was to evaluate the contribution of an expert assessment performed by an occupational hygienist to the diagnosis of OA. The specific aim was to compare workplace exposures identified by an occupational hygienist and by chest physicians in subjects with positive SICs and subjects with asthma, but with a negative SIC.

METHODS: SICs were performed in 120 cases: 67 were positive and 53 were negative. A clinician assessed occupational exposures to sensitizers during a routine clinical evaluation preceding the performance of the SIC. An expert assessment of occupational exposures was performed by an occupational hygienist blind to the result of the SIC.

RESULTS: The occupational hygienist identified the causal agent in 96.7% of the 61 cases of positive SIC. In 33 (62.3%) cases of negative SICs, the occupational hygienist identified ≥1 sensitizing agent(s) that had not been identified by the clinician.

CONCLUSION: The hygienist identified the causal agent in almost all subjects with OA. In contrast, the clinician failed to identify potential exposures to sensitizers in >60% of the negative SIC subjects, which may have resulted in some subjects being misdiagnosed as not having OA.

Key Words: *Expert assessment of occupational exposure; Occupational asthma; Occupational hygienist; Specific inhalation challenge*

Étude sur l'asthme professionnel : les cliniciens échouent-ils à repérer des expositions professionnelles?

HISTORIQUE : Des épreuves d'inhalation spécifiques (ÉIS) permettent de déterminer l'agent responsable de l'asthme professionnel (AP). Un clinicien peut échouer à repérer un agent précis en milieu de travail, qui peut donner lieu à un mauvais diagnostic. Un hygiéniste du travail a utilisé la méthode d'expertise pour évaluer l'exposition professionnelle dans les études épidémiologiques.

OBJECTIF : La présente étude visait principalement à évaluer l'apport de l'expertise d'un hygiéniste du travail pour diagnostiquer un AP. Plus précisément, elle visait à comparer l'exposition professionnelle décelée par un hygiéniste du travail et par des pneumologues chez des sujets dont l'ÉIS était positive ainsi que chez des sujets asthmatiques dont l'ÉIS était négative.

MÉTHODOLOGIE : Cent vingt cas ont subi une ÉIS; 67 étaient positifs et 53, négatifs. Un clinicien a évalué l'exposition professionnelle aux agents de sensibilisations dans le cadre d'une évaluation clinique normale précédant une ÉIS. Un hygiéniste du travail a procédé à l'expertise de l'exposition professionnelle sans connaître les résultats de l'ÉIS.

RÉSULTATS : L'hygiéniste du travail a déterminé l'agent causal chez 96,7 % des 61 cas d'ÉIS positives. Dans 33 cas d'ÉIS négatives (62,3 %), il a repéré au moins un agent de sensibilisation non perçu par le clinicien.

CONCLUSION : L'hygiéniste du travail a déterminé l'agent causal chez la plupart des sujets atteints d'AP. En revanche, le clinicien a échoué à déceler l'exposition potentielle à des agents sensibilisants chez plus de 60 % des sujets dont l'ÉIS était positive, ce qui a pu donner lieu à un diagnostic erroné d'absence d'AP.

Specific inhalation challenge (SIC) tests are considered by work-related asthma experts to be the reference test for diagnosing sensitizer-induced occupational asthma (OA) (1). These tests expose the patient to the suspected agent to induce an asthmatic reaction. SIC tests can be negative when the patient is not challenged with the sensitizing agent that causes his or her OA (2-6). It is essential to limit the occurrence of negative tests caused by the lack of identification of the causal agent during the investigation of OA because subjects with OA will experience a worsening of their condition if maintained at work with the same conditions of exposures (7-10).

The assessment of occupational exposures is an important step in the clinical investigation of work-related asthma (WRA). Clinicians usually rely on the occupational history of the workers, their own knowledge and experience, and on material safety data sheets (MSDS) obtained from the employers to identify occupational exposures and potential sensitizers present at the workplace. However, a comprehensive identification of every occupational exposure is complex and some relevant occupational exposures may be overlooked (11,12). Workers from many industries are typically not exposed to a single sensitizing agent, but to several agents (13). Occupational hygienists have an extensive knowledge of workplaces and of the type of exposures occurring during a specific task. The 'expert assessment' method has been developed in the framework of population-based case-control epidemiological studies whereby hygienists assess exposures from occupational histories (14,15). This method is regarded as being precise in the retrospective evaluation of workplace exposures when no quantitative exposure measurements are available. Despite the fact that a few studies have evaluated the validity and reliability of this expert assessment method (15-17), none have assessed its contribution to the diagnosis of OA in a clinical context. The broad aim of the present study was to assess the contribution of an expert assessment performed by an occupational hygienist to the clinical investigation of OA. The specific aim was to compare workplace exposures detected by clinicians and an expert assessment performed by an occupational hygienist in WRA subjects with positive and negative SICs.

METHODS

Study design

The present study was a clinical analysis comparing occupational exposures identified by clinicians specialized in the field of WRA and by an occupational hygienist expert in exposure assessment for epidemiological studies. Subjects had participated in a study in which

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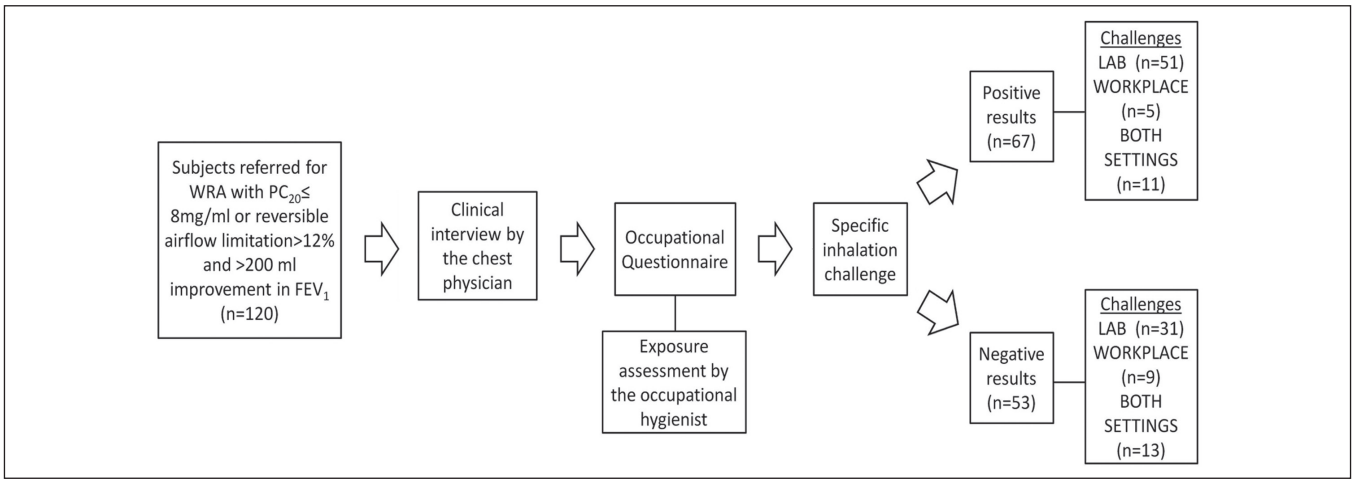

Figure 1) *Summary of the different steps of subject assessment. FEV_1 Forced expiratory volume in 1 s; LAB Laboratory; PC_{20} Concentration of methacholine causing a 20% decrease in FEV_1; WRA Work-related asthma*

the occupational exposures were assessed by an occupational hygienist between 2005 and 2008 in two Quebec tertiary care centres specialized in the field of WRA (18). Each subject's exposures had previously been assessed by one of the expert clinicians in the field of WRA in Montreal and Quebec City (18).

Subjects

All workers referred for a WRA evaluation to two Quebec tertiary clinics between 2005 and 2008 were invited to participate in the study. The diagnosis of asthma was retained if reversible airflow limitation was demonstrated (forced expiratory volume in 1 s [FEV_1] <80% predicted and FEV_1/forced vital capacity <0.7 with an improvement in FEV_1 ≥12% (and ≥200 mL) postbronchodilator) or, in absence of reversible airflow limitation, a provocative concentration of methacholine inducing a 20% fall in FEV_1 <8 mg/mL was demonstrated. Subjects with a worsening of their asthma symptoms when at work who had a positive SIC were defined as OA, whereas subjects with a worsening of their asthma symptoms at work with a negative SIC were defined as work-exacerbated asthma. The study was approved by the Ethics Committees of Sacré-Coeur Hospital and the *Institut universitaire de cardiologie et de pneumologie de Québec* (IUCPQ) and was conducted in accordance with the amended Declaration of Helsinki (Ethical approval number Sacré-Coeur Hospital: CER2005-07-30;2010-139; IUCPQ: CER1202). All subjects provided written consent.

Physician assessment of occupational exposures

The clinical assessment of occupational exposures in subjects suspected of WRA was performed by one of seven chest physicians (Sacré-Cœur Hospital, n=4; IUCPQ, n=3) expert in the field of WRA as part of a routine clinical assessment before the performance of the SIC test. The exposure history performed by the physician was focused on the potential exposures to sensitizers identified when the respiratory symptoms occurred or worsened at work (1). MSDS of products used in the workplace were obtained from the employer by either the Quebec workers' compensation board (*Commission de la santé et de la sécurité du travail)* or the physician in charge of the assessment.

Expert assessment of occupational exposures

A questionnaire consisting of a series of 15 questions related to the employer (activities, products, processes), the occupation (job title, task description, machines, material used) and the work environment (presence of dusts, smoke, fumes, gases, vapors, use of protective equipment, work performed by other workers) was administered face-to-face to each subject by trained staff at the clinic to describe the last job held by each subject when the diagnosis of asthma was made (18).

The expert assessment and coding of occupational exposures were performed by an occupational hygienist (DB) following a methodology developed for the reconstruction of past exposures in studies of occupational cancer (14) and widely used in community-based case-control studies (19). The occupational hygienist assigned exposures from a preestablished list of 41 occupational agents within five generic categories: five inorganic dusts, 10 organic aerosols, four combustion/pyrolysis fumes, seven gases and mists, and 15 organic chemicals (18). These agents are sensitizers known to induce OA and irritants either common in the workplace or already hypothesized for work-exacerbated asthma. The occupational hygienist was blind to the medical diagnosis (OA or work-exacerbated asthma) of all subjects in the study. All agents were coded on an ordinal scale (low, moderate, high) for the following parameters: concentration of agents present in the workplace environment; degree of the rater's confidence that exposure occurred (reliability); and exposure frequency. The score on reliability is a three-point scale that indicates the degree of certainty of the coder regarding the occupational exposure of the worker. The coder indicates whether he is certain that the exposure occurred (reliability 3), believes it is probable (reliability 2) or considers it possible but not probable (reliability 1). The score of reliability is part of the method of exposure assessment by expertise, which is considered to be the most accurate method for assessing chemical exposures in community-based case-control studies (15).

Information sources included the questionnaire, technical data sheets, the industrial chemistry and occupational hygiene literature, several databases, and occasional contacts with experts in specific fields (18). MSDS obtained from employers by the *Commission de la santé et de la sécurité du travail* and the clinicians were sent to the occupational hygienist along with the occupational questionnaire. The occupational hygienist also obtained additional MSDS from the product suppliers' websites. If needed, the occupational hygienist was able to contact the research assistant at the tertiary care centres for any additional questions to be directed to the patient.

SIC test

SICs were performed in the laboratory or at the workplace (20). On the first day, subjects were exposed to a sham substance to ensure their asthma was stable. On subsequent days, they were progressively exposed to the occupational agent identified by the chest physician and suspected of causing their asthma. When the challenge was negative in the laboratory or when the work exposure could not be reproduced in the laboratory, the SICs were performed at the workplace under the supervision of a respiratory technologist, who assessed their respiratory function hourly over 7 h over two consecutive days. A SIC was considered to be positive if there was a 20% fall in FEV_1 following exposure. A methacholine challenge was performed at the end of the control day as well as at the end of the last day of exposure.

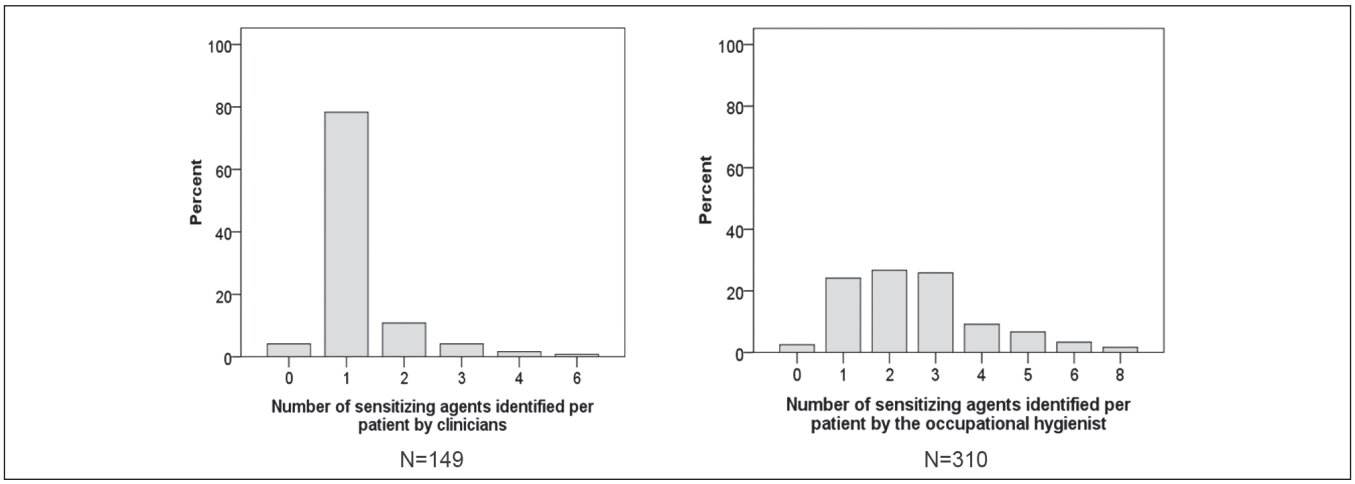

Figure 2) *Frequency distribution of the number of sensitizing agents identified per patient by the occupational hygienist and by the clinician in all cases of work-related asthma*

Data analysis

The SIC test was considered to be the reference test to diagnose occupational asthma. Therefore, all subjects who had a positive SIC after exposure to the agent tested were considered to be true positive cases.

Because the investigation was focused on identifying cases of OA, the identification of workplace exposures was limited to 25 agents and categories known to be or to contain potential occupational sensitizers namely: acrylates, adhesives, amines, anhydrides, animal aerosols, enzymes, flour, formaldehyde, gases and mists, grains, gums, hardeners, inorganic aerosols, isocyanates, latex, metals and their compounds, metal fumes, molds and yeasts, pharmaceuticals, plants, resins, textile dusts, woods and other organic chemicals (eg, azodicarbonamide).

Occupational exposure to sensitizers detected by the occupational hygienist was assessed on a nominal scale; exposed or nonexposed independently of level, frequency and reliability. Potential exposures identified by the clinician were recoded to match the same categories as the occupational hygienist. A Student's *t* test was performed to compare the average number of occupational agents identified per patient between the occupational hygienist and the chest physicians.

RESULTS

The subjects' characteristics had been described in a previous study (18). One hundred twenty participants (positive SIC, n=67; negative SIC, n=53) were enrolled in the present study (Figure 1). The clinical characteristics of the subjects are reported in Table 1.

The hygienist identified, on average, more potential sensitizing agents per patient (mean [± SD] 2.5±1.5) than the clinician (1.2±0.8; P<0.001) (Figure 2).

TABLE 1
Subject characteristics

	Work-exacerbated asthma (n=53)	Occupational asthma (n=67)
Male sex, %	56.6	67.1
Age, years	43.1±11.6	42.1±10.3
Atopy, %	64.2	74.6
Ever smokers,%	75.5	53.7
Pack-years in ever-smokers	18.1±19.3	16.3±13.5
Years with asthma	6.4±10.6	4.5±8.8
Subjects reporting asthma before exposure, n (%)	11 (20.8)	16 (23.9)
Time between onset of asthma symptoms and diagnosis, years	2.4±4.4	1.8±3.2
Duration of exposure before symptom onset, years	8.2±9.9	6.3±8.5
Duration of exposure after symptom onset, years	2.5±3.0	3.7±4.4
FEV_1 , % predicted	79.7±16.6	86.0±15.4
FEV_1/FVC	73.0±9.8	75.3±9.2
PC_{20}, mg/mL, geometric mean (95% CI)	2.3 (1.5–3.4)	3.5 (2.2–5.6)

Data presented as mean ± SD unless otherwise indicated. FEV_1 Forced expiratory volume in 1 s; FVC Forced vital capacity; PC_{20} Concentration of methacholine causing a 20% decrease in FEV_1

Identification of sensitizers in subjects with positive SIC by the clinician and the occupational hygienist

The agents responsible for OA as identified by the industrial hygienist and the clinicians are presented in Table 2. There were six cases of OA (five SICs performed in the workplace and one SIC performed in both settings) where the causing agent was not identified. However, these patients experienced a sustained 20% decrease of their FEV_1 during the SIC performed at the workplace.

The expert assessment of occupational exposures by the occupational hygienist identified the causing agent of OA in 59 subjects (96.7%) of the 61 for whom a causing agent had been identified by the SIC test. There were only two cases in which the occupational hygienist did not identify the causal agents (one each for isocyanate and flour). In these 59 patients, the occupational hygienist identified a total of 60 exposures to sensitizing agents which were identical to the causal agents identified by the clinician (in one patient, flour and gum were identified as causal agents). The reliability of the occupational exposures identified by the occupational hygienist was high in 95% of cases, moderate in 1.7% of cases and low in 3.3% of cases.

Identification of sensitizers in subjects with a negative SIC by clinicians and the occupational hygienist

In 33 of 53 subjects with a negative SIC, the occupational hygienist identified exposures to one or more potential sensitizers that had not been identified by the clinician (Table 3). The occupational hygienist identified 78 such exposures among these subjects. The hygienist detected sensitizing agents in SICs that had been performed only in the laboratory, at work and at both locations. Among these 33 subjects, there were 24 challenges performed only in the laboratory, three challenges performed only in the workplace and six challenges performed in both settings. Eighty-nine percent of the sensitizing agents identified by the occupational hygienist among these 33 patients had high and moderate degree of reliability (high, 67.6%; moderate, 21.6%; low, 10.8%). In the remaining 20 subjects with a negative SIC,

TABLE 2
Sensitizing agents identified by the occupational hygienist and the clinicians in subjects with positive specific inhalation challenge (SIC) tests

Sensitizers identified by the occupational hygienist	Agent tested during SIC	Causal agent	SIC
Grain (barley), **enzymes (maltine)**	Grain (malt, barley)	**Grain (malt)**	L
Flour, enzymes (alpha-amylase)	Flour (wheat flour)	**Flour (wheat flour)**	L
Isocyanates (MDI), adhesives	Isocyanates (MDI)	**Isocyanates (MDI)**	L, W
Flour, grain, pharmaceuticals (oreomycin, rumensin)	Flour (wheat flour)	**Flour** (wheat flour)	L, W
Gum, flour	Gum, flour	**Gum, flour**	L
Metal fumes, metals and their compounds, amines, **isocyanates**	Isocyanates (HDI)	**Isocyanates (HDI)**	L
Metal fumes, **flour**, enzymes(alpha-amylase), adhesives	Flour (wheat flour)	**Flour (wheat flour)**	L
Formaldehyde, metals and their compounds, wood, **animal aerosols (fur)**, amines	Animal aerosols (beaver fur), formaldehyde	**Animal aerosols (beaver fur)**	L
Animal aerosols	Animal aerosols(beef skin)	**Animal aerosols**	L,W
Formaldehyde, **animal aerosols**	Animal aerosols (rat litter)	**Animal aerosols**	L
Flour	Flour (wheat flour)	**Flour (wheat flour)**	L
Wood, **aerosols derived from animals**	Animal aerosols (rat litter)	**Animal aerosols**	L
Pyrolysis fumes (colophony), formaldehyde, metals and their compounds	Resins (colophony)	**Resins (colophony)**	L
Wood, **animal aerosols (rat urine proteins)**	Animal aerosols	**Rat litter**	L
Metals and their compounds, **resin (colophony)**	Resins (welding on colophony resin)	**Colophony resin**	L
Flour, molds and yeasts (baker's yeast-zymase), enzymes (alpha-amylase)	Flour (rye flour)	**Flour (rye flour)**	L
Flour	Flour (multigrain, rye)	**Flour (multigrain)**	L
Wood, adhesives	Wood (exotic wood)	**Wood (exotic wood)**	L
Flour	Flour (wheat flour)	**Flour (wheat flour)**	L
Metal fumes (welding), **isocyanates (MDI)**	Isocyanates (MDI)	**Isocyanates (MDI)**	L
Wood	Wood (red cedar)	**Wood (red cedar)**	L
Amines, **isocyanates**, resin	Isocyanates (MDI)	**Isocyanates (MDI)**	L
Amines, **isocyanates (HDI)**, resin (epoxy)	Isocyanates (HDI), resine (epoxy), amines	**Isocyanates (HDI)**	L
Flour, enzymes	Flour (rye flour)	**Flour (rye flour)**	L
Isocyanates, solvent (styrene)	Isocyanates (MDI)	**Isocyanates (MDI)**	L
Animal aerosols (crab aroma)	Animal aerosols (snow crab)	**Nebulized snow crab**	L
Metals and their compounds (steel dust), **isocyanates**	Isocyanates (MDI)	**Isocyanates (MDI)**	L
Gases and mists (cooking fumes), flour (corn flour), plants (spices), inorganic aerosols (metabisulfite)	Inorganic aerosols (metabisulfite), spices, plant (boiled eggplant)	**Plant (boiled eggplant)**	L,W
Adhesives (2-ethyl cyanoacrylate), acrylates (ethyl methacrylate, methacrylic acid)	Acrylates (cyano-acrylate, methacrylate)	**Acrylates (cyano-acrylate, methacrylate)**	L
Wood, **isocyanates (TDI)**	Isocyanates (TDI)	**Isocyanates (TDI)**	L
Flour	Flour (wheat)	**Flour (wheat)**	L
Metal fumes (welding), flour, grain	Flour (wheat)	**Flour (wheat)**	L
Flour	Flour (wheat flour)	**Flour (wheat flour)**	L
Animal aerosols (crab aroma)	Animal aerosols (crab aroma)	**Crab aroma**	L
Wood	Wood (exotic wood)	**Wood (exotic wood)**	L,W
Metal fumes, metals and their compounds, **isocyanates**, hardeners, acrylates	Isocyanates (HDI, IPDI)	**Isocyanates (IPDI)**	L
Wood	Wood (red and white cedar dust)	**Red and white cedar dust**	L,W
Animal aerosols	Animal aerosols (shrimp)	**Shrimp**	L
Resin, azodicarbonamide	Azodicarbonamide	**Azodicarbonamide**	L
Formaldehyde, wood, adhesives	Wood (red cedar)	**Red cedar**	L
Metal fumes, formaldehyde, metals and their compounds, amines, **isocyanates (MDI)**	Isocyanates (MDI)	**Isocyanates (MDI)**	L
Wood	Wood (oak and cherry dust)	**Oak and cherry dust**	L
Flour (animal feed), wood (wood shavings), molds and yeasts, **animal aerosols (dust of sows)**, latex	Animal aerosols (pig bristle)	**Animal aerosols (pig bristle)**	L
Metal fumes, metals and their compounds, **isocyanates**, hardeners, acrylates	Isocyanates (HDI)	**Isocyanates (HDI)**	L
Flour, molds and yeasts, enzymes(alpha-amylase)	Flour (white flour)	**Flour (white flour)**	L
Metal fumes, metals and their compounds (grinding), **animal aerosols (wool dust)**	Textile dust	**Textile dust**	W
Metal fumes, metals and their compounds	Metal fumes (welding mild steel, welding stainless steel)	**Welding mild steel**	L
Gases and mists (glutaraldehyde), pharmaceuticals, **latex**	Latex	**Latex**	L

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TABLE 2 – CONTINUED
Sensitizing agents identified by the occupational hygienist and the clinicians in subjects with positive specific inhalation challenge (SIC) tests

Sensitizers identified by the occupational hygienist	Agent tested during SIC	Causal agent	SIC
Wood, adhesives	Wood (white cedar), acids (plicatic acid)	**Wood (white cedar)**	L
Acids (acetic acid), metals and their compounds (aluminum), **wood**	Wood (pine dust), Paint (latex primer paint)	**Wood (pine dust)**	W
Animal aerosols (cracking crab legs)	Animal aerosols (crab extracts)	**Crab extracts**	L
Isocyanates, hardeners, acrylates	Isocyanates (HDI)	**Isocyanates (HDI)**	L
Metal fumes, metals and their compounds, **wood**	Wood (birch dust and aspen dust)	**Birch and aspen dust**	W
Metal fumes, metals and their compounds (mild steel, stainless steel, and aluminum grinding)	Metal fumes (argon welding on aluminum, mild steel welding)	**Argon welding on aluminum**	L
Aerosols derived from animals (decortication of crabs)	Animal aerosols (crab)	**Crab**	L,W
Flour, enzymes(alpha-amylase, xylanase)	Flour (wheat flour)	**Flour (wheat flour)**	L
Wood	Wood (white cedar)	**Wood (white cedar)**	L
Animal aerosols (lobster and crab aromas)	Aerosols derived from animals (lobster and crab extracts)	**Lobster and crab extracts**	L
Formaldehyde, **wood (medium-density fibreboard dust)**	Wood	**Fibreboard dust**	L
No sensitizers identified	Flour (wheat dust, soybean dust), wood (white pine dust)	Wheat dust, soybean dust	L
Formaldehyde, wood, adhesives, metal fumes (welding)	Isocyanates (MDI)	Isocyanates (MDI)	L
Formaldehyde, metals and their compounds, pharmaceuticals, pesticides, biocides	Acrylates (methyl methacrylate), acids (alginate)	Unknown	L,W
Amines, acrylates (sodium methacrylate)	Copolymer of quaternary acrylate salt and acrylamide	Unknown	L,W
Wood (wood pulp), molds and yeasts, adhesives	Tampon dust	Unknown	L,W
Metal fumes, metals and their compounds, isocyanates	Isocyanates (MDI), metal fumes	Unknown	L,W
Metal fumes (welding), amines (ethanolamine)	Metal fumes (stainless steel)	Unknown	W
Animal aerosols (leather dust), isocyanates, adhesives	Unknown	Unknown	W

Exposures in bold refer to causal agents identified by the hygienist, information inside parentheses refers to specific agents. HDI Hexamethylene diisocyanate; IPDI Isophorone diisocyanate; L Laboratory; MDI Methylene diphenyldiisocyanate; TDI Toluene diisocyanate; W Workplace

the hygienist did not identify one or more sensitizing agent that the clinician had not identified.

DISCUSSION

The present study showed that the expert analysis by an occupational hygienist is reliable in identifying the causal agent in the vast majority of cases of OA. In contrast, the clinicians failed to identify some potential sensitizing agents that were detected by the occupational hygienist in a majority of the subjects who experienced a negative SIC.

Our study is the first to assess the ability of an expert assessment of occupational exposures in identifying workplace sensitizers in workers with an objective diagnosis of occupational asthma. Two previous studies had assessed the ability of the expert assessment method in detecting the presence of chemicals in the workplace from information obtained from regulatory visits to working sites (16,17). In these studies, the expert assessment method was compared with a gold standard, which consisted of air sampling measurements of substances measured during regulatory visits**.** In our study, however, no air sampling measurements were available. Furthermore, there is no air sampling measurement method for several sensitizing agents associated with OA in the workplace environment (eg, animal aerosols, plants and latex).

In the present study, the occupational hygienist did not identify the causal agent in two patients with a positive SIC. The first patient was a sawmill machine operator who had a positive SIC to an isocyanate contained in a glue he used to bond wood pieces. The occupational hygienist suspected an exposure to formaldehyde because formaldehyde-based glues were frequently used in this industry during the study period while isocyanate-based adhesives were not. The second patient who worked in a mining company suffered from OA caused by wheat flour, which was not used in this industry. However, the patient was exposed for two years to wheat dust originating from silos belonging to a factory in close proximity to the mining company. Accidental exposure to wheat was mentioned in the questionnaire, but was discarded by the occupational hygienist because no explanation was given on its origins.

The occupational hygienist identified, on average, more sensitizing agents per patient with WRA compared with the clinician. This result was expected given the differing objectives of the two assessments and the more complete set of tools used by the occupational hygienist, notably an exhaustive checklist of agents from which to code potential workplace exposures as well as an extensive knowledge of the different work processes. However, one may also argue that the physicians would have been able to detect more sensitizers because it is their focus to identify agents susceptible to cause OA.

The occupational hygienist detected sensitizing agents, which were not identified by the physician in subjects with both positive and negative SIC tests. When patients were exposed to several sensitizers, clinicians may have selected the most relevant ones without establishing an exhaustive list of all the potential sensitizers. Furthermore, when an SIC was found to be positive, it is likely that no further effort was made to identify other potential sensitizers in the majority of cases. There is a possibility that some of the workers who had negative SICs may have been misdiagnosed as not having OA. Misdiagnosis is possible in the subjects who had SIC tests performed only in the laboratory because exposures in the laboratory do not account for the presence of all potential exposures present in the workplace environment. Furthermore, negative tests can also occur when the subjects had been removed from exposure for a long period of time. Although misdiagnoses are less likely in SICs performed at the workplace than in the laboratory, they cannot be totally ruled out, as shown in a previous study in which 7% of the subjects who had a negative challenge at the workplace were subsequently diagnosed with OA (5). Sensitizing agents that were present in the workplace before the onset of sensitization can be absent during the performance of SIC at the workplace.

TABLE 3
Negative specific inhalation challenges (SICs) in which the occupational hygienist identified one or more sensitizers not identified by clinicians

Agents identified by the occupational hygienist	Agents tested during SIC	SIC
Metal fumes	Amine (ethyl ethylenediamine)	L
Isocyanates, **metal fumes, metals, hardeners, adhesives, solvents (styrene), acrylates**	Isocyanates (HDI, MDI)	L
Wood, adhesives	Dusts from workplace	L
Wood, **isocyanates**	Wood (mixture of maple, birch, cherry wood, red cedar, and oak)	L
Isocyanates, **metal fumes**	Isocyanate (MDI)	L & W
Isocyanates, **metal fumes, metals , hardeners, acrylates**	Isocyanates (HDI, IPDI)	L
Other gases and mists (glutaraldehyde)	Latex	L
Isocyanates, **metal fumes, metals, hardeners, adhesives, solvent (styrene), acrylates**	Isocyanates (HDI, IPDI)	L
Other inorganic aerosols (persulfate), **formaldehyde, amines, acrylates**	Other inorganic aerosols (persulfate), mixture of hairstyling products (dyes, lighteners, perm)	L
Acrylates, **formaldehyde, pharmaceutical (eugenol), latex**	Acrylate (methacrylate)	L
Isocyanates, **adhesives**	Isocyanate (MDI)	L
Flour, grain, **molds and yeasts (molds in truck)**	Flour (soya, wheat), grain (sesame)	L
Pharmaceuticals, **latex**	Pharmaceutical (glucosamine), aerosols derived from animals (crustacean skeleton powder)	L & W
Flour, **metal fumes**	Flour (wheat), isocyanates (HDI, IPDI)	L
Formaldehyde	None	W
Acrylates, amines, **wood, hardeners, adhesives**	Acrylates (cyanoacrylate, methyl methacrylate), amine (ethylenetriamine), resin (polyester)	L & W
Isocyanates, **metal fumes, metals and their compounds, hardeners, acrylates, latex**	Isocyanate (HDI)	L
Wood, **metal fumes**	Wood (mixture of pine, red cedar, medium-density fibreboard, teak, walnut)	L & W
Formaldehyde, **hardeners, adhesives**	Formaldehyde, isocyanate (HDI)	L
Wood, adhesives, acrylates	None	W
Isocyanates, **metal fumes, metals, hardeners**	Isocyanates (HDI, IPDI)	L
Aerosols derived from animals, **wood**	Aerosols derived from animals (pork litter)	L & W
Formaldehyde, metal fumes, amines, isocyanates	Formaldehyde	L
Metals, **amines**	Metals and their compounds (aluminum powder)	W
Metal fumes, **formaldehyde, metals, anhydrides**	Metal fumes (welding on mild steel)	L
Formaldehyde, **wood, adhesives**	Formaldehyde, isocyanate (MDI)	L
Metal fumes, metals and their compounds, **formaldehyde, anhydrides**	Metal fumes (welding on mild steel), metals and their compounds	L
Hardeners, isocyanates, metal fumes, metals	Isocyanate (HDI)	L
Flour, **aerosols derived from animals, amines**	Flour (wheat)	L & W
Flour, **formaldehyde, aerosols derived from animals**	Flour (wheat)	L
Amines, adhesives (epoxy), **hardeners, acrylates**	Amine (aliphatic polyamine), resin (epoxy)	L
Isocyanates, **metal fumes, metals, adhesives**	Isocyanates (HDI, MDI)	L
Solvent (styrene), **wood, hardeners, adhesives**	Solvent (styrene)	L

Information inside parentheses refers to the specific agent tested during the SIC; Exposures in bold refer to exposures not identified by the clinicians; Type of SIC: L Laboratory; W Workplace. HDI Hexamethylene diisocyanate; IPDI Isophorone diisocyanate; MDI Methylene diphenyl diisocyanate

In contrast, the fact that clinicians identified less sensitizers than the occupational hygienist does not necessarily mean that the test was falsely negative. The proportion of exposures rated as highly reliable was not as high in the negative cases compared with those that were positive. It is, therefore, possible that in those cases, clinicians intentionally overlooked the presence of a sensitizer because the probability of causal relationship between the agent and the occurrence of the asthma was low. Additional testing with all agents identified by the occupational hygienist would certainly be expansive, time consuming and difficult to implement in clinical practice. Furthermore, there is no evidence that this additional testing would result in a positive SIC. Another study testing the agents identified by the occupational hygienist and overlooked by the clinician would be needed to test the cost effectiveness of an expert assessment of exposure during the investigation of occupational asthma.

The present study had some limitations. Because the clinical interview preceded the administration of the occupational questionnaire, the clinical interview could have possibly prompted a better recollection of past exposure by the patient at the moment he/she was answering the questions of the occupational questionnaire. The fact that both assessors could rely on MSDSs to detect potential exposures to sensitizers may have increased the number of positive SICs in which they have identified the same causal agent. However, the main limitation of the present study is that we were not able to assess the causality of sensitizing agents identified by the occupational hygienist in negative SIC subjects because it was not possible to perform another SIC test in these patients. Although the data were collected at the same time as the investigation, the data collection, coding and analysis took much longer than the investigation. When the results of the occupational hygienist data were available, the investigation had been finished for a few months and the decision of the WCB made.

In conclusion, expert assessment of occupational exposures by an occupational hygienist is a method capable of identifying the causal agent in a patient with OA. Although this method is unlikely to be applicable in the routine investigation of occupational asthma, it may be useful in situations when no sensitizing agent can be identified by clinicians in subjects with a history highly suggestive of OA.

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