ORIGINAL ARTICLE

Occupational risk factors associated with work-exacerbated asthma in Quebec

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ABSTRACT

Background There is limited information regarding the occupational exposures of subjects with a diagnosis of work-exacerbated asthma (WEA).

Objectives To: (1) identify potential specific occupational, chemical, biological and physical agents associated with incident cases of WEA and (2) compare these agents with occupational exposures of occupational asthma (OA) and non-work-related asthma (NWRA) cases.

Methods Subjects were workers with work-related asthma (WRA) or NWRA referred between 2005 and 2008 to two Quebec clinics specialised in the field of WRA. Specific inhalation challenges were performed to differentiate OA from WEA. Work exposures were assessed using a detailed occupational questionnaire. Exposures to 41 chemical and biological agents were coded in a semiquantitative way according to a combination of indices for concentration in workplace air, frequency and confidence of exposure by an occupational hygienist expert in occupational exposure coding. This expert was blind to the medical status of WEA, OA or NWRA. Five physical agents were coded on a yes/no scale.

Results 153 subjects were enrolled (53 WEA, 67 OA and 33 NWRA). WEA cases were significantly more exposed to ammonia, engine exhaust fumes, silica, mineral fibres, aerosol propellants and solvents, and significantly less exposed to animal derived dust and enzymes than were OA cases. Exposure to physical conditions did not differ between WEA and OA.

Conclusions Exposures associated with WEA differ from those associated with OA in this study. A proportion of subjects with WEA may suffer from low-dose irritant asthma, which remains a hypothesis to be tested.

What this paper adds

- There is little information on the occupational agents encountered in the workplaces where subjects with WEA are diagnosed. Additional information is urgently needed.
- We were able to identify specific exposures associated with the diagnosis of WEA: ammonia, engine exhaust fumes, silica, mineral fibres, aerosol propellants and solvents.
- Special attention should be given to asthmatic subjects working in workplaces where those agents are found in significant concentration.

INTRODUCTION

Asthma is considered to be 'work-related' when there is a relationship between the symptoms of asthma and the workplace. Work-related asthma (WRA) encompasses (1) asthma that is induced by exposure to a specific agent at the workplace (ie, occupational asthma (OA) and irritant-induced asthma) and (2) pre-existing or coincident asthma that is exacerbated by a workplace-related stimulus (ie, work-exacerbated asthma (WEA)).[1] Differentiating OA from WEA has large implications for the workers. In Quebec, OA is recognised as an occupational lung disease and compensated as such whereas subjects with WEA do not receive any financial compensation in the majority of cases.

More than 350 different occupational agents present in a wide range of occupations have been identified as potential causes of OA.[2] In contrast, occupational agents associated with WEA have not been clearly identified. Only a few studies have characterised exposures associated with WEA, usually with broad categories for type of agent or occupation. These studies were linked to surveillance programmes,[3] were relying on self-report of work exposure in subjects enrolled in a health maintenance organisation[4] or were observational studies describing the agents identified in subjects with a diagnosis of WEA.[5] However, none of these studies included an objective diagnosis of OA or WEA made by the reference test, specific inhalation challenges (SIC), consistently in all subjects. An objective diagnosis of WEA or OA can be achieved by: (1) obtaining a thorough history of WRA, (2) confirming the diagnosis of asthma by performing a spirometry and/or methacholine challenge and (3) establishing the diagnosis WEA or OA by performing serial peak-flow monitoring or SIC.[1]

The occupational agents associated with the occurrence of WEA are likely to have irritant properties.[3 5 6] Paint fumes, solvents and hydrochloric acid have been identified in workers who were compensated for WEA in Ontario (Canada).[5] The Sentinel Event Notification System for Occupational Risks (SENSOR) asthma programme has identified mineral and organic dusts, indoor air pollutants, chemicals, cleaning agents, smoke and glues in subjects with WEA.[3] WEA has also been associated with other exposures, which are not specific to the workplace such as temperature, and physical exertion.[6–9] Second-hand smoke has also

been identified as a cause for WEA.[5 10] Most of these epidemiological studies relied on self-reports of workers to characterise their workplace exposures, which have been shown to underestimate the actual exposures.[11] To our knowledge, no study to date has assessed in a detailed manner the type of occupational agents to which workers with an objective diagnosis of WEA were exposed by using a subject by subject assessment by experts in industrial chemistry and hygiene. A subject by subject assessment by experts in industrial chemistry and hygiene has been developed for the reconstruction of past exposures in a study of occupational cancer.[12] This methodology is considered the most accurate method for assessing chemical exposures in community-based case-control studies.[13] It has never been used before in the study of WEA in such a detailed manner. The objectives of this study were to: (1) identify potential specific occupational chemical, biological and physical agents associated with incident cases of WEA and (2) compare those agents with occupational exposures of OA and non-work-related asthma (NWRA) cases.

METHODS

Study design

This is a descriptive study and hypothesis-screening study of the occupational exposures of workers with WRA (OA and WEA) and NWRA conducted between 2005 and 2008 in two Quebec tertiary centres specialised in the field of WRA. In those centres, the diagnosis of OA and WEA was made according to the reference diagnostic tests, SIC.[14]

Subjects

All workers with asthma proven by reversible airflow limitation or airway hyper-responsiveness (provocative concentration of methacholine inducing a 20% fall in FEV_1 equal or lower than 8 mg/ml) referred for WRA to two Quebec tertiary clinics between 2005 and 2008 were invited to participate in the study. A diagnosis of OA was made if the SIC was positive whereas WEA was defined as the worsening of asthma symptoms at work with a negative SIC. In Quebec, all subjects suspected of WRA who file a claim to the Workers Compensation Board Commission de la santé et de la sécurité au travail (CSST) undergo an SIC irrespective of their occupational exposures for establishing the diagnosis of OA. Workers with NWRA were recruited among the new referrals for asthma seen in the same tertiary clinics during the same time period. Those subjects were workers referred to a tertiary clinic for confirmation of asthma diagnosis or because their asthma was difficult to control but did not complain of worsening of their asthma symptoms when at work. This group of subjects was enrolled as a reference group to assess whether occupations/exposures differ between asthmatic workers with (WRA) and without (NWRA) a worsening of their asthmatic symptoms at work. The study was approved by Sacré-Coeur and Laval Hospitals' research ethics committees (no: 205-07-30). All subjects gave their written consent.

PROCEDURES

Spirometry

Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were performed according to the standards of the ATS.[15] Predicted values of FEV_1 and FVC were taken from Crapo.[16]

Skin-prick testing

Skin-prick tests with 12 common inhalant allergen extracts and a negative (diluent) and positive (histamine 10 mg/ml) control were performed by the modified prick method as described by Pepys.[17] A result was documented as positive if the wheal was ≥2 mm in diameter compared with the negative control.

Specific inhalation challenges

SIC were performed as previously described.[18] Methacholine inhalation challenge was performed as previously described[19] at the end of the day and repeated 7 h after the end of exposure to the offending agent on the day when an asthmatic reaction occurred or on the last day of exposure in the case of a negative result. A positive challenge was defined by a sustained 20% fall in FEV_1 after exposure to the offending agent. Quebec has a unique compensation system for occupational respiratory diseases requiring the performance of SIC in every worker who files a claim for possible OA irrespective of his/her occupational exposures. When the clinician does not identify any obvious agent responsible of OA or when there are too many potential causal agents, the SIC are performed at the workplace instead of the laboratory.

Occupational questionnaire

A general occupational questionnaire was used, similar to the one developed for a case-control study of occupational cancer.[20] It consists of a series of 15 broad questions relating to the employer (activities, products, processes), the occupation (job title, task description, machines, materials used) and the work environment (presence of dusts, smoke, fumes, gases, vapours; use of protective equipment, work performed by other workers). The questionnaire was administered face-to-face to each subject by staff at the clinic to describe the last job held by each subject when the diagnosis of asthma was made.

Occupational exposure assessment

Job titles were coded according to the National Occupational Classification.[21] This was done by an occupational hygienist who also carried out the coding of potential exposures. He assigned exposures from a pre-established list of 41 chemical or biological agents within five generic categories: five inorganic dusts and fibres, 10 organic aerosols, four combustion/pyrolysis fumes, seven gases and mists and 15 organic chemicals. The agents could be specific substances (eg, silica, formaldehyde) or mixtures (eg, tobacco smoke, exhausts fumes) or categories (eg, acids, adhesives). They were chosen to encompass a large spectrum of allergens known to be associated with OA and of irritants either already hypothesised for WEA or common in the workplace. Five physical agents suspected of being associated with WEA (heat, cold, humidity, dryness and physical strain) were added to the list for a total of 46 agents. The hygienist was blind to the medical status (OA, WEA or NWRA) of all the cases in the study. For chemical and biological agents judged as possibly present above background environmental levels coding was carried out with a three-level semiquantitative estimate (low=1, medium=2, high=3) for concentration in workplace air, frequency of exposure and the coder's degree of confidence that the exposure actually occurred. For the five physical agents coding was merely on a yes/no scale (exposed/non-exposed). Information sources included the questionnaire, technical and material safety data sheets of the substances handled, the industrial chemistry and occupational hygiene literature, several data bases and web sites, and occasional contacts with experts in specific fields.

Statistical analysis

Clinical characteristics of WEA, OA and NWRA subjects were summarised (table 1). The equality of means of continuous variables was tested using the ANOVA F test, whereas the equality of proportions was tested using the Pearson χ^2 statistic for dichotomous variables. The p values of these tests are presented in table 1.

As to exposure characterisation, it was not obvious how to combine and classify *a priori* the ranked categories of exposure 'concentration', 'frequency' and 'confidence'. Accordingly, various combinations and rankings of these three exposure dimensions were tried in turn in various regression models for each agent to see which exposure metric could best differentiate the three asthma groups. The whole statistical analysis was thus conducted in a hypothesis-screening perspective.

Statistical analyses were conducted using the Stata (V.9) software package.[22] For each of the three comparison groups, simple OR with corresponding exact Fisher 95% CI and two-sided p values were computed (Stata's 'epitab cc') for the simple dichotomous 'yes/no' exposure variable in turn for each agent of interest.[23] Cornfield's confidence limits were used when an estimated OR was either 0 or infinite. As well, 10 different composite indices combining frequency, concentration and confidence scores were tried in logistic regressions for each exposure agent using OA-NWRA, WEA-NWRA and WEA-OA comparisons in turn as outcome, so as to select the composite exposure index that resulted in the largest number of ORs statistically significant at the bilateral 0.05 p value (95% CI) (see online supplementary file).

The simpler dichotomous 'exposure/non-exposure' variable was nearly as efficient as any of the cumulative exposure indices to obtain significant associations with the aforementioned asthma group contrasts at the bilateral 0.05 p value or 95% CI level. For simplicity, this paper thus presents only ORs based on exposure/non-exposure to each agent that had either a significant OR as per Fisher's exact p value ≤0.05 or a significant score χ^2 test for trend[24 25] across the four composite exposure indices' ordinal categories ('none, low, medium, high' as per online supplementary file) combined with a trend test using the composite exposure index (see online supplementary file) across the four exposure indices' ordinal categories (coded numerically as '1, 2, 3, 4') also at the 0.05 p value level. The p value of the χ^2 trend test is frequently used to test for a linear trend across ranked exposure categories and may be more powerful than the dichotomy-based OR.

In addition, stepwise logistic regressions were used to control for potential confounders (age, smoking, occupational exposure to heat, cold, humidity, dryness and physical strain). Although most of these were statistically significant when comparing WEA or OA with NWRA relative to most of the 46 chemical/physical agents; only smoking was frequently significant when comparing WEA with OA. In any case, the main chemical/physical agent effect did not change statistically significantly after controlling for these potential confounders, and missing values and indefinite ORs often prevented a valid multivariate logistic regression. Therefore, only crude ORs and trends are presented in this paper.

Missing values and multi-colinearity prevented multiple logistic regression modelling to analyse many agents simultaneously. Instead, the total number of presumed 'sensitisers' and 'irritants' (some agents were counted as both) to which a person was exposed were summed separately, and these two variables were entered in a stepwise forward logistic regression procedure along with some potential confounders: age, sex, number of cigarettes smoked per day, heat (or cold), humidity (or dryness) and physical strain. The tentative classification between sensitisers and irritants was performed according to the knowledge of the occupational hygienists (DB, MG) and the clinician (CL) specialised in the field of WRA. Various cut-offs and categorisations of the sensitisers and irritants variables were tried but did not alter the statistical inferences. The stepwise regression procedure was carried on for each of three asthma groups' comparisons. The p value for entry in the stepwise model was 0.10, and the p value for removal was 0.15. As far as occupations were concerned, ORs with 95% CI and Cornfield's confidence limits were computed for each four-digit occupational title.

Table 1 Characteristics of the study subjects

	WEA	OA	NWRA	p Value
N	53	67	33	
Sex, (% males)	56.6	67.1	42.4	0.07
Age, y (mean±SD)	43.1±11.6	42.1±10.3	35.5±9.7	<0.01
Atopy, %	64.2	74.6	93.9	<0.01
Ever smokers, %	75.5	53.7	51.5	0.06
Pack-years in ever-smokers	18.1±19.3	16.3±13.5	5.7±5.5	0.03
Years with asthma	6.4±10.6	4.5±8.8	15.9±11.9	<0.01
Subjects reporting asthma prior to exposure, n (%)	11 (20.8)	16 (23.9)	NA	0.72
Years between onset of asthma symptoms and diagnosis	2.4±4.4	1.8±3.2	3.2±5.8	0.42
Years of exposure before symptom onset	8.2±9.9	6.3±8.5	NA	0.32
Years of exposure after symptom onset	2.5±3.0	3.7±4.4	NA	0.08
FEV_1% predicted	79.7±16.6	86.0±15.4	84.4±16.7	0.11
FEV_1 to FVC	73.0±9.8	75.3±9.2	75.0±9.3	0.36
PC_{20}, mg/ml (geometric mean (95% CI)	2.3 (1.5 to 3.4)	3.5 (2.2 to 5.6)	1.4 (1.0 to 2.1)	0.04

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NWRA, non-work-related asthma; OA, occupational asthma; PC_{20}, provocative concentration of methacholine inducing a 20% fall in FEV_1; WEA, work-exacerbated asthma.

RESULTS

Clinical characteristics of the subjects

In all, 153 subjects were enrolled (WEA=53, OA=67 and NWRA=33). Their demographic and clinical characteristics are described in table 1.

Main occupations and occupational agents

Overall, 89 occupations were identified among the 153 subjects. The most frequent job titles (more than three subjects per occupation) were (four-digit National Occupational Classification code, number of subjects): food and beverage processing labourers and machine operators (9461 plus 9617, 10), welders and related machine operators (7265, eight), fish plant and fish processing workers (9463 plus 9618, seven), motor vehicle body repairers (7322, seven), bakers (6252, five), woodworking machine operators (9513, four) and cabinet makers (7272, four).

Overall, 44 of the 46 agents (chemical, biological and physical) were coded at least once in the 153 subjects. The exceptions (never coded) were asbestos and sulphur dioxide. The least coded (less than 10 times) were gum and plants (one); textile dust, anaesthetics, anhydrides and tobacco smoke (two); grain (four); mineral dusts and mould (six); latex,

pharmaceutical products and aerosol propellants (six); and enzymes, alkalis and resins (eight). Table 2 presents the frequencies of agents with 10 or more occurrences, with the main occupations associated with each agent, that is, those representing 10% or more of the workers exposed to that agent. The more frequently coded agents (30 times or more) were metals and compounds and wood (30); pesticides/biocides (32); cold (43); humidity (48); cleaning products (51); physical strain (58); solvents (74); and heat (75).

Associations with specific occupations

Workers with OA tended to work more often as food and beverage processing labourers and machine operators than workers with NWRA (OR with Cornfield's confidence limit >1.61, p=0.05). Bakers and food and beverage processing machine operators (OR<0.65, p=0.07) tended to be more at risk to have a diagnosis of OA than WEA whereas plastic products assemblers, finishers and inspectors (OR>1.5, p=0.08) tended to be more at risk to have WEA than OA.

Chemical, biological and physical agents identified in workers with WEA, OA and NWRA

Several agents were found to be associated with either WEA or OA diagnoses or with both in comparisons between these cases and NWRA subjects (table 3).

When compared with OA, WEA cases were more exposed to ammonia, engine exhaust fumes, silica, mineral fibres, aerosol propellants and solvents, but less exposed to animal derived dust, and enzymes (table 4).

Tables 3 and 4 include only substances showing a tendency test with a p trend ≤0.05 or a significant OR.

Association with exposure to physical agents

When compared with NWRA, workers with WEA or OA were significantly more frequently exposed to heat and humidity and physical strain. However, the greater physical strain did not reach statistical significance for WEA cases (p=0.11; table 3).

Stepwise logistic regression analysis

After adjusting for smoking, age, gender and four physical factors in the workplace, OA cases were 2.2 times (95% CI 1.3 to 3.8) more exposed to sensitisers than were NWRA controls, whereas WEA cases were neither more nor less exposed to sensitisers than NWRA controls. In a similar regression model, WEA cases were 1.6 times (95% CI 1.1 to 2.1) more exposed to irritants than were NWRA controls, whereas OA cases were neither more nor less exposed to irritants than NWRA controls.

Using a similar regression model to compare WEA with OA cases, WEA cases were 60% more exposed to irritants (OR=1.6, 95% CI 1.2 to 2.0) than were OA cases.

Heat, dryness or physical strain did not discriminate statistically significantly among OA, WEA and NWRA cases after controlling for age, sex, smoking, number of sensitisers and number of irritants in the workplace. Smoking (number of pack years) was statistically associated with WEA cases compared with NWRA controls (p=0.04) and with OA cases versus NWRA controls (p=0.02).

Table 2 Occupational agents most frequently coded (n≥10) and corresponding occupations (≥10%)

Agents by category	Exposed workers (n)	Main occupations
Gases and mists		
NO_2	13	Welders and related machine operators; motor vehicle body repairers
Ozone	10	Welders and related machine operators; motor vehicle body repairers
Ammonia	19	Hairstylists and barbers; chemical plant machine operators
Acids	28	*
Formaldehyde	20	Welders and related-machine operators; hairstylists and barbers; woodworking machine operators
Pyrolysis, combustion fumes		
Engine exhaust fumes	23	Motor vehicle body repairers
Pyrolysis fumes	17	Motor vehicle body repairers; welders and related machine operators
Metal fumes	29	Motor vehicle body repairers; welders and related machine operators; construction millwrights and industrial mechanics
Inorganic dusts, fibres		
Silica	14	Motor vehicle body repairers
Mineral fibres	10	Motor vehicle body repairers
Metals and compounds	30	Welders and related machine operators; motor vehicle body repairers
Organic aerosols		
Animal-derived aerosol	22	Fish plant workers; fish processing labourers; veterinary and animal health technologists and technicians
Wood	30	Cabinet makers; woodworking machine operators
Flour	22	Bakers; process control and machine operators—food and beverage processing; labourers in food, beverage and tobacco processing
Organic chemicals		
Acrylates	13	Motor vehicle body repairers; hairstylists and barbers
Paints	28	Motor vehicle body repairers; welders and related machine operators; painters and coaters—industrial
Adhesives	24	Cabinet makers
Degreasing/ stripping agents	15	Motor vehicle body repairers; cooks
Cleaning agents	51	*
Hardeners	16	Motor vehicle body repairers; plastic products assemblers, finishers and inspectors; painters and coaters—industrial
Isocyanates	24	Motor vehicle body repairers
Amines	20	Hairstylists and barbers; insulators
Pesticides/biocides	32	*
Solvents	74	*
Physical agents		
Heat	75	*
Cold	43	*
Humidity	48	*
Dryness	18	Welders and related machine operators
Physical strain	58	*

*All occupations represent less than 10% of the workers exposed.

DISCUSSION

Since there is limited information on the occupational exposures associated with WEA, the main objective of this study was to identify potential specific occupational chemical and physical agents associated with incident cases of WEA. Furthermore, we wanted to compare occupational exposures of subjects with OA and WEA since the type of agents to which the workers are exposed may help to differentiate OA and WEA in clinical practice especially in centres which do not have access to SIC.

Table 3 Occupational agents associated with WEA, OA in comparison with NWRA

Agents	Odds of exposure by case title: NWRA (n=33) (n1/n0)	WEA (n=53) (n1/n0)	OA (n=67) (n1/n0)	WEA vs NWRA: OR (95% CI)	p Trend	OA vs NWRA: OR (95% CI)	p Trend
Gases and mists							
Ammonia	1/32	11/42	7/60	8.4 (1.1 to 371.7)	0.02	3.7 (0.4 to 173.4)	0.29
Combustion/pyrolysis fumes							
Pyrolysis fumes	0/33	8/45	9/58	>1.5 (1.5 to)	0.02	>1.3 (1.3 to)	0.06
Metal fumes	1/32	15/38	13/54	12.6 (1.7 to 547.9)	<0.01	7.7 (1.0 to 337.4)	0.03
Inorganic dusts and fibres							
Silica	1/32	10/43	3/64	7.4 (1.0 to 332.8)	0.15	1.5 (0.1 to 81.2)	0.85
Mineral fibres	0/33	7/46	3/64	>1.3 (1.3 to)	0.04	>0.4 (0.4 to)	0.25
Metals and compounds	3/30	12/41	15/52	2.9 (0.7 to 17.4)	0.02	2.9 (0.7 to 16.6)	0.03
Organic dusts							
Animal derived dust	2/31	6/47	14/53	2.0 (0.3 to 21.1)	0.21	4.1 (0.8 to 39.1)	0.01
Wood	2/31	10/43	18/49	3.6 (0.7 to 35.6)	0.07	5.7 (1.2 to 53.3)	0.02
Flour	0/33	6/47	16/51	>1.0 (1.0 to)	0.05	>2.6 (2.6 to)	<0.01
Organic chemicals							
Acrylates	0/33	8/45	5/62	>1.5 (1.5 to)	0.02	>0.7 (0.7 to)	0.13
Paints	0/33	16/37	12/55	>3.6 (3.6 to)	0.01	>1.8 (1.8 to)	0.01
Adhesives	0/33	14/39	10/57	>3.0 (3.0 to)	<0.01	>1.5 (1.5 to)	0.03
Degreasing and stripping agents	0/33	8/45	7/60	>1.5 (1.5 to)	0.03	>1.0 (1.0 to)	0.06
Hardeners	0/33	11/42	5/62	>2.4 (2.4 to)	0.07	>0.7 (0.7 to)	0.12
Isocyanates	0/33	10/43	14/53	>1.9 (1.9 to)	0.01	>2.2 (2.2 to)	0.01
Solvents	9/24	35/18	30/37	5.2 (1.8 to 15.2)	0.01	2.2 (0.8 to 6.1)	0.02
Physical agents							
Heat	9/24	30/23	36/31	3.5 (1.2 to 10.1)		3.1 (1.2 to 8.7)	
Humidity	3/30	21/32	24/43	6.6 (1.7 to 37.1)		5.6 (1.5 to 31.1)	
Physical strain	7/26	20/33	31/36	2.3 (0.8 to 7.2)		3.2 (1.1 to 9.9)	

n0, number of subjects not exposed; n1, number of subjects exposed; NWRA, non-work-related asthma; OA, occupational asthma; p trend across ranked exposure categories: zero, low, medium, high; WEA, work-exacerbated asthma.

The group of workers with NWRA was referred in a tertiary centre because of an inadequate control of asthma. During their assessment, the investigators did not identify the workplace as a potential cause for poor asthma control. In contrast to the comparison between WEA and OA, the NWRA control group may have suffered from a referral bias since work exposure was not a reason for a potential referral. Nevertheless, this control group allowed us to identify a number of specific exposures in workers diagnosed with WEA.

Table 4 Occupational agents associated with WEA compared with OA

Agents	Odds of exposure by case title: WEA (n=53) (n1/n0)	OA (n=67) (n1/n0)	WEA vs OA: OR (95% CI)	p Trend
Gases and mists				
Ammonia	11/42	7/60	2.2 (0.7 to 7.4)	0.05
Combustion/pyrolysis fumes				
Engine exhaust fumes	13/40	6/61	3.3 (1.1 to 11.4)	0.01
Inorganic dust, fibres				
Silica	10/43	3/64	5.0 (1.2 to 29.3)	0.03
Mineral fibres	7/46	3/64	3.2 (0.7 to 20.2)	0.02
Organic aerosols				
Animal derived dust	6/47	14/53	0.5 (0.1 to 1.5)	0.04
Enzyme	0/53	7/60	0.0 (0 to 0.6)	0.02
Organic chemicals				
Aerosol propellants	5/48	1/66	6.9 (0.7 to 330.0)	0.05
Solvents	35/18	30/37	2.4 (1.1 to 5.4)	0.03

n0, number of subjects not exposed; n1, number of subjects exposed; OA, occupational asthma; p trend across ranked exposure categories: zero, low, medium, high; WEA, work-exacerbated asthma.

The identification of occupational agents associated with the diagnosis of WEA is particularly useful in clinical practice where the OA and WEA can be difficult to differentiate. Since the likelihood of the diagnosis of OA or WEA also depends on the occupational agents to which the subjects are exposed, knowing the agents associated with WEA will facilitate the diagnosis of this condition.

This is the first study on WRA to have assessed occupational exposures to chemical, biological and physical agents based on a hygienist's expert opinion blind to the diagnoses of OA, WEA and NWRA. Furthermore, this detailed assessment of the occupational exposures was made in association with a diagnosis of OA and WEA made using objective criteria (SIC) consistently among all subjects with WRA.

Expert assessment methodology has been increasingly used in case-control epidemiological studies to characterise occupational exposures.[26] To our knowledge, this is the first time that such a methodology is used for characterising the exposures of work-related asthmatic subjects in such detail. Exposure to occupational agents can be assessed in epidemiological studies in different ways. Job-exposure matrices have been developed for assessing the exposures associated with a risk of developing

OA.[27–29] Blanc *et al* proposed to assess the job exposures by asking the workers whether or not their job exposed them to vapour, gas, dusts or fumes.[30] Some other studies used a risk set approach to assess the association between asthma exacerbation and occupational exposure. Henneberger *et al* assessed the occupational exposure of subjects experiencing severe asthma exacerbation objectively by using a job-exposure matrix.[31] This job-exposure matrix assessed the exposure semiquantitatively for only three types of work-related exposure: biological dusts, mineral dusts and gas and fumes.[32] Another study assessed the work exposure of subjects with a confirmed diagnosis of asthma and symptoms of WEA.[9] Occupational exposures were assessed by patients' self-report of broad exposure categories (dusts, chemical agents, abnormal temperature…). The expert assessment performed in this study concerned the type of occupations but not the type of occupational exposures.

One of the limitations of our study is the limited sample size. We were not able to conduct a multivariate analysis for each agent exposure while including a large number of covariates. Still, the agents found to be associated with WEA with the expert opinion method corroborate previous uncertain findings or hypotheses, suggesting that our results are statistically and clinically significant. Thus, ammonia and solvents were previously reported to be associated with WEA in records for worker compensations files.[5] Diesel exhaust fume exposure has been shown to reduce lung function in adults with asthma.[33] Inorganic dust was previously reported to be associated with WEA[3] but this is the first time to our knowledge that exposure to silica is associated with a diagnosis of WEA.

Exposures to animal dust and enzymes were confirmed as being risk factors significantly associated with the diagnosis of OA but not with WEA. The association of those well-known occupational sensitisers with the diagnosis of OA shows that our methodology for assessing occupational exposure was reasonably valid. This study found well-recognised low-molecular-weight agents such as isocyanates or metals associated with the diagnosis of OA compared with NWRA, but these agents were also found to be as frequently associated with WEA as with OA. The workers who were exposed to chemicals were exposed to multiple occupational agents. The concomitant exposure to chemical sensitisers and irritants is likely to explain that those agents were observed as frequently in OA as in WEA.

Previous studies that reported occupations associated with WEA relied mostly on self-report of occupations. Surveillance data from SENSOR identified broad occupation and industry categories (services industry, technical sales and administrative support occupations) were more frequently associated with WEA than new onset asthma.[3] However, there is a substantial risk of misclassification both in the diagnosis of asthma and WEA since asthma was not confirmed by objective measures. In a previous study, 57.5% of the subjects complaining of symptoms suggestive of WRA were not asthmatic according to objective criteria.[34] In our study, the risk of diagnosis misclassification is low considering the exhaustive clinical investigation performed. In spite of different definitions of WEA and different study populations (general population vs tertiary clinic), we also found inorganic dust and more specifically silica among agents associated with a greater risk to have WEA than OA.

A minority of our subjects with WEA (20.8%) reported having asthma prior to the exposure to those substances. Since exposure to irritants has been shown to be associated with an excess of incident cases of asthma,[35] chronic exposures to those substances may well also induce new-onset asthma. Therefore, although this is not possible to confirm by an objective test, a proportion of our subjects defined as having WEA may suffer from 'low-dose irritant asthma'.

In conclusion, occupational exposures to ammonia, engine exhaust fumes, silica, mineral fibres, aerosol propellants and solvents were found to be associated with the diagnosis of WEA. Whether a prolonged exposure to those agents can induce asthma needs to be investigated.

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Competing interests CL has received grant money from the (NIOSH) CDC, CIHR, AllerGen NCE and the Institut de recherche Robert-Sauvé en santé et sécurité au travail in the last 3 years. She has participated in industry-funded research projects with several pharmaceutical companies: AstraZeneca, GlaxoSmithKline and Cephalon. She has also participated in advisory committees for several pharmaceutical companies: AstraZeneca, Merck, GlaxoSmithKline and Novartis in the last 3 years. L-PB has the following to disclose—Advisory Boards, support for the production of educational materials and lecture fees: AstraZeneca, GlaxoSmithKline, Merck and Novartis. Sponsorship for investigator-generated research: AstraZeneca, GSK and Merck Frosst. Governmental: Adviser for the Conseil du Médicament du Québec; member of the Quebec Workmen Compensation Board Respiratory Committee Organizational; Chair of the Canadian Thoracic Society Respiratory Guidelines Committee; holder of the Laval University Chair on knowledge Transfer, Prevention and Education in Respiratory and Cardiovascular Health (in part supported by AstraZeneca); member of the asthma committee of the World Allergy Organisation; Canadian representative of the Global Alliance Against Chronic Respiratory Diseases (GARD) of WHO; member of the Working Groups the American Thoracic Society and European Respiratory Society on: (1) Severe Asthma; (2) Asthma Control and (3) Obesity and Asthma; and Chair of the organizing Committee of the 2012 World Asthma Congress (Interasma).

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