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Application of the New Asthma-Specific Job Exposure Matrix: A Study in Quebec Apprentice Cohort Exposed to Isocyanates

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Abstract

Background: Recently, the first asthma-specific Job Exposure Matrix (JEM) was updated to occupational asthma-specific JEM (OAsJEM). Our study aimed to evaluate the association between continued exposure to isocyanates and incident work-related chest symptoms in former car-painting apprentices and to compare the associations using the first and new OAsJEMs.

Methods: We used data from an inception cohort of male car-painting apprentices. Post-apprenticeship exposure to isocyanate during follow-up was evaluated using the first asthma-specific JEM ("exposed"=1 or "not exposed"=0) and the new OAsJEM (high=2, medium=1, and none=0). Association between occupation exposure to isocyanate and incidence of work-related rhinoconjunctival and chest symptoms were evaluated through cox regression models, adjusted for age, smoking, wheezing, and non-specific bronchial hyperresponsiveness.

Results: The agreement between the two JEMs (exposed vs non-exposed to isocyanate) was perfect (kappa coefficient=0.946, $p<0.001$). There were only five subjects who were classified as non-exposed based on the first JEM, but had a medium exposure to isocyanate based on the new OAsJEM. Exposure to isocyanate increased the risk of occupational chest symptoms in the high-exposure category (hazard ratio [HR] 2.7, 95% CI 1.1 – 6.6) and the medium category (HR 2.9, 95% CI 0.3 – 30.0) compared to the reference group based on the new OAsJEM, whereas an HR of 2.5 (95% CI 1.0-6.2) was observed from the first JEM. Both JEMs yielded an inconclusive association between exposure to isocyanates and the risk for work-related rhino-conjunctivitis.

Conclusion: The asthma-specific JEM and OAsJEM consistently showed that isocyanate exposure increased the risk of incident work-related chest symptoms.

Keyword: asthma, job exposure matrix, OAsJEMs, JEMs, industrial exposure, occupational asthma

Introduction

Environmental and occupational etiological agents causing asthma are widespread and it is often difficult to identify a specific cause. Identification of occupational exposures associated with asthma can help prevent the disease by removing the worker from exposure. Isocyanates, classified as low molecular weight agents, are known to cause immunological or non-immunological asthma, according to the intensity of exposure (i.e., the latter occurs in the case of acute or high exposure)¹. Isocyanates have a wide range of uses such as metal coating, paint, foamed plastics, and glue.

In general population, it is difficult to identify the industrial exposure agents and estimate the exposure level. Therefore, an asthma-specific Job Exposure Matrix (JEM) was developed by Kennedy et al, in 2000 to evaluate occupational exposures from a population-based study². The asthma-specific JEM evaluated exposures to 22 specific agents classified into high molecular weight agents, low molecular weight agents, and mixed environments and irritants. This study² shows that when JEM is combined with an expert evaluation step to verify exposure estimates in poorly

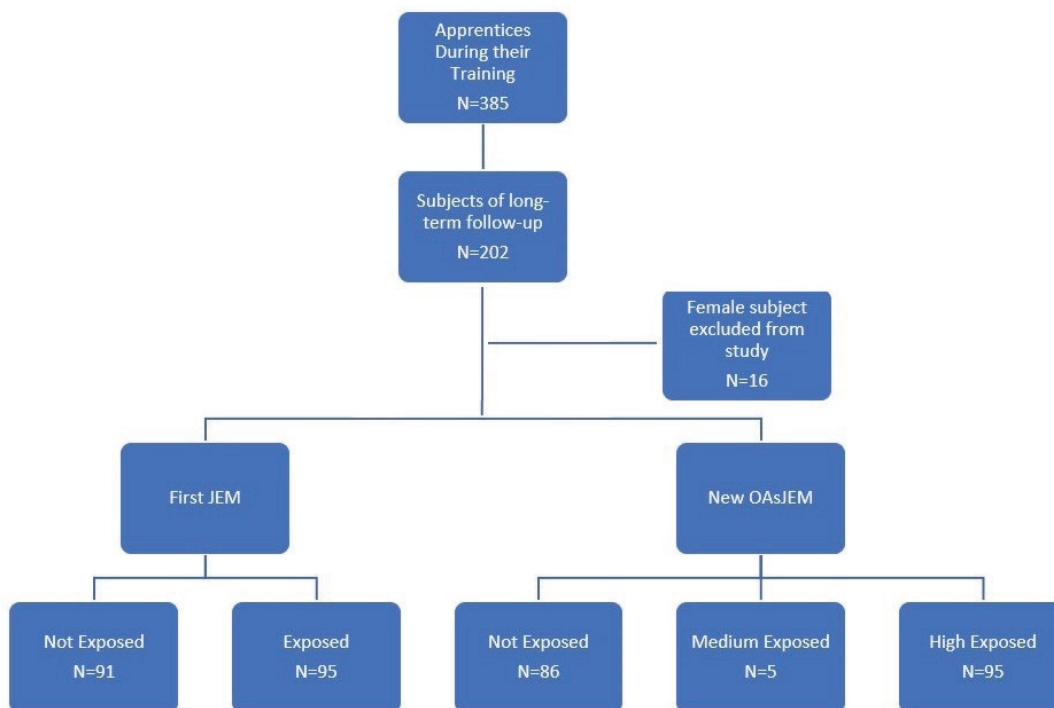
defined jobs, this could result in a higher specificity by reducing misclassification error and hence, a stronger exposure-outcome association than the use of JEM alone. Le Moual et al.³ recently updated this JEM by the Occupational Asthma Specific JEM (OAsJEM), which evaluated occupational exposures to 30 sensitizers/irritants classified into seven large groups entitled HMW sensitizers, mites, microbial exposure, LMW sensitizer, irritants, highly reactive chemicals, and biocides.

This study aimed to evaluate the association between continued exposure to isocyanates and the incident of work-related upper and lower respiratory symptoms in former car-painting apprentices and to compare the associations using the first and new JEMs.

Methods

Study Population

The data was derived from a prospective cohort study of 385 apprentices of car painting during their 18-month apprenticeship between 1999 and 2002 in Quebec. They were evaluated on entering and 4 to 9 years after the end of the training, which was conducted on 202



Supplementary Figure 1. Flowchart of participants in the study

available subjects (Supplementary Fig. 1).⁴

Measurements

Standardized Respiratory Questionnaires, work and clinical history questionnaires, spirometry, and PC₂₀ (methacholine bronchial-challenge tests that cause 20% fall in forced expiratory volume in 1 second) were performed. Our trained nurses administered the questionnaires; there was no missing value of symptoms variables. We did not impute missing objective tests when they were not administered.

Outcome definition

Incident work-related rhino-conjunctival symptoms were defined as reporting at least one eye or nasal problem at work during the long-term follow-up and did not report these symptoms during the apprenticeship. Incident work-related chest symptoms were defined as reporting cough, wheezing, shortness of breath, and/or chest tightness at work during the long-term follow-up but did not report any of these symptoms during the apprenticeship. Due to a lack of sufficient number of cases, work-related sensitization and bronchial hyperresponsiveness were not evaluated.

Assessment of isocyanate exposure

The occupational hygienists coded each job using the International Standard Classification of Occupations (ISCO-88) system (for example, the 7142 code was assigned to varnishers and related painters)⁵. Subsequently, ISCO codes were linked to each JEM. The first asthma-specific JEM was classified with two exposure levels: “exposed” =1 or “not exposed” =0. Jobs with a strong likelihood of exposure to isocyanates were assigned as “exposed.” The new OAsJEM was classified with three exposure levels: high exposed=2, medium exposed=1, and not exposed=0. High exposure was defined as having a high probability of exposure and moderate-to-high intensity, medium exposure was defined as having a low-to-moderate probability or low intensity. For both JEMs, the expert verification step is recommended.^{2,3} Nonetheless, this step was not done because the objective was to compare the agreement between the two JEMs. Some jobs that were flagged as “need verification by an expert” by default were classified as “unexposed.”

Data Analysis

Outcomes were the incident cases of work-related rhino-conjunctival and chest symptoms post-apprenticeship. The agreement between the exposure categories (exposed vs. non-exposed) based on the first and the new OAsJEM was assessed with kappa statistics (i.e., the medium and high exposures based on the new OAsJEM were combined). Cox regression was used to evaluate the risk of developing the outcomes in association with continued exposure to isocyanates. The analysis was adjusted to age, smoking, wheezing, and non-specific bronchial hyper-responsiveness (NSBHR) at the end of the apprenticeship. NSBHR was defined as a sustained fall in forced expiratory volume in one second >20% from baseline value after exposure to ≤ 16 mg/ml methacholine. The reference group was defined as being unexposed based on the JEMs. The majority (>90%, n=186) of the subjects were males and therefore our analysis was done on male subjects. All data analyses were performed using IBM SPSS for Windows version 27.0 (SPSS, Inc., Chicago, IL).

Results

Of 186 subjects, 21% reported wheezing, 3.8% reported chest tightness, 14% shortness of breath, 5.4% coughing, 17.2% phlegm, and 7.5% asthma. In this cohort, 43% had a smoking history and 53% were overweight or obese (BMI ≥ 25 kg/m²). The proportion of subjects who had PC₂₀ ≤ 32 mg/mL at the end of the apprenticeship was 21.5% (Supplementary Table 1). The description of demographic and clinical characteristics of the subjects were published somewhere.⁴

Overall, there were 86 subjects classified as non-exposed while 95 as exposed to isocyanates based on both JEMs. Only five subjects were classified as non-exposed based on the first JEM but had a medium exposure to isocyanate based on the new OAsJEM (Supplementary Table 2). The agreement between exposed and non-exposed categories based on the two JEMs was perfect (kappa coefficient=0.946, p<0.001).

Using the new OAsJEM, exposure to isocyanate increased the risk of occupational chest symptoms in the high-exposure category (hazard ratio [HR] 2.7, 95% CI 1.1 – 6.6) and the medium category (HR 2.9, 95%

Supplementary Table 1. Characteristics of male subjects at the follow up

| Characteristics at the end of the apprenticeship | Missing value | Distribution |
|---|---------------|-------------------|
| Age (median, interquartile range in years) | 21 | 26.9 (24.8, 29.6) |
| Current smoker (%) | | 80 (43.0) |
| BMI \geq 25 kg/m ² (overweight or obese) (%) | 3 | 97 (53.0) |
| Reported wheezing (%) | | 39 (21.0) |
| Reported chest tightness (%) | | 7 (3.8) |
| Reported shortness of breath (%) | | 26 (14.0) |
| Reported coughing (%) | | 10 (5.4) |
| Reported phlegm (%) | | 32 (17.2) |
| Reported asthma (%) | | 14 (7.5) |
| Predicted FEV ₁ (mean (SD) in %) | 3 | 100.4 (13.4) |
| Predicted FEV ₁ <80% (%) | 3 | 11 (5.9) |
| PC ₂₀ \leq 16 mg/mL (%) | 11 | 31 (16.7) |
| PC ₂₀ \leq 32 mg/mL (%) | 11 | 40 (21.5) |

BMI: body mass index; FEV₁: forced expiratory volume in one second; PC₂₀: methacholine concentration that cause a 20% fall in FEV₁ in bronchial challenge test; SD: standard deviation.

Supplementary Table 2. Agreement on isocyanates exposure between the first and new OAsJEM

| First JEM | New OAsJEM | | | Total |
|-------------|-------------|-----------------|---------------|-------|
| | Not exposed | Medium exposure | High exposure | |
| Not exposed | 86 | 5 | 0 | 91 |
| Exposed | 0 | 0 | 95 | 95 |
| Total | 86 | 5 | 95 | 186 |

CI 0.3 – 30.0) compared to the reference group. From the first JEM, we obtained an overall HR of 2.5 (95% CI 1.0-6.2). No association was observed between exposure to isocyanates and the risk for work-related rhino-conjunctivitis, according to both JEMs (Table 1).

Discussion

Our study indicated that similar estimates were generated when using the asthma-specific JEM and the OAsJEM regarding the association between isocyanate exposure and the incident of work-related respiratory outcomes.

Lama et al⁴ reported good agreements between self-reporting, investigator scoring, and the first JEM in

identifying isocyanates exposure. A study investigating the association between exposures and asthma in healthcare workers found that the agreement between self-reporting and job-task-exposure-matrix especially in cleaning products, adhesives/solvents, and gases/vapors exposures were close to each other⁶. However, it was also emphasized that reporting bias due to self-report was undeniable.

Due to the complex associations between asthma occurrence and the excess of occupational exposures, it is necessary to establish and develop more reliable methods than self-reporting with multidisciplinary approaches to prevent differential misclassification of agents responsible for the disease. While the first JEM created for this purpose resulted in dichotomization of exposed vs. non-exposed,² the new OAsJEM

Table 1. Associations between incidence of occupational respiratory outcomes and continued exposure to isocyanates

| Clinical outcome | i/n | Incident work-related rhino-conjunctivitis symptoms | | P-value | i/n | Incident work-related chest symptoms | | P-value |
|----------------------------------|-------|---|----------|---------|-------|--------------------------------------|----------|---------|
| | | HR* | 95% CI | | | HR** | 95% CI | |
| Asthma-specific JEM ⁴ | | | | | | | | |
| Exposed | 11/76 | 1.1 | 0.4-2.7 | 0.875 | 19/82 | 2.5 | 1.0-6.2 | 0.043 |
| Not exposed | 13/74 | | | | 9/77 | | | |
| OAsJEM JEM ⁵ | | | | | | | | |
| High exposure category | 11/76 | 1.1 | 0.4-2.8 | 0.860 | 19/82 | 2.7 | 1.1-6.6 | 0.038 |
| Medium exposure category | 1/5 | 1.2 | 0.2-10.0 | 0.842 | 1/5 | 2.9 | 0.3-30.1 | 0.364 |
| Not exposed | 12/69 | | | | 8/72 | | | |

*Adjusted for age, smoking, wheezing, and NSBHR at the end of apprenticeship

** Adjusted for age, smoking, and NSBHR at the end of apprenticeship

may reduce the possibility of misclassification as it included non-exposed, medium exposed, and highly exposed categories.³ To our best knowledge, there is no study comparing the first and the new OAsJEM for isocyanate exposure. In our study, isocyanate exposure was evaluated using both JEMs and they showed a very good agreement (k=0.92).

Similar to previous study of continued exposure of occupational allergens, we found that continued exposure to isocyanate could cause wheezing and a decrease in PC₂₀.⁷ We did not observe a gradual increase in the risk of occupational chest symptoms between the medium and high exposure category, but the number of subjects in the medium category was very small. Moreover, since all subjects come from cohorts of apprentices, they tend to have jobs with the same post-apprenticeship exposure. This may explain the perfect agreements between JEMs (Table 2).

Both JEMs do not evaluate specific tasks of each job nor the specific content materials of isocyanates as well as metal and welding fumes. A study by Dumas et al⁸.

reported the application of a job-task-exposure-matrix (JTEM) for evaluating major disinfectant exposure among healthcare workers. It indicated that evaluating specific contents and job tasks could substantially reduce the misclassifications and determine more reliable exposure-outcome associations. Another limitation of our study is its small sample size of a homogeneous group of workers, therefore exposure assessment could not be evaluated according to the workplace-specific tasks.

Conclusion

Very good agreement for evaluating exposure to isocyanates was observed between the asthma-specific JEM and OAsJEM. Similar estimates were generated when using the first and the new OAsJEM regarding the association between isocyanate exposure and the incidence of respiratory outcomes. Further analysis is required with different exposure types and larger studies.

Key Messages

What is already known about this subject?

- It is difficult to establish an exposure-outcome association between industrial exposure agents and occupational asthma due to a huge variety of exposure agents and the complex pathogenesis of asthma.
- Job exposure matrices (JEM)s have been created to help to easily identify occupation exposure especially in a large population-based cohort and to prevent differential misclassification error.
- No previous study compared isocyanates exposure assessment using the first asthma-specific JEM and the new OAsJEMs.

What are the new findings?

- A very good agreement between the two JEMs was observed for isocyanate exposure assessment.
- Isocyanate exposure increased the risk of incident work-related chest symptoms. Consistent findings were obtained when using both JEMs.
- No association was observed for work-related rhinoconjunctivitis whatever the JEM used.

How might this impact policy or clinical practice in the foreseeable future?

Comparison of the asthma-specific JEM and new OAsJEM for different exposure agents should be conducted with larger populations.

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initiated the current study. B.A. and L.S. took part in the acquisition and management of data. S.P. and L.S. performed the analysis under the supervision of E.S. and N.L.M. B.A., E.S., H.N.K, and S.P. prepared the manuscript; D.G. and N.L.M. critically reviewed the manuscript.

Ethical, Considerations & Disclosure (s) (e.g., IRB information, consent process, if applicable): The study was carried out and approved by the ethics committee at Hôpital du Sacré-Cœur de Montréal (CER 2010-171).

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