

### Chronic occupational exposures to irritants and asthma in the CONSTANCES cohort

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| 1                | CHRONIC OCCUPATIONAL EXPOSURES TO IRRITANTS AND   |  |  |  |  |  |  |  |
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| 2                | ASTHMA IN THE CONSTANCES COHORT   |  |  |  |  |  |  |  |
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- 27 Key words: Current asthma, Asthma Symptom score, Occupational exposure, Solvents,
- 28 Cleaning products and disinfectants, Job-exposure matrix, Population-based cohort

#### 29 Abstract

30 **Objectives.** The impact of chronic occupational exposures to irritants on asthma remains 31 discussed. We studied the associations between occupational exposures and asthma, with 32 specific interest for chronic exposure to irritants, including disinfectants/cleaning products 33 (DCPs) and solvents.

34 Methods. Cross-sectional analyses included 115,540 adults (55% women, mean age 43 years, 35 10% current asthma) working at inclusion in the French population-based CONSTANCES 36 cohort (2012-2020). Current asthma was defined by ever asthma with symptoms, medication 37 or asthma attacks (past 12 months), and the asthma symptom score by the sum of 5 respiratory 38 symptoms (past 12 months). Both lifetime and current occupational exposures were assessed 39 by the Occupational Asthma-specific Job-Exposure Matrix (OAsJEM). Associations were 40 evaluated by gender using logistic and binomial negative regressions adjusted for age, smoking 41 status and body mass index.

42 Results. In women, associations were observed between current asthma and lifetime exposure 43 to irritants (odds ratio: 1.05, 95%CI 1.00-1.11), DCPs (1.06, 1.00-1.12) and solvents (1.06, 44 0.98-1.14). In men, only lifetime exposure to DCPs (1.10, 1.01-1.20) was associated with 45 current asthma. Lifetime exposure to irritants was associated with higher asthma symptom score 46 both in women (mean score ratio: 1.08, 95% CI 1.05-1.11) and men (1.11, 1.07-1.15), especially 47 for DCPs (women: 1.09, 1.06-1.13, men: 1.21, 1.15-1.27) and solvents (women: 1.14, 1.10-1.19, men: 1.10, 1.05-1.15). For current exposures, no consistent associations were observed 48 49 with current asthma and asthma symptom score.

50 **Conclusions**. Lifetime occupational exposures to irritants were associated with current asthma 51 and higher asthma symptom score. These exposures should be carefully considered in asthma

52 management.

### 53 KEY MESSAGES

### 54 -What is already known on this topic?

55 Chronic occupational exposure to irritants is common, but its impact on asthma remains 56 discussed and few epidemiologic studies considered this specific issue.

### 57 -What this study adds?

- 58 This study in 115,540 French adults brings new knowledge supporting a deleterious impact of
- 59 chronic occupational exposures to irritants on current asthma and asthma symptoms.

### 60 -How this study might affect research, practice or policy?

- 61 Reduction of occupational exposure to irritants, including disinfectants/cleaning products and
- 62 solvents, should be included in asthma prevention strategies, and considered by clinicians in
- 63 asthma management.

### 64 INTRODUCTION

65 Workplace exposures are an important contributor to the burden of adult asthma [1,2]. 66 About 15% of adult asthma cases are caused by occupational exposures [3], and 20% of adults with asthma have exacerbations at work [3,4]. Occupational asthma can be caused by sensitizers 67 68 (e.g., flours, latex, diisocyanates) and irritants [1,5]. Sensitizer-induced asthma, which involves 69 an immunologic mechanism, is a well-known type of occupational asthma [6], and has largely 70 been described in case series or surveillance programs [7]. A second type of occupational 71 asthma corresponds to asthma caused by non-immunological irritant mechanisms, which have 72 not been precisely identified yet. Irritant-induced asthma can appear after a single acute 73 exposure to very high levels of irritants (reactive airway dysfunction syndrome (RADS), or 74 Brooks' syndrome), but may also occur following a delayed onset after chronic exposures to 75 irritants, even in absence of high peak exposures [8–10]. The role of chronic exposures, whether 76 in the past or currently, to irritants has been less documented [9,10] and is probably 77 underestimated and involved in a substantial number of occupational asthma cases [11]. 78 Because causality for chronic exposure irritant-induced asthma cannot be established with certainty at individual level (given the lack of appropriate clinical tests), epidemiological 79 80 studies are particularly important to evaluate causality at population level [8,9].

81 Only a limited number of studies have considered the impact on asthma of chronic 82 occupational exposures to irritants as a broad category [8,12], and they showed heterogeneous 83 results. Among studies using the asthma-specific job exposure-matrix (AsJEM) [12], one study observed a positive association for physician diagnosed asthma [13], whereas three studies did 84 85 not show any associations [14-16]. However, these studies [14-16] used a former version of 86 the matrix [12], which poorly evaluated chronic exposures to irritants. The AsJEM has been 87 updated in 2018 and renamed as Occupational Asthma-specific JEM (OAsJEM) with a focus 88 on improving assessment of irritant exposures [17]. Since then, the OAsJEM has been used in 89 several epidemiological studies (https://oasjem.vjf.inserm.fr/paper-list/). Two of them studied 90 associations of chronic occupational exposures to irritants with asthma [18,19], and both found 91 positive associations.

92 Irritant agents are frequent at work and include a wide variety of agents. Studies
93 investigating specific agents have mostly focused on Disinfectants and Cleaning Products
94 (DCPs), which contain irritant substances, and are now recognized as a cause of asthma [20–
95 23]. Among irritants, solvents are also commonly used in workplaces, but associations with

asthma have been less documented [18,24–26]. In France, about 17% of workers are exposed
to organic solvents [27,28], which have been identified as causal agents of work-related asthma
in the latest report from the National Network for Occupational Disease Vigilance and
Prevention (RNV3P). Further epidemiological studies are still needed to evaluate the impact of
chronic exposures to irritants, especially solvents, in asthma.

101 Therefore, we aimed to examine the association between chronic occupational 102 exposures to irritants, including DCPs and solvents, evaluated by the OAsJEM [17], and 103 asthma, evaluated through dichotomous and semi-quantitative standardized methods, in 104 CONSTANCES, a large French population-based cohort.

### 105 MATERIALS AND METHODS

### 106 Study population

107 CONSTANCES is a French general population-based cohort [29]. Between 2012 and 108 2020, 220,000 participants aged 18-69 years were recruited in 21 Health Prevention Center 109 ('Centres d'examens de santé') across France. CONSTANCES included people affiliated to the 110 main national health insurance (about 85% of the French population) [29]. At enrolment, self-111 administered questionnaires were sent to participants to collect data including lifestyle, health, 112 as well as a full job history where occupations were first coded according to the French 113 classifications of occupations ('Profession et Catégories Socio-professionnelles', PCS 2003, 114 https://www.insee.fr/fr/information/2400059) and of activities ('Nomenclature d'Activités 115 Française', NAF, https://www.insee.fr/fr/information/2406147). Our analyses are based on 116 inclusion data available in early 2022, totalizing 205,203 participants enrolled since 2012.

### 117 Asthma

118 Asthma was evaluated through dichotomous and semi-quantitative approaches by standardized questionnaire at recruitment. We used standardized definitions of asthma similar 119 120 to those previously used in European Community Respiratory Health Survey (ECRHS) and in 121 the Epidemiological study on the Genetics and Environments of Asthma (EGEA) [30,31]. Ever 122 asthma was defined by a positive answer to the question "have you ever had asthma?". Current 123 asthma was defined among participants with ever asthma by the report in the past 12 months of 124 asthma attacks or symptoms (wheezing, woken up with chest tightness, attack of shortness of 125 breath at rest, attack of shortness of breath after exercise, and woken up by attack of shortness of breath), or use of an asthma treatment. We also considered age at asthma onset and 126 127 distinguished adult-onset asthma (>16 years) and childhood-onset asthma ( $\leq 16$  years). As

previously described and validated [32], the asthma symptom score, a semi-quantitative score ranging from 0 to 5, was defined as the sum of 5 asthma symptoms reported in the past 12 months: breathless while wheezing, woken up with chest tightness, attack of shortness of breath at rest, attack of shortness of breath after exercise, and woken up by attack of shortness of breath.

#### 133 Occupational exposures

134 After the transcoding of job history of all participants from PCS 2003 occupation codes 135 International Standard Classification of Occupation (ISCO)-88 into codes 136 (https://www.ilo.org/public/english/bureau/stat/isco/isco88/major.htm), the OAsJEM [17] was 137 applied to job histories to estimate exposure to 30 agents assigned to 3 groups [17]: High 138 Molecular Weight (HMW) sensitizers, Low Molecular Weight (LMW) sensitizers and irritants 139 (Table S1). The latter included a total of 19 specific agents, including organic solvents, bleach 140 and cleaning products. Each exposure was evaluated in 3 levels: high (high probability of 141 exposure and moderate to high intensity), medium (high probability and low intensity' or low 142 probability and moderate to high intensity), no (unlikely to be exposed; low probability and low 143 intensity). We studied 5 groups of exposures: the 3 main exposures of interest: irritants (large 144 group), DCPs (indoor cleaning products, bleach and high-level chemical disinfectants) and 145 organic solvents; and HMW sensitizers and LMW sensitizers (large groups) which are known 146 asthmagens and were expected to be associated with asthma outcomes. We examined each 147 exposure in 2 categories (exposed vs a reference group non-exposed to any exposure in the 148 JEM) and 3 categories (medium exposure, high exposure, vs non-exposed reference group). 149 Two main temporalities were considered: lifetime and current exposures, corresponding to the 150 maximum exposure level during the entire work history, and during the last 2 years, 151 respectively. Among the 19 irritant agents, nine agents were also classified as low molecular 152 weight (LMW) sensitizers in the OAsJEM, because both mechanisms have been suggested 153 (Table S1). When considering irritant exposures, sensitivity analyses excluding these nine 154 agents were also performed.

### 155 Statistical analysis

156 Cross-sectional associations between occupational exposure estimated by the OAsJEM 157 and asthma and the asthma symptom score, were evaluated by logistic regressions (Odds ratio 158 (OR)) and negative binomial regressions (Mean Scores ratios (MSR)) respectively. All analyses 159 were adjusted for age, body mass index (BMI), and smoking status. As job tasks and asthma 160 phenotypes may vary according to gender, all associations were assessed separately in women

and men, and interaction tests were performed by fitting the interaction term in the models, aspreviously done in CONSTANCES [26].

163 **RESULTS** 

### 164 *Population characteristics*

165 We excluded participants without job history (n=34,098), not working at inclusion 166 (n=47,085), without any respiratory data (n=1,415), or without information on ISCO-88 job 167 codes (n= 1,038), BMI or smoking status (n=6,027) (Figure S1), yielding a population of 168 115,540 participants. We performed analyses on asthma symptom score for 111,892 169 participants and on current asthma for 107,299 subjects. Excluded participants differed from 170 included participants in terms of age, sex, BMI, education or smoking habits but no differences 171 were seen regarding asthma outcomes (Table S2). The mean age was approximately 43 years 172 and 55% of the participants were women. The characteristics of the participants by gender are 173 presented in Table 1. Two-thirds of the participants had more than a high school degree, about 174 20% were current smokers and 40% were overweight or obese. More than 30% of the 175 participants had at least one asthma symptom during the last 12 months, 14% had ever asthma 176 and 10% had current asthma. According to OAsJEM estimates, 40% of the participants had 177 lifetime exposure to irritants, including 25% to DCPs and 23% to organic solvents. Women 178 were more exposed to DCPs and sensitizers than men. Men had higher proportions of 179 occupational exposures to irritants in general and organic solvents.

### 180 Occupational exposures and current asthma

181 Among men, lifetime exposure to irritants was not associated with current asthma (Table 182 2). We only observed a single and slight positive association between lifetime occupational 183 exposure to DCPs and current asthma (OR 1.10, 95% CI 1.01-1.20). Among women, we 184 observed weak but positive associations between lifetime exposure to irritants (OR 1.05, 95%) 185 CI 1.00-1.11) and current asthma, especially for DCPs (OR 1.06, 95% CI 1.00-1.12). When 186 taking account of levels of exposures (Figure 1), slightly higher associations were found for 187 high exposures to irritants (OR 1.13, 95% CI 1.05-1.22) and DCPs (OR 1.17, 95% CI 1.08-188 1.26) and current asthma in women. When removing potential LMW sensitizers exposures from 189 the irritant exposure category, we found similar significant results (Table S3). In contrast, for 190 organic solvents, no dose-response association was observed according to exposure level. 191 Interaction tests between gender and exposures were also performed. Significant interactions 192 were observed for irritants and organic solvents (Table 2).

We also made analyses considering the age at asthma onset (childhood-onset ( $\leq$ 16 years), adult-onset (>16 years)). The association of DCPs with current asthma was slightly more pronounced for childhood-onset asthma in men (Tables S4), whereas associations of irritants and DCPs with current asthma were significant only for adult-onset asthma in women (Table S5). No other significant associations were observed.

For known sensitizers, we found weak but positive associations between lifetime exposures to HMW sensitizers and current asthma in both men and women, whereas no association were observed for LMW sensitizers (Table 3).

Last, regarding associations between current occupational exposures to irritants and current asthma, results were less consistent (Table S6). We did not find positive associations and even observed some inverse associations in men and women. We also observed inverse associations between current exposures to sensitizers and current asthma in men and women.

### 205 Occupational exposures and asthma symptom score

In men, we observed significant and positive associations between all irritant exposures and higher mean asthma symptom scores (Table 2). In addition, associations were higher for high-level exposures (MSR ranging from 1.18 to 1.28) than for medium-level exposures (MSR ranging from 1.07 to 1.17) (Figure 2).

210 Regarding the asthma symptom score in women, we observed significant positive 211 associations for lifetime occupational exposures (in 2 classes) to irritants, DCPs and organic 212 solvents with MSR ranging from 1.08 to 1.14 (Table 2). When discriminating medium and high 213 levels of exposures to irritants and DCPs, MSR were higher for the latter (Figure 2). Regarding, 214 interaction tests between gender and exposures, we observed significant interactions for 215 exposures to DCPs and not for irritants and organic solvents (Table 2), contrary to results 216 obtained for current asthma. Medium levels of irritants and DCPs were associated with 217 significantly higher mean score ratios in men than in women, whereas no interaction by gender 218 was observed for high-level exposures (Figure 2). When excluding potential LMW sensitizers 219 exposures from the irritant category, we found similar results (Table S3).

For known sensitizers we also observed positive associations between lifetime exposure to both HMW and LMW sensitizers and a higher asthma symptom score in women and men (Table 3).

Last, regarding associations between current occupational exposures to irritants and asthma symptom score, we found positive associations in men and women but weaker than associations obtained with lifetime exposures (Table S6). We also found inverse associations between current exposures to sensitizers and asthma symptom score in women.

### 227 **DISCUSSION**

In a large French population-based study, we found that lifetime occupational exposures to irritants was associated with a higher asthma symptom score in women and men. Lifetime occupational exposures to irritants was also associated with slightly increased risk of current asthma in women; in men, positive associations with current asthma were only suggested for DCPs. Overall, our results bring new support for an association between chronic occupational exposures to irritants and asthma.

234 Results from previous epidemiological works on this question using JEMs were 235 inconsistent. Two studies used the OAsJEM, and found associations between chronic exposure 236 to irritants and a specific asthma endotype characterized by neutrophilic inflammation and 237 oxidative stress [19] and current adult-onset asthma [18]. Among studies using the former 238 asthma-specific JEM, which evaluated less accurately irritant exposures, most did not detect 239 associations between occupational exposures to low/moderate levels of irritants and asthma 240 [14], its severity [15] or its development [16], although one reported a positive association with 241 current asthma [13].

242 In the past 10 years, evidence has increased for a deleterious role of DCPs in asthma. 243 Our results are consistent with previous occupational epidemiological studies among healthcare 244 workers and cleaners which found associations between exposures to DCPs, estimated mostly 245 with questionnaires, and asthma [23,33] and a meta-analysis concluding that occupational 246 exposures to cleaning products are associated with a higher risk of asthma [22]. These results 247 are also homogeneous with the scarce studies in population-based cohorts using the updated 248 OAsJEM which suggested associations of chronic occupational exposure to DCPs with asthma 249 and its control [18,19] or older works with the AsJEM [34] or the N-JEM [21], adapted from 250 the AsJEM for Northern countries.

Regarding solvents, we observed significant associations between lifetime exposures and a higher asthma symptom score in both men and women. Fewer significant associations were found for current asthma than for the asthma symptom score. Our results are consistent

with a previous work in CONSTANCES using self-reported exposure to solvents, and a population-based solvent-specific JEM [26], a case-control study in Norway and a cohort study in Singapore which observed associations between occupational exposures to solvents and asthma [24,25].

258 In our analyses, we used two standardized definitions of asthma: current asthma and the 259 asthma symptom score. Compared to a dichotomous definition of asthma, the semi-quantitative 260 score, which defines asthma as a continuum, increases power to identify risk factors for asthma 261 [32]. In particular, this score does not include the term "asthma", with the aim to further 262 decrease possible diagnostic bias due to challenges in asthma diagnosis [32,35], and leading to 263 both under- and over-diagnosis of the disease [36]. When studying occupational exposures, this 264 score is particularly relevant because occupational asthma is under-recognized in clinical 265 practice. Using the asthma symptom score may help revealing associations by including 266 subjects not identified as asthmatics [1,32]. In our results, associations between exposures and 267 respiratory outcomes differed between asthma symptom score and current asthma. Although 268 mean score ratios and odds ratio are not directly comparable, we observed more significant 269 associations between occupational exposures and the asthma symptom score than with current 270 asthma. This disparity supports our hypothesis that occupational asthma is under-recognized 271 [37]. Occupational exposures to irritants may also be associated with a specific asthma 272 phenotype, which is less documented and may not commonly be recognized as asthma. This 273 was previously suggested in a study of healthcare workers, in which exposure to disinfection 274 products was associated with a profile "undiagnosed/untreated asthma" (identified by 275 hierarchical clustering), characterized by numerous asthma symptoms, but low proportion of 276 physician diagnosed asthma, and moderate use of asthma medications [38].

277 In our study, we applied the recently updated asthma-specific JEM (OAsJEM) [17] to 278 assess occupational exposures. In occupational epidemiological studies, using a JEM, rather 279 than a questionnaire to assess exposure, is considered to reduce the risk of differential 280 misclassification between participants with or without the disease of interest. However, using 281 a JEM could also induce non-differential misclassification, partly due to disparities in tasks and 282 work conditions between subjects within a same job, which may be taken into account only by 283 applying a job-task-exposure matrix [39]. Transcoding operations which converted PCS 2003 284 French job codes into ISCO-88 international job codes could also introduce misclassification. 285 In a previous work in the French NutriNet-Santé cohort, where jobs were directly coded into 286 ISCO-88 classification (no transcoding), positive and higher associations were observed

287 between occupational exposures to irritants estimated with the OAsJEM and current adult-onset 288 asthma [18]. Associations between occupational exposures and asthma also differed according 289 to gender. We found more positive associations between lifetime occupational exposures to 290 irritants and current asthma in women than in men, but associations between irritant exposures 291 and asthma symptom score were generally stronger in men than in women, with significant 292 interactions in some cases. These differences could be explained by disparities in jobs and also 293 tasks between women and men within the same job [40]. Distinct sex-related 294 pathophysiological mechanisms might also contribute to these discrepancies between men and 295 women [41,42].

296 We observed more positive and stronger associations with asthma when studying 297 lifetime exposures than for current exposures. Furthermore, in contrast to lifetime exposures, 298 we observed some inverse associations between current exposures and both current asthma and 299 symptom score. This difference in findings for current and lifetime exposure was observed not 300 only for exposure to irritants, but also for well-known sensitizers (HMW and LMW agents), 301 especially in women. This phenomenon could partly be explained by a healthy worker effect, 302 which implies that working people are in better health than non-working people and asthmatics 303 with more symptoms could avoid more often tasks and jobs exposing them to irritants. This 304 selection bias can act at two levels: at recruitment (hire effect) and during employment (survivor 305 effect) [43]. In our study, the weaker associations observed with current exposures compared 306 to lifetime exposures could be explained by the fact that the subjects with asthma or asthma 307 symptoms have left past occupations with exposures that could worsen their health status. It 308 has been suggested that selection bias during employment is more important for women than 309 for men [43]. Beyond inverse associations observed when investigating current exposure, a 310 healthy worker effect (including hire effect) may have generally led to an underestimation of 311 associations in our study, and partly explain the modest associations observed. Interestingly, 312 associations observed for irritants exposure were of similar magnitude or higher than those 313 observed for HMW and LMW sensitizers, which are well-known causes of occupational 314 asthma.

This work is one of the first to assess associations between occupational exposures to irritants, using the updated OAsJEM, and asthma and asthma symptom score in a large general population cohort. One of the main strengths is the large size of the cohort, which favours the detection of even modest associations. One original feature of the analyses is to evaluate asthma according to several standardized definitions in a cohort from the general population and not in

320 a specific occupational sample (e.g., healthcare workers and cleaners). However, our study was 321 limited by its cross-sectional design, which prevents determining accurately whether exposure 322 occurred before or after asthma onset. In women, associations between irritant exposures and 323 current asthma were restricted to current adult-onset asthma, but in men DCPs exposures were 324 associated with current childhood-onset asthma. A lower statistical power with 2 times less 325 current adult-asthma in men than in women could partly explain the absence of significant 326 associations with adult-onset asthma in men. These findings probably also reflect an impact of 327 occupational exposures on both new onset asthma and the activity or aggravation of a pre-328 existing (including childhood-onset) disease, which both have important consequences at 329 individual and society level [1]. Despite the use of a JEM to limit recall bias with respect to 330 exposure assessment, recall bias with respect to occupational history may still have occurred. 331 However, collection of occupational histories has been shown to be a reliable and valid method 332 [44]. Finally, our conclusions are limited by the relatively low observed associations with 333 ORs/MSR of 1.10 to 1.30 which should be interpreted with caution. More longitudinal data and 334 improved assessment of exposure to specific agents are needed to clarify the role of irritants in 335 asthma.

### 336 CONCLUSION

The results of this cross-sectional analysis in a large population-based cohort support the hypothesis of a deleterious role of chronic exposure to irritants, particularly DCPs and solvents, with regard to current asthma and asthma symptom score. These data suggest that irritant exposures, which are very common at the workplace, should be reduced to protect workers' respiratory health through industry-specific exposure reduction strategies. Clinicians should consider occupational exposures to irritants as a potential risk factor and recommend to avoid such exposures in patients with asthma or asthma-like symptoms.

344

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- 371

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#### Table 1 : Description of study population 489

|   | Men         | Women       |
|---|-------------|-------------|
|   | n = 51,865  | n = 63,675  |
| Age, Mean, (sd)   | 43.3 (10.7) | 43.0 (10.7) |
| BMI   |             |             |
| <25   | 53.2        | 67.1        |
| 25-29.9   | 36.4        | 22.2        |
| ≥30   | 10.4        | 10.7        |
| Education   |             |             |
| < High school   | 20.7        | 15.0        |
| High school   | 14.7        | 15.1        |
| 2-3 years post-secondary                                | 27.9        | 32.9        |
| 4-5 years post-secondary                                | 39.4        | 36.8        |
| Other   | 0.2         | 0.2         |
| Smoking habits  |             |             |
| Non smoker  | 45.2        | 50.9        |
| Former smoker   | 33.9        | 30.2        |
| Current smoker  | 20.9        | 18.9        |
| Asthma symptoms score                                   |             |             |
| 0   | 71.8        | 67.8        |
| 1   | 17.4        | 19.8        |
| 2   | 6.2         | 7.1         |
| 3   | 2.6         | 3.0         |
| 4   | 1.3         | 1.5         |
| 5   | 0.8         | 0.8         |
| Mean (sd)   | 0.5 (0.9)   | 0.5 (0.9)   |
| Ever asthma   | 14.9        | 14.4        |
| Current asthma  | 9.9         | 10.4        |
| Asthma medication (in participants with current asthma) | 71.7        | 69.0        |
| Lifetime occupational exposures                         |             |             |
| Irritants   | 43.2        | 37.0        |
| DCPs  | 18.5        | 32.9        |
| Organic solvents  | 29.8        | 18.2        |
| HMW Sensitizers   | 16.3        | 27.4        |
| LMW Sensitizers   | 31.5        | 34.1        |

Data are presented as % unless otherwise stated;

BMI = Body Mass Index; HMW = High Molecular Weight; LMW = Low Molecular Weight;

490 491 492 DCPs = Disinfectants Cleaning Products

|                  | Current asthma   |                        |                      |                        |         | Asthma symptom score |                              |                       |                              |         |
|------------------|------------------|------------------------|----------------------|------------------------|---------|----------------------|------------------------------|-----------------------|------------------------------|---------|
|                  | Men (n = 47,873) |                        | Women $(n = 59,426)$ |                        |         | Men $(n = 50,438)$   |                              | Women $(n = 61, 454)$ |                              |         |
|                  | n                | Odds Ratio<br>[95% CI] | n                    | Odds Ratio<br>[95% CI] | p inter | n                    | Mean Score Ratio<br>[95% CI] | n                     | Mean Score Ratio<br>[95% CI] | p inter |
| Ref              | 26,922           | 1                      | 37,157               | 1                      |         | 28,504               | 1                            | 43,315                | 1                            |         |
| Irritants        | 20,515           | 0.97 [0.91-1.03]       | 21,847               | 1.05 [1.00-1.11]       | 0.01    | 21,471               | 1.11 [1.07-1.15]             | 22,525                | 1.08 [1.05-1.11]             | 0.14    |
| DCPs             | 6,898            | 1.10 [1.01-1.20]       | 18,197               | 1.06 [1.00-1.12]       | 0.87    | 7,164                | 1.21 [1.15-1.27]             | 18,725                | 1.09 [1.06-1.13]             | 0.005   |
| Organic solvents | 11,471           | 0.93 [0.87-1.01]       | 8,282                | 1.06 [0.98-1.14]       | 0.002   | 11,944               | 1.10 [1.05-1.15]             | 8,472                 | 1.14 [1.10-1.19]             | 0.27    |

Table 2 : Associations between lifetime occupational exposure to irritants, DCPs, organic solvents and current asthma or asthma symptom score

Logistic regressions and binomial negative regressions adjusted for age, BMI and smoking habits

|                 | Current asthma |                        |                      |                        |         | Asthma symptoms score |                              |                       |                              |         |  |
|-----------------|----------------|------------------------|----------------------|------------------------|---------|-----------------------|------------------------------|-----------------------|------------------------------|---------|--|
|                 | Men (n =       | = 47,873)              | Women $(n = 59,426)$ |                        |         | Men $(n = 50,438)$    |                              | Women $(n = 61, 454)$ |                              |         |  |
|                 | n              | Odds Ratio<br>[95% CI] | n                    | Odds Ratio<br>[95% CI] | p inter | n                     | Mean Score Ratio<br>[95% CI] | n                     | Mean Score Ratio<br>[95% CI] | p inter |  |
| Ref             | 26,922         | 1                      | 37,157               | 1                      |         | 28,504                | 1                            | 43,315                | 1                            |         |  |
| HMW Sensitizers | 38,174         |                        | 51,180               |                        |         | 35,019                |                              | 52,958                |                              |         |  |
| Exposed         | 6,240          | 1.12 [1.02-1.22]       | 14,023               | 1.05 [0.98-1.11]       | 0.41    | 6,515                 | 1.16 [1.10-1.23]             | 14,471                | 1.05 [1.02-1.09]             | 0.001   |  |
| Medium          | 3,893          | 1.09 [0.98-1.22]       | 6,670                | 1.00 [0.91-1.09]       | 0.51    | 4,063                 | 1.17 [1.09-1.24]             | 6,704                 | 1.05 [1.01-1.10]             | 0.01    |  |
| High            | 2,347          | 1.16 [1.02-1.33]       | 7,533                | 1.09 [1.00-1.18]       | 0.94    | 2,452                 | 1.16 [1.07-1.25]             | 7,767                 | 1.06 [1.01-1.11]             | 0.04    |  |
| LMW Sensitizers | 39,307         |                        | 50,950               |                        |         | 41,377                |                              | 52,711                |                              |         |  |
| Exposed         | 12,385         | 0.96 [0.89-1.03]       | 13,793               | 1.03 [0.96-1.09]       | 0.04    | 12,873                | 1.09 [1.05-1.14]             | 14,224                | 1.04 [1.00-1.08]             | 0.06    |  |
| Medium          | 9,353          | 0.95 [0.88-1.03]       | 12,333               | 1.03 [0.97-1.11]       | 0.12    | 9,733                 | 1.06 [1.02-1.12]             | 12,714                | 1.03 [1.00-1.07]             | 0.28    |  |
| High            | 3,032          | 0.99 [0.87-1.12]       | 1,460                | 0.96 [0.81-1.14]       | 0.67    | 3,140                 | 1.18 [1.10-1.27]             | 1,510                 | 1.09 [0.99-1.19]             | 0.15    |  |

Table 3 : Associations between lifetime occupational exposure to known sensitizers and current asthma or asthma symptom score

Logistic regressions and binomial negative regressions adjusted for age, BMI and smoking habits



### Figure 1 : Associations between lifetime occupational exposure to irritants and current asthma according to exposure level

Odds Ratios and 95% Confidence intervals \* Interaction between gender and exposure



### Figure 2 : Associations between lifetime occupational exposure to irritants and asthma symptom score according to exposure level Lifetime exposures and asthma score - Men Lifetime exposures and asthma score - Women

Mean Score ratios and 95% Confidence intervals \* Interaction between gender and exposure