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Occupational exposures to irritants and sensitizers, asthma and asthma control in the NutriNet-Santé cohort

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35 **Abstract**

36 **Background.** The role of chronic occupational exposures to irritants in asthma remains not
37 well-defined. Few studies have examined their associations with asthma and its control.

38

39 **Objective.** To study the associations of occupational exposures with asthma and its control,
40 with specific interest for irritants, including disinfectants/cleaning products (DCP) and solvents.

41

42 **Methods.** Analyses included 4469 adults (3792 with neither asthma nor respiratory symptoms,
43 677 with current asthma; 75.9% women, mean age 54 years) of a case-control study (2018)
44 from the French NutriNet-Santé cohort. Current asthma was defined by ever asthma with
45 symptoms, medication or asthma attacks in the past 12 months, adult-onset asthma by age at
46 first asthma attack > 16 years, and uncontrolled asthma was defined by an Asthma Control Test
47 (ACT) score <20. Ever/current exposures were assessed with the Occupational Asthma-specific
48 Job-Exposure Matrix (OAsJEM). Associations were evaluated by multinomial logistic
49 regressions adjusted for sex, age, smoking status and body mass index.

50

51 **Results.** Ever exposures to sensitizers (High Molecular Weight [HMW]: OR 1.53, 95%CI 1.18-
52 2.00, and Low Molecular Weight [LMW]: 1.42, 1.09-1.87), irritants (1.32, 1.03-1.68), and DCP
53 (1.43, 1.10-1.85) were associated with current adult-onset asthma. Significant associations
54 between ever exposures and uncontrolled adult-onset asthma were observed for HMW (2.69,
55 1.52-4.78) and LMW (2.27, 1.24-4.37) sensitizers, irritants (2.32, 1.36-3.95), and DCP (2.59,
56 1.48-4.54). Results were similar for current exposures, with higher ORs. No association was
57 observed with solvents.

58

59 **Conclusion.** Occupational exposures to both sensitizers and irritants were associated with
60 current adult-onset asthma and uncontrolled asthma. Irritant and sensitizing agents should be
61 carefully considered in asthma management.

62 **Highlights box:**

63 **What is already known about this topic?** The role of chronic occupational exposures to
64 irritants in asthma remains not well-defined. Few studies have examined their associations
65 with asthma and especially with its control.

66 **What does this article add to our knowledge?** Occupational exposure to irritants and
67 particularly disinfectants/cleaning products is associated with current adult-onset asthma and
68 uncontrolled asthma.

69 **How does this study impact current management guidelines?** Irritant exposure should be
70 considered in asthma management, notably in workers with uncontrolled asthma.

71 **Key words:** Asthma, Occupational exposure, Cleaning products, Disinfectants, Irritants,
72 Job-exposure matrix, Population-based cohort

73

Abbreviations used

ACT – Asthma Control Test

BMI – Body Mass Index

CI – Confidence Interval

DCP – Disinfectants and Cleaning Products

ECRHS – European Community Respiratory Health Survey

HMW – High Molecular Weight

JEM – Job-Exposure Matrix

LMW – Low Molecular Weight

OR – Odds Ratio

VCD - Vocal Cord Dysfunction

74

75 **Introduction**

76 About 15% of adult asthma cases are attributable to occupational exposures and 20% of
77 workers with pre-existing asthma have their symptoms worsened at work.^{1,2} Reducing
78 workplace exposures contributing to new-onset or uncontrolled asthma may have a beneficial
79 impact on respiratory health.³ At present, more than 500 occupational agents have been
80 recognized as asthmagens.⁴

81 Depending on the type of causative exposure, occupational asthma is divided into two
82 categories: sensitizer-induced asthma and irritant-induced asthma.⁴ The first involves
83 sensitization (immunological mechanisms) and appears after a latency period. It has been
84 described to represent up to 85% of recognized occupational asthma cases.⁵ The second (non-
85 immunological mechanisms) appears after a single acute exposure (reactive airway dysfunction
86 syndrome (RADS)) or following persistent low to moderate level exposures to irritant agents,
87 and is estimated to account for 5 to 20% of occupational asthma cases.⁶ Until now, while
88 sensitizers-induced asthma is well known,⁷ irritant-induced asthma has been less fully
89 documented and its prevalence is probably underestimated, especially regarding the role of
90 repeated low-level exposures.^{8,9} A recent study found that only 48% of occupational asthma
91 cases (excluding RADS) were due to recognized sensitizers,¹⁰ suggesting that chronic low-level
92 exposures to irritants would be involved in a substantial number of occupational asthma cases.
93 The number of epidemiological studies suggesting the role of low and chronic exposure to
94 irritants in asthma are limited.⁶ or mainly focused on cleaning agents.¹¹ Results from previous
95 epidemiological studies are heterogeneous: using an asthma-specific job-exposure matrix,¹² no
96 associations were observed between occupational exposures to low/moderate levels of irritants
97 and asthma outcomes in three studies¹³⁻¹⁵, whereas a significant association was observed in
98 one study¹⁶. Using the new Occupational Asthma-specific Job Exposure Matrix (OAsJEM), a
99 significant association was observed between exposure to irritants and a specific asthma
100 endotype¹⁷. Further epidemiological studies are still needed to evaluate the role of chronic
101 exposures to irritants in asthma.

102 Beyond preventing asthma development, asthma management aims at achieving and
103 maintaining asthma control.¹⁸ A review of the literature shows, from population-based
104 epidemiological studies, that work-exacerbated asthma is common with a median prevalence
105 estimated to 21.5%.² Furthermore, in comparison with asthma unrelated to work, work
106 exacerbated asthma is associated with a lower quality of life, more daily symptoms and
107 consultations with physicians, suggesting a poor asthma control.² Identification and reduction

108 of environmental exposures contributing to uncontrolled asthma are crucial.¹⁸ However,
109 epidemiological studies on the associations of chronic irritant exposures at work with asthma
110 control are still scarce.^{19–22}

111 The deleterious role in asthma of workplace exposures to Disinfectants and Cleaning
112 Products (DCP), which contain both irritants (e.g., bleach) and sensitizers (e.g., glutaraldehyde,
113 quaternary ammonium compounds),²³ is increasingly emphasized.¹¹ In the past decade, several
114 occupational epidemiological studies, both in population-based cohorts^{24–26} and in specific
115 work environments such as nurses and cleaners,^{27–29} showed associations between DCP and
116 asthma. Among irritants, solvents are also a common exposure. In France, about 15% of
117 workers are exposed to solvents³⁰ but associations with asthma have been less explored.^{31–33}
118 For both DCP and solvents, epidemiological studies reported associations with asthma but very
119 few focused on asthma control.^{19,20}

120 In this study, we aimed to investigate the associations of occupational exposure to
121 irritants, including DCP and solvents, as well as exposures to well-known astmagens such as
122 high molecular weight (HMW) and low molecular weight (LMW) sensitizers, with current
123 adult-onset asthma and uncontrolled asthma. For this purpose, we used the recently updated
124 OAsJEM³⁴ in a large population-based cohort, NutriNet-Santé.

125 **Materials and methods**

126 *Study population*

127 The NutriNet-Santé study is a French web-based cohort started in 2009.³⁵ Its aim is to
128 evaluate the relationship between nutrition and chronic diseases.³⁵ More than 171,000 adults
129 have been included so far. At baseline and regularly during follow-up, participants complete a
130 set of questionnaires on anthropometry, lifestyle characteristics, health, occupation and diet.
131 The cohort was precisely described elsewhere.³⁵ During follow-up, participants were invited to
132 complete additional non-mandatory questionnaires, including two on respiratory health in 2016
133 and 2018, and one on occupation in 2018. All participants gave electronic informed consent
134 and the study, registered at <https://clinicaltrials.gov/ct2/show/NCT03335644> was approved by the
135 International Research Board of the French Institute for Health and Medical Research (IRB
136 Inserm Paris, France; n° 0000388FWA00005831) and the "Comité National Informatique et
137 Liberté" (CNIL n°908450 and n° 909216).

138 *Current asthma and asthma control*

139 Respiratory health was evaluated by standardized questionnaires. Respectively 40,179
140 and 39,026 participants completed the respiratory questionnaires in 2016 and 2018 (Figure E1).
141 We used definitions of asthma similar to those previously used in the European Community
142 Respiratory Health Survey (ECRHS).³⁶ Ever asthma was defined as a positive answer to the
143 question “have you ever had asthma?” in 2016 or 2018. Current asthma in 2018 (at the same
144 period of occupational exposure measure) was defined, among participants with ever asthma,
145 by the report in the past 12 months of symptoms (wheezing or whistling in the chest, woken up
146 with a feeling of tightness in the chest, an attack of shortness of breath that came on when being
147 at rest, an attack of shortness of breath that came on following strenuous activity, woken by an
148 attack of shortness of breath), use of an asthma treatment or asthma attacks. A more stringent
149 definition of current asthma was also used based on the self-report of a diagnosis confirmation
150 by a physician (participants with an asthma diagnosis not confirmed by a physician were
151 excluded from the analyses). Adult-onset asthma and childhood-onset asthma were defined by
152 asthma with reported age of a first asthma attack >16 years old and ≤16 years old, respectively.
153 Studying both adult and childhood-onset asthma was relevant as asthma could be induced or
154 aggravated by workplace exposures. Asthma control was evaluated, among participants with
155 current asthma in 2018, by the Asthma Control Test (ACT).³⁷ The ACT score (range 5-25)
156 relies on 5 standardized questions on frequency of symptoms (daily and nocturnal), use of the
157 rescue inhaler or nebulizer medication and subjective perception of the effect of asthma on daily
158 life, during the past 4 weeks.

159 *Occupational exposures*

160 In 2018, 30,610 participants completed a questionnaire about their work history. Among
161 them, we assessed occupational exposures in a case-control sample (Figure E1). In brief, we
162 selected 4101 “cases” (1393 participants with ever asthma and 2708 with symptoms³⁸ but no
163 asthma) and 4101 “controls” (reference group) among participants with neither asthma nor
164 symptoms, paired on age (± 5 years) and sex.³⁹ The complete job history of these 8202
165 participants was coded by an expert, according to the International Standard Classification of
166 Occupation (ISCO)-88. For the present analyses, we excluded the 2708 participants with
167 symptoms only because we could not estimate asthma control among them but we retained their
168 paired “controls” to improve statistical power for analyses. Then, we used the new occupational
169 asthma-specific job-exposure matrix OAsJEM, which has been described in detail elsewhere.³⁴
170 Briefly, the OAsJEM estimates exposure to 30 occupational agents divided into 3 groups:
171 HMW sensitizers, LMW sensitizers and irritants (Table E1). Each exposure is evaluated in 3

172 levels: high (high probability of exposure and moderate to high intensity), medium (low to
173 moderate probability or low intensity of exposure), no (unlikely to be exposed; low probability
174 and low intensity). We studied 5 groups of exposures: the 3 main groups of the JEM (HMW
175 sensitizers, LMW sensitizers and irritants), and 2 subset groups of irritants (organic solvents
176 and DCP, which include indoor cleaning products, bleach and high-level chemical
177 disinfectants; see Table E1). We examined each exposure in 2 categories (exposed *vs.* non-
178 exposed) and 3 categories (medium exposure, high exposure, or non-exposed). The OAsJEM
179 was applied to complete job histories of the participants. Two main temporalities were
180 considered: ever and current exposures, respectively corresponding to the maximum exposure
181 level during the entire work history and during the past 2 years. We also defined exposure in
182 the past 5 years by the maximum occupational exposure level in this period.

183 *Statistical analyses*

184 Associations between occupational exposures and current asthma according to age of
185 onset (current childhood-onset asthma and current adult-onset asthma *vs.* reference group), and
186 associations between occupational exposures and asthma control (controlled asthma [ACT
187 score ≥ 20] and uncontrolled asthma [ACT score < 20]²¹ *vs.* reference group (neither asthma
188 nor symptoms)) were assessed by multinomial logistic regressions. Among participants with
189 current asthma, we also examined asthma control comparing participants with uncontrolled
190 asthma to those with controlled asthma (logistic regression). Analyses were adjusted for gender,
191 age, smoking status (non-smoker, former or current smoker) and Body Mass Index (BMI) in 3
192 categories (<25 , $25-29.9$, ≥ 30 kg/m²). In all analyses, the reference group for exposures was
193 participants without any exposure. Sensitivity analyses included analyses restricted to women
194 (75% of study population) and current workers, respectively, and were stratified by BMI (≤ 25 ,
195 >25 kg/m²) and smoking status. We also conducted two other sensitivity analyses using a more
196 stringent asthma definition and with an irritant category variable excluding all agents which are
197 also classified as potential LMW sensitizers.³⁴ We used SAS 9.4 (SAS Institute Inc., Cary,
198 North Carolina, USA).

199 **Results**

200 *Participants' characteristics*

201 After excluding participants with symptoms but without asthma (n=2708), and those
202 with no/incomplete job history, missing values for BMI or without current asthma (Figure E1),

203 analyses were conducted in 4469 participants. Among them, 677 had current asthma, including
204 551 participants with controlled asthma and 126 with uncontrolled asthma (Table I, Figure E1).

205 Participants were 54.0 years on average (standard deviation 12.6), 75.9% were women,
206 and 68.9% were active workers. Among participants with current asthma, 52.8% had adult-
207 onset asthma and 83.2% an asthma diagnosis confirmed by a physician. Compared to
208 participants from the reference group, current adult-onset asthmatics were more likely to be
209 obese (≥ 30 kg/m²; 21.5% vs. 8.7%, $p < 0.001$) whereas there was no significant difference on
210 education level and smoking status (Table I). Regarding occupational exposures, 37.5% of
211 participants were ever exposed to irritants, 22.5% to DCP, 9.9% to organic solvents, 20.9% to
212 HMW sensitizers and 21.9% to LMW sensitizers (Table I).

213 *Associations between occupational exposures and current asthma*

214 In our main analyses, we observed no associations between ever, past 5 years or current
215 occupational exposures and childhood-onset asthma (Table II).

216 Conversely, positive and significant associations were observed between occupational
217 exposures to HMW and LMW sensitizers, irritants and DCP, and adult-onset asthma, whether
218 for ever, current or past 5 years exposures. When using the 3-category exposures variables, high
219 exposure to HMW sensitizers and medium exposure to DCP were significantly associated with
220 adult-onset asthma. Odds Ratios (ORs) were generally higher for the high exposure category
221 (Table II). We observed a higher OR with current exposure than with ever exposure. No
222 significant association was observed for exposures to organic solvents.

223 Results were very similar for analyses restricted respectively to women (data not shown)
224 and current workers although slightly attenuated for the latter one (data not shown). When
225 stratifying by BMI, significant associations with current adult-onset asthma were observed for
226 HMW sensitizers, LMW sensitizers and DCP only in participants with BMI ≥ 25 kg/m².
227 Differences with participants with BMI < 25 kg/m² were not significant (all p -interaction > 0.05 ,
228 data not shown). No significant difference was observed between ever and never smokers (not
229 shown, p interaction > 0.05 for all exposures). Results were similar when using the more
230 stringent asthma definition confirmed by a physician (Table E2).

231 Lastly, in analyses excluding asthmagens classified as LMW sensitizers from the irritant
232 group, we also found significant associations between ever and current exposures and adult-
233 onset asthma (Table E3).

234 *Associations between occupational exposures and asthma control*

235 We found positive significant associations with ORs>2 between ever exposures to all
236 agents except organic solvents and uncontrolled adult-onset asthma: 2.69 (95%CI 1.52-4.78)
237 for HMW sensitizers, 2.27 (1.24-4.37) for LMW sensitizers, 2.32 (1.36-3.95) for irritants, and
238 2.59 (1.48-4.54) for DCP (Figure 1). When using 3-category exposures variables, associations
239 were significant between both medium and high levels of ever exposures to irritants, DCP, and
240 HMW and LMW sensitizers, and uncontrolled asthma (Table E4). Associations were also
241 significant for current occupational exposures with higher ORs: 3.43 (1.26-9.34) for HMW
242 sensitizers, 2.81 (0.99-8.00) for LMW sensitizers, 3.62 (1.55-8.45) for irritants, and 3.76 (1.54-
243 9.18) for DCP. No associations were found between ever occupational exposures and controlled
244 asthma whereas significant associations between current exposures to HMW and LMW
245 sensitizers and controlled asthma were observed. Results were very similar when using the
246 asthma definition based on a diagnosis confirmed by a physician (Table E5) and associations
247 between current exposures to irritants and DCP and controlled asthma became significant.

248 When using participants with controlled asthma as reference, significant associations
249 were observed between ever exposures to HMW sensitizers (OR 2.07, 95%CI 1.08-3.94),
250 irritants (2.10, 1.14-3.84) and DCP (2.24, 1.18-4.26) and uncontrolled asthma (Table E6). No
251 significant associations were observed for analyses on current exposures. Lastly, when
252 excluding all LMW sensitizers exposures from our irritant exposure variable, we observed
253 significant and similar associations to those observed in our main analyses (Table E7). Results
254 were also similar to main analyses when restricted to women (not shown). When stratifying by
255 BMI, we observed significant associations between all exposures studied, including organic
256 solvents, and an increased risk of uncontrolled asthma only in participants with BMI<25 kg/m²
257 (p interaction ranging from 0.05 to 0.10, Table E8). We observed similar associations in ever
258 and never smokers (not shown, all p interaction > 0.05).

259 **Discussion**

260 In a large French population-based study, we observed significant associations between
261 occupational exposure to irritants, disinfectant and cleaning products, HMW and LMW
262 sensitizers and current adult-onset asthma. We also found significant associations between
263 these exposures and uncontrolled adult-onset asthma, both when compared to the reference
264 group and when compared to participants with controlled asthma.

265 Regarding HMW and/or LMW sensitizers, our findings are consistent with previous
266 epidemiological studies which found significant associations with new-onset asthma,^{24,25}
267 current asthma¹⁶ or uncontrolled adult-onset asthma¹⁹ and further confirm these known
268 associations.⁴

269 Our results bring new evidence for a positive association between chronic occupational
270 exposures to irritants and asthma, which was inconsistent in epidemiological studies. A few
271 studies found associations between exposure to low/moderate levels of irritants and asthma¹⁶
272 or with a specific endotype of current asthma.¹⁷ Others, all using the previous Asthma-specific
273 JEM (AsJEM),¹² did not detect associations between occupational exposures to low/moderate
274 levels of irritants and asthma,¹³ asthma severity¹⁴ or its development.¹⁵

275 Associations between chronic exposure to occupational irritants and asthma control are
276 even less documented. Aside from studies about DCP, very few studies focused on irritants at
277 large and their associations with uncontrolled asthma. In participants from two Danish cohort
278 studies, Skaaby et al. did not find significant associations between occupational exposures to
279 irritants and asthma exacerbations, which is a slightly different concept.⁴⁰ In ECRHS, no
280 association was observed between exposures to irritants and uncontrolled adult onset-asthma,¹⁹
281 using the AsJEM.¹²

282 In the past decade, evidence of a deleterious role of DCP in asthma increased. Our
283 results are consistent with epidemiological studies which found associations between
284 occupational exposures to DCP and asthma, in particular among healthcare workers and
285 cleaners.²⁷⁻²⁹ Few epidemiological studies considered distinctively childhood-onset asthma
286 from adult-onset asthma^{14,19,25} and our work adds evidence on the association of DCP
287 specifically with adult-onset asthma. Associations between occupational use of DCP and
288 uncontrolled asthma are also rarely documented. In a cohort of U.S. nurses, associations
289 between occupational disinfectant exposures and uncontrolled asthma, were significant and
290 similar for both childhood-onset and adult-onset asthma.²⁰ An epidemiological study in the
291 ECRHS described associations between occupational exposures to cleaning agents and
292 uncontrolled adult-onset asthma for both past 12-month and past 10-year exposures.¹⁹ Our
293 findings on DCP are in line with these previous investigations.

294 Our results differ from the rare studies on associations between solvents and asthma
295 which showed modest but significant associations with asthma^{31,32} and a higher asthma
296 symptom score.³³ This discrepancy in results about solvents may be due to variations between

297 study populations. The NutriNet-santé cohort has greater proportions of participants with a high
298 education level and women than other population-based cohorts. As a consequence, specific
299 exposures to solvents may differ between cohorts. To the best of our knowledge, no previous
300 study has examined the relation between solvents and uncontrolled asthma.

301 Analyses on asthma control stratified by BMI showed significant associations only in
302 participants with normal weight. No such difference was observed for current asthma. Although
303 these findings are difficult to interpret, the strong association between high BMI and
304 uncontrolled asthma may render an additional risk with occupational exposure more difficult
305 to observe in obese and overweighted participants. In contrast, a higher effect of household
306 cleaning sprays on current asthma has been previously suggested among overweight/obese
307 women, although the difference was not significant.⁴¹ Further investigations are needed
308 especially as there is no other study on this particular issue for occupational exposures and
309 asthma control.

310 In this work, we used standardized definition of asthma and studied childhood-onset and
311 adult-onset asthma distinctively. We observed significant and robust associations only with
312 adult-onset asthma strengthening the plausibility of the role of occupational exposures to
313 irritants in asthma. In addition, we explored asthma control, a key concept in the management
314 of asthma. Regarding of treatment decisions and modifications, it is now considered as more
315 relevant and useful than asthma severity.⁴² We used a validated definition incorporating
316 multiple aspects such as symptoms and daily life impact of the disease.³⁷ Determinants of
317 asthma control, especially in occupational environment, are less documented than determinants
318 of asthma development but also asthma severity which was used in older studies.¹⁴ Thus, our
319 study provides additional data regarding the negative impact of irritants and DCP on asthma
320 control. In spite of using standardized and validated asthma definitions, disease
321 misclassification is still possible as irritant-induced asthma share common symptoms with other
322 conditions such as vocal cord dysfunction.⁸ However, our results remained similar when a more
323 stringent definition for asthma was used, including self-report of confirmation of asthma
324 diagnosis by a physician.

325 In our study, we used the new OAsJEM to evaluate occupational exposures. JEM are
326 preferred to self-report in epidemiological studies on work related asthma, to reduce the risk of
327 differential misclassification between asthmatics and non-asthmatics participants.⁴³ However,
328 using a JEM induce non-differential misclassification, partly due to heterogeneity in tasks and

329 work conditions between subjects in the same job, and could underestimate associations
330 between exposures and outcomes.⁴³ Despite this potential underestimation, we observed
331 statistically significant associations with high odds ratios (>2). The new OAsJEM³⁴ compared
332 to the AsJEM,¹² also improves evaluation of associations with asthma outcomes. The OAsJEM,
333 in comparison with the AsJEM, evaluates more occupational agents (30 vs. 22), especially
334 chronic exposure to irritant agents, and classifies exposures in more precise semi-quantitative
335 metrics (instead of in yes/no). Until now only few studies used it in regard to asthma-related
336 outcomes among adults.^{17,40,43}

337 To the best of our knowledge, this work is one of the only studies to use the OAsJEM
338 in a large cohort and to investigate associations between occupational exposures to irritants,
339 including DCP, and both adult-onset asthma and uncontrolled adult-onset asthma. Notable
340 strengths of our study include the large size of the cohort, providing power to detect even
341 modest associations. Our study is also one of the first from the general population (i.e., not
342 restricted to specific workers). However, our study also has some weaknesses including its
343 cross-sectional design. In addition, this cohort may not be adequate to study the role of solvents
344 and asthma outcomes as exposure to solvents is rare in this population including mostly women
345 with high educational level. Furthermore, our study population is not representative of the
346 general French population because of overrepresentation of women and more educated
347 participants.

348 To conclude, results from this large French population-based study, showed that
349 occupational exposure to sensitizers, irritants and DCP is associated with current adult-onset
350 asthma and may lead to poor asthma control. Since DCP and irritants are common exposures at
351 work, their harmful effects on respiratory health, including asthma and poor asthma control
352 may be consequential and costly. These exposures should be regarded carefully in workplaces
353 to prevent asthma and improve life quality of workers. Occupational clinicians should consider
354 such exposures and advise to reduce it in workers with asthma.

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Table I: Description of the study population

	All n=4469	Reference group* n=3792	Current asthma		Asthma control test	
			Childhood -onset n=317	Adult- onset n=354	ACT ≥ 20 n=551	ACT < 20 n=126
Women	75.9	75.6	74.8	80.8	77.3	78.6
Age, Mean, (sd)	54.0 (12.6)	54.3 (12.6)	48.9 (12.5)	56.1 (11.9)	52.4 (12.7)	54.1 (12.8)
Asthma symptom score						
0	87.6	0	15.8	20.9	21.8	3.2
1	3.9	0	24.0	26.8	29.8	8.0
≥2	8.5	0	60.2	52.3	48.4	88.8
Mean ± Standard deviation	0.3 (0.9)	0	2.1 (1.5)	1.8 (1.5)	1.7 (1.4)	3.1 (1.3)
Asthma age onset after 16 yo	52.8	0	0	100	51.7	54.8
Asthma with diagnosis confirmed by physician	83.2	0	85.8	80.8	82.8	84.9
Current respiratory medication	15.0	3.1	80.1	83.6	78.2	96.8
BMI						
<25	64.1	65.8	56.5	53.4	56.4	46.8
25-29.9	25.6	25.4	27.4	25.1	25.8	29.4
≥30	10.3	8.8	16.1	21.5	17.8	23.8
Education						
< High school	14.0	14.6	7.6	12.8	8.0	20.8
High school	10.9	11.1	8.6	11.3	10.2	9.6
2-3 years post-secondary	32.8	32.5	36.3	32.0	33.2	36.8
4-5 years post-secondary	41.5	41.0	46.5	43.1	47.8	31.2
Other	0.8	0.8	1.0	0.8	0.8	1.6
Smoking habits						
Non smoker	47.4	47.4	50.8	43.8	48.5	41.3
Former smoker	42.6	42.8	37.8	45.8	41.0	46.0
Current smoker	10.0	9.8	11.4	10.4	10.5	12.7
Currently working	68.9	68.5	80.8	62.4	73.0	61.9
Occupational exposures (ever)						
HMW Sensitizers	20.9	20.4	19.2	28.0	22.3	30.2
LMW Sensitizers	21.9	21.6	20.2	26.8	23.8	23.0
Irritants	37.5	37.3	35.0	41.5	37.0	44.4
DCP	22.5	22.1	21.5	28.8	23.4	32.5
Organic solvents	9.9	10.0	10.1	8.5	9.1	9.5

Data are presented as % unless otherwise stated; missing data for asthma age onset n=6

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

DCP = Disinfectants Cleaning Products

Current respiratory medication: use of treatment to improve respiratory health or an asthma treatment in the past 12 months

*By definition, only participants without asthma and without respiratory symptoms are included in the reference group.

Asthma symptom score: ranging from 0 to 5, was defined as the sum of 5 asthma symptoms reported in the past 12 months

Table II: Associations between occupational exposures and current asthma according to age of onset

Current asthma	Ever exposure			Exposures last 5 years			Current exposure		
	n	Childhood-onset asthma Odds ratio (IC95%)	Adult-onset asthma Odds ratio (IC95%)	n	Childhood-onset asthma Odds ratio (IC95%)	Adult-onset asthma Odds ratio (IC95%)	n	Childhood-onset asthma Odds ratio (IC95%)	Adult-onset asthma Odds ratio (IC95%)
HMW Sensitizers	3239			2718			2070		
Ref.	2306	1	1	2176	1	1	1641	1	1
Exposed	933	0.92 [0.68-1.25]	1.53 [1.18-2.00]	542	0.89 [0.62-1.29]	1.49 [1.06-2.08]	429	0.89 [0.60-1.34]	1.82 [1.24-2.65]
Medium	466	0.70 [0.45-1.09]	1.27 [0.88-1.82]	264	0.68 [0.39-1.18]	1.10 [0.67-1.81]	213	0.59 [0.31-1.12]	1.14 [0.63-2.04]
High	467	1.16 [0.80-1.70]	1.81 [1.31-2.50]	278	1.12 [0.71-1.77]	1.88 [1.25-2.83]	216	1.23 [0.75-2.01]	2.54 [1.63-3.97]
LMW Sensitizers	3284			2726			2075		
Ref.	2306	1	1	2176	1	1	1641	1	1
Exposed	978	0.92 [0.68-1.24]	1.42 [1.09-1.87]	550	0.81 [0.56-1.19]	1.43 [1.01-2.00]	434	0.81 [0.54-1.23]	1.74 [1.19-2.55]
Medium	862	0.95 [0.70-1.30]	1.49 [1.13-1.97]	523	0.87 [0.60-1.26]	1.44 [1.02-2.03]	411	0.87 [0.57-1.31]	1.75 [1.19-2.58]
High	116	-	-	27	-	-	23	-	-
Irritants	3979			2945			2248		
Ref.	2306	1	1	2176	1	1	1641	1	1
Exposed	1673	0.91 [0.71-1.18]	1.32 [1.03-1.68]	769	0.83 [0.60-1.15]	1.36 [1.01-1.84]	607	0.80 [0.56-1.16]	1.64 [1.16-2.31]
Medium	1301	0.97 [0.74-1.28]	1.30 [1.00-1.69]	659	0.90 [0.65-1.26]	1.37 [1.00-1.99]	534	0.82 [0.57-1.20]	1.59 [1.11-2.28]
High	372	0.71 [0.43-1.17]	1.36 [0.92-2.00]	110	-	-	73	-	-
DCP	3313			2771			2113		
Ref.	2306	1	1	2176	1	1	1641	1	1
Exposed	1007	0.93 [0.69-1.25]	1.43 [1.10-1.85]	595	0.82 [0.57-1.18]	1.43 [1.03-2.12]	472	0.80 [0.53-1.19]	1.69 [1.17-2.43]
Medium	808	1.00 [0.73-1.37]	1.39 [1.05-1.85]	524	0.91 [0.63-1.32]	1.45 [1.03-2.04]	431	0.84 [0.56-1.26]	1.66 [1.13-2.42]
High	199	0.63 [0.32-1.27]	1.54 [0.97-2.46]	71	-	-	41	-	-
Organic solvents	2746			2317			1744		
Ref.	2306	1	1	2180	1	1	1641	1	1
Exposed	440	0.99 [0.66-1.48]	0.96 [0.63-1.46]	141	0.79 [0.45-1.36]	0.27 [0.04-1.99]	103	0.49 [0.20-1.25]	0.82 [0.32-2.10]
Medium	392	1.04 [0.68-1.56]	1.10 [0.73-1.68]	135	-	-	99	0.51 [0.20-1.28]	0.86 [0.34-2.20]
High	48	-	-	2	-	-	4	-	-

Multinomial logistic regressions adjusted for age, sex, smoking habits and BMI; - not enough participants for analyses

High: high probability of exposure and moderate to high intensity; Medium: low to moderate probability or low intensity of exposure

Figure 1: Associations between occupational exposures and asthma control in participants with current adult-onset asthma

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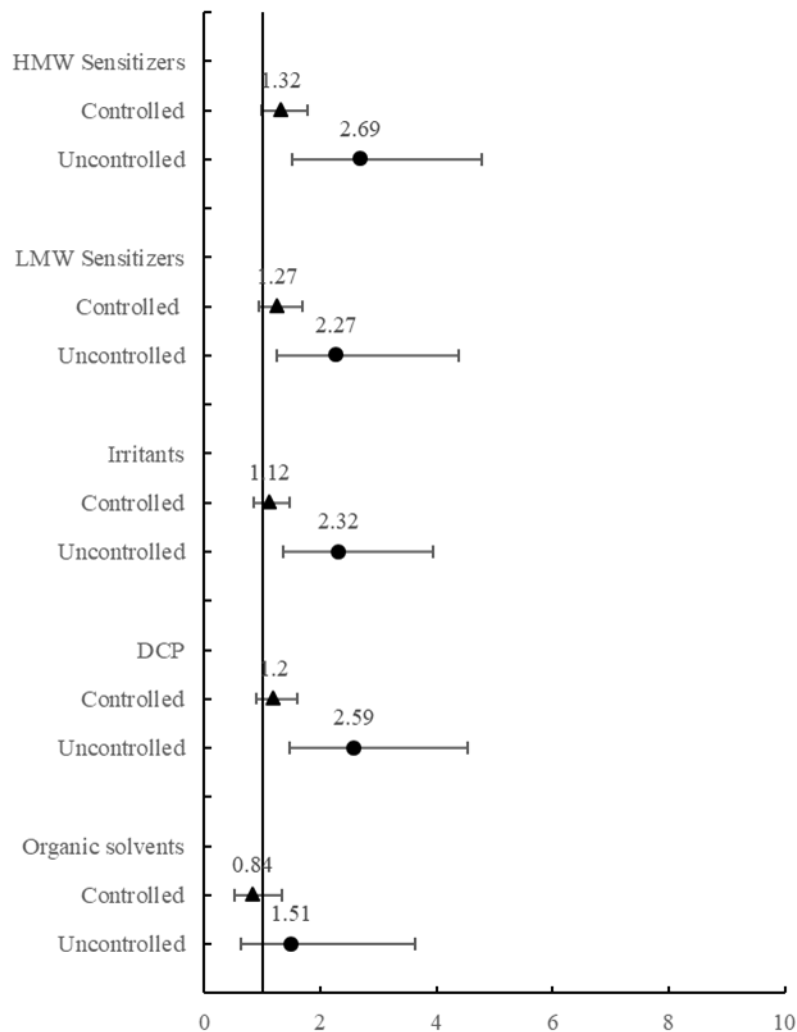
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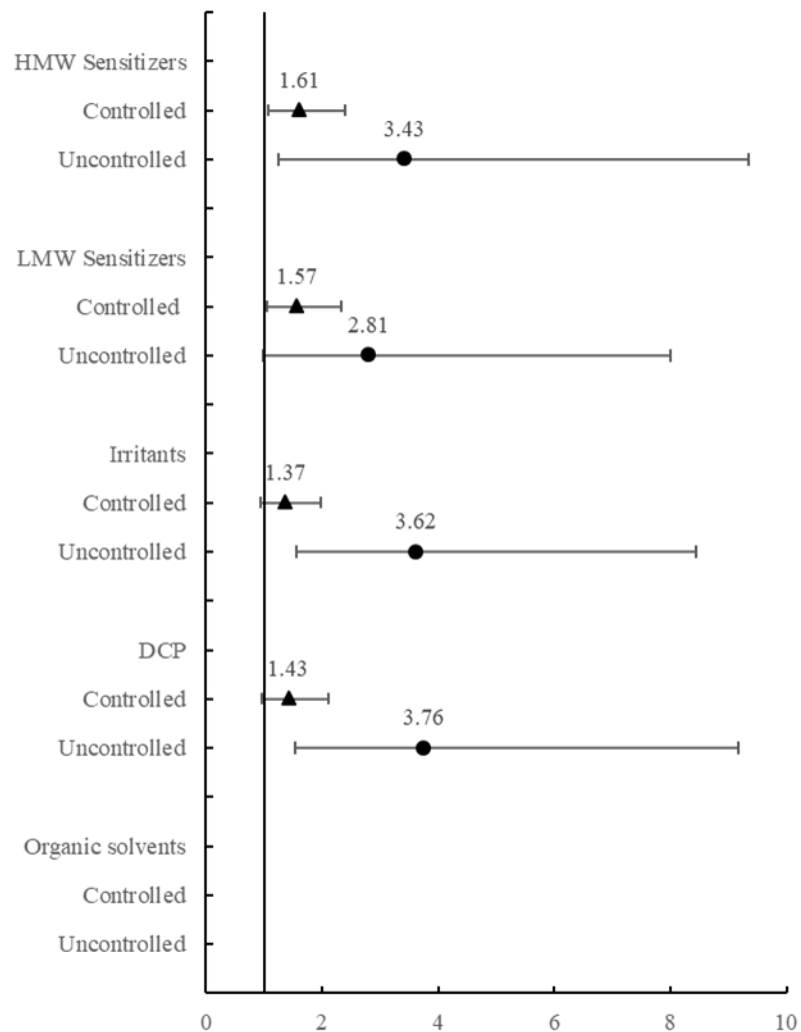
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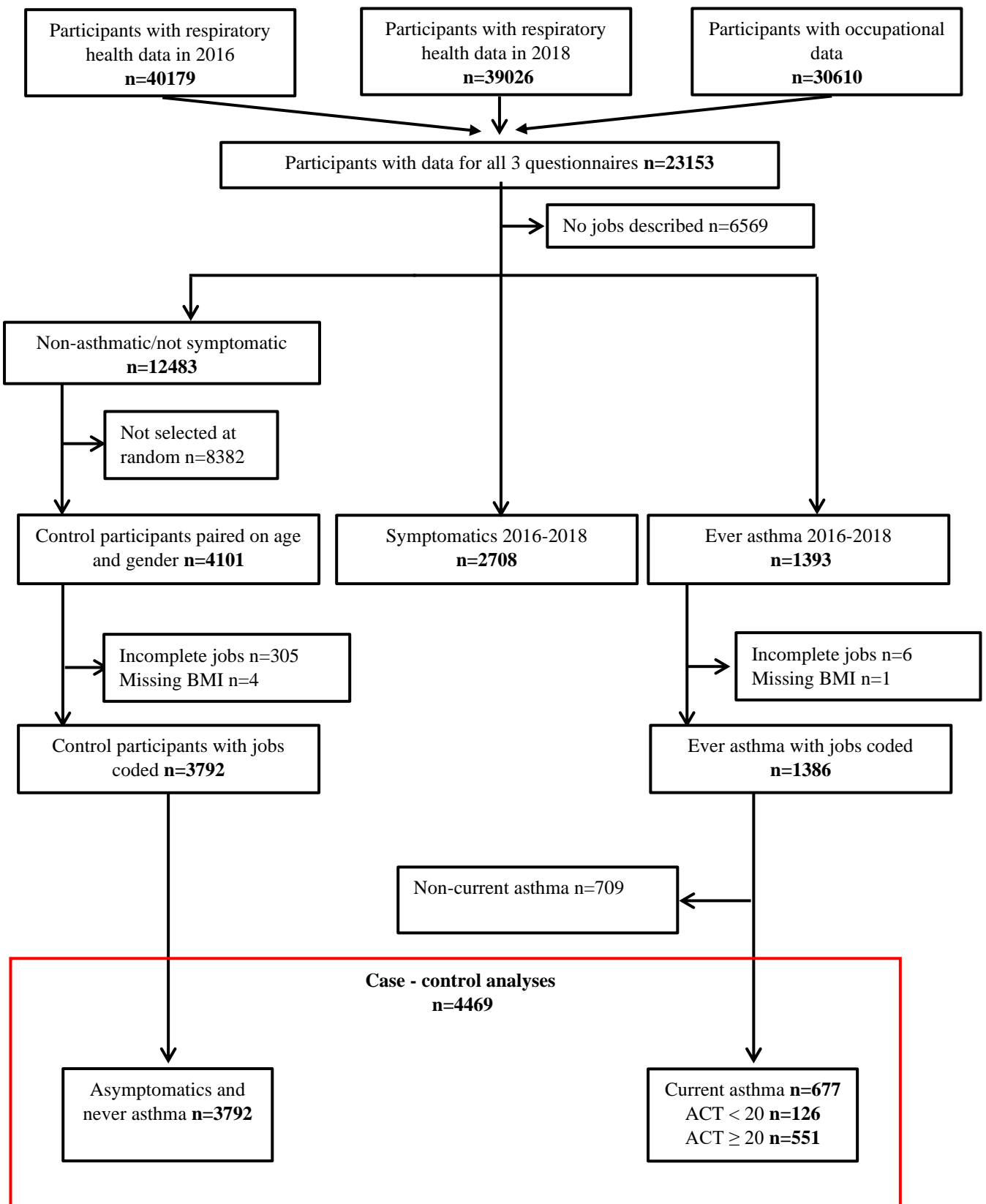
Ever exposures



Current exposures



Odds Ratios and 95% Confidence intervals



Occupational exposures to irritants and sensitizers, asthma and asthma control in the NutriNet-Santé cohort

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Table E1: List of individual agents of OasJEM classified in 3 large groups in the new occupational asthma-specific JEM

Agents, n=30	HMW sensitizer	LMW Sensitizer	Irritant
Animals	1		
Fish/shellfish	1		
Flour	1		
Foods	1		
Plant-related dusts	1		
House dust mites	1		
Storage mites	1		
Plant mites	1		
Enzymes	1		
Latex	1		
Textiles	1		1
Moulds			1
Endotoxin			1
Drugs	1	1	
High-level chemical disinfectants		1	1
Aliphatic amines		1	1
Isocyanates		1	1
Acrylates		1	1
Epoxy resins		1	1
Persulfates/henna		1	1
Wood		1	1
Metal		1	1
Metal working fluids		1	1
Herbicides			1
Insecticides			1
Fungicides			1
Indoor cleaning			1
Bleach			1
Organic solvents			1
Exhaust fumes			1

Figure E1: Flowchart

Table E2: Associations between occupational exposures and current asthma (diagnosed by physician) according to age of onset

Current asthma	Ever exposure			Current exposure		
	n	Childhood-onset asthma	Adult-onset asthma	n	Childhood-onset asthma	Adult-onset asthma
		Odds ratio (IC95%)	Odds ratio (IC95%)		Odds ratio (IC95%)	Odds ratio (IC95%)
HMW Sensitizers	3154			2009		
Ref.	2246	1	1	1593	1	1
Exposed	908	0.94 [0.68-1.31]	1.58 [1.18-2.11]	416	0.92 [0.60-1.41]	1.92 [1.26-2.93]
Medium	457	0.72 [0.45-1.16]	1.36 [0.92-2.02]	209	0.56 [0.28-1.14]	1.31 [0.69-2.47]
High	451	1.19 [0.79-1.78]	1.80 [1.26-2.57]	207	1.31 [0.78-2.19]	2.56 [1.55-4.23]
LMW Sensitizers	3200			2014		
Ref.	2246	1	1	1593	1	1
Exposed	954	0.96[0.70-1.32]	1.46 [1.08-1.96]	421	0.83 [0.53-1.29]	1.83 [1.19-2.81]
Medium	841	0.99 [0.71-1.37]	1.56 [1.16-2.11]	399	0.88 [0.57-1.38]	1.87 [1.22-2.89]
High	113	0.77 [0.33-1.81]	0.64[0.23-1.78]	22	-	-
Irritants	3879			2185		
Ref.	2246	1	1	1593	1	1
Exposed	1633	0.95 [0.72-1.25]	1.37 [1.05-1.79]	592	0.85 [0.58-1.25]	1.76 [1.20-2.58]
Medium	1268	1.00 [0.74-1.33]	1.35 [1.01-1.81]	522	0.87 [0.58-1.29]	1.77 [1.19-2.63]
High	365	0.79 [0.48-1.33]	1.41 [0.92-2.15]	70	-	-
DCP	3230			2052		
Ref.	2246	1	1	1593	1	1
Exposed	984	0.94[0.69-1.30]	1.52 [1.14-2.02]	459	0.82 [0.53-1.26]	1.80 [1.20-2.71]
Medium	790	1.01 [0.73-1.42]	1.52 [1.11-2.06]	420	0.86 [0.56-1.34]	1.83[1.21-2.79]
High	194	0.65 [0.31-1.36]	1.53 [0.92-2.55]	39	-	-
Organic solvents	2676			1695		
Ref.	2246	1	1	1593	1	1
Exposed	430	1.02 [0.66-1.57]	0.96 [0.60-1.52]	102	0.57 [0.23-1.46]	0.86 [0.3-2.44]
Medium	383	1.09 [0.7-1.69]	1.10[0.69-1.76]	98	0.59 [0.23-1.50]	0.90 [0.32-2.57]
High	47	-	-	4	-	-

Multinomial logistic regressions adjusted for age, sex, smoking habits and BMI; - not enough participants for analyses

High: high probability of exposure and moderate to high intensity; Medium: low to moderate probability or low intensity of exposure

Table E3: Associations between occupational exposures and current asthma according to age of onset

Current asthma	Ever exposure			Current exposure		
		Childhood onset asthma	Adult-onset asthma		Childhood onset asthma	Adult-onset asthma
	n	Odds ratio (IC95%)	Odds ratio (IC95%)	n	Odds ratio (IC95%)	Odds ratio (IC95%)
Irritants without LMW sensitizers*	3771			2101		
Ref.	2	1	1	1641	1	1
Exposed	1465	0.91 [0.70-1.20]	1.34 [1.04-1.72]	460	0.79 [0.53-1.19]	1.85 [1.29-2.66]
Medium	1124	1.00 [0.75-1.34]	1.32 [1.00-1.74]	389	0.81 [0.52-1.25]	1.82 [1.24-2.68]
High	341	0.62 [0.36-1.07]	1.37 [0.92-2.04]	71	-	-

Multinomial logistic regressions adjusted for age, sex, smoking habits and BMI

High: high probability of exposure and moderate to high intensity

Medium: low to moderate probability or low intensity of exposure; yo = years old

*Irritant exposure excluding agents also classified as LMW sensitizers

Table E4: Associations between occupational exposures and asthma control in participants with current adult-onset asthma

Asthma Control Test	Ever exposure			Current exposure		
		ACT \geq 20	ACT<20		ACT \geq 20	ACT<20
	n	Odds ratio (IC95%)	Odds ratio (IC95%)	n	Odds ratio (IC95%)	Odds ratio (IC95%)
HMW Sensitizers	3007			1894		
Ref.	2134	1	1	1497	1	1
Exposed	873	1.32 [0.98-1.77]	2.69 [1.52-4.78]	397	1.61 [1.08-2.40]	3.43 [1.26-9.34]
Medium	443	1.06 [0.70-1.59]	2.60 [1.28-5.30]	202	1.10 [0.60-2.01]	-
High	430	1.59 [1.11-2.27]	2.80 [1.40-5.59]	195	2.15 [1.33-3.49]	5.67 [1.96-16.4]
LMW Sensitizers	3049			1901		
Ref.	2134	1	1	1497	1	1
Exposed	915	1.27 [0.94-1.70]	2.27 [1.24-4.37]	404	1.57 [1.05-2.34]	2.81 [0.99-8.00]
Medium	805	1.30 [0.96-1.78]	2.45 [1.39-4.63]	381	-	-
High	110	0.98 [0.44-2.16]	-	23	-	-
Irritants	3698			2062		
Ref.	2134	1	1	1497	1	1
Exposed	1564	1.12 [0.86-1.47]	2.32 [1.36-3.95]	565	1.37 [0.94-1.98]	3.62 [1.55-8.45]
Medium	1211	1.11 [0.83-1.48]	2.34 [1.33-4.13]	496	1.28 [0.86-1.90]	4.10 [1.75-9.61]
High	353	1.16 [0.75-1.80]	2.24 [1.01-4.92]	69	2.02 [0.93-4.42]	-
DCP	3073			1937		
Ref.	2134	1	1	1497	1	1
Exposed	939	1.20 [0.90-1.61]	2.59 [1.48-4.54]	440	1.43 [0.96-2.12]	3.76 [1.54-9.18]
Medium	749	1.18 [0.86-1.63]	2.49 [1.36-4.57]	400	1.36 [0.90-2.06]	4.08 [1.67-9.95]
High	190	1.27 [0.75-2.17]	2.92 [1.22-7.03]	40	-	-
Organic solvents	2542			1595		
Ref.	2134	1	1	1497	1	1
Exposed	408	0.84 [0.52-1.33]	1.51 [0.63-3.63]	98	0.63 [0.23-1.83]	-
Medium	362	0.95 [0.60-1.52]	1.74 [0.72-4.20]	94	-	-
High	46	-	-	4	-	-

Multinomial logistic regressions adjusted for age, sex, BMI and smoking habits

Exposure were evaluated by the OAsJEM (<http://oasjem.vjf.inserm.fr/>) : High: high probability of exposure and moderate to high intensity; Medium: low to moderate probability or low intensity of exposure

Table E5: Associations between occupational exposures and asthma control in participants with current adult-onset asthma diagnosed by physician

Asthma Control Test	Ever exposure			Current exposure		
		ACT \geq 20	ACT<20		ACT \geq 20	ACT<20
	n	Odds ratio (IC95%)	Odds ratio (IC95%)	n	Odds ratio (IC95%)	Odds ratio (IC95%)
HMW Sensitizers	2952			1856		
Ref.	2097	1	1	1468	1	1
Exposed	855	1.37 [0.99-1.90]	2.71 [1.47-4.99]	388	1.82 [1.16-2.86]	2.91 [0.92-9.18]
Medium	436	1.07 [0.67-1.71]	2.97 [1.43-6.16]	200	1.32 [0.68-2.55]	-
High	419	1.66 [1.12-2.46]	2.46 [1.14-5.31]	188	2.35 [1.37-4.03]	4.27 [1.22-15.0]
LMW Sensitizers	2994			1863		
Ref.	2097	1	1	1468	1	1
Exposed	897	1.33 [0.96-1.85]	2.21 [1.16-4.21]	395	1.79 [1.14-2.81]	2.16 [0.63-7.4]
Medium	790	1.40 [1.00-1.96]	2.49 [1.31-4.75]	373	-	-
High	107	-	-	22	-	-
Irritants	3632			2022		
Ref.	2097	1	1	1468	1	1
Exposed	1535	1.21 [0.89-1.63]	2.23 [1.25-3.97]	554	1.59 [1.05-2.40]	3.06 [1.19-7.85]
Medium	1188	1.20 [0.87-1.66]	2.22 [1.20-4.09]	488	1.56 [1.01-2.41]	3.40 [1.33-8.70]
High	347	1.24 [0.76-2.00]	2.28 [0.98-5.27]	66	1.81 [0.69-4.72]	-
DCP	3022			1899		
Ref.	2097	1	1	1468	1	1
Exposed	925	1.32 [0.96-1.82]	2.63 [1.45-4.78]	431	1.60 [1.03-2.50]	3.41 [1.28-9.04]
Medium	739	1.33 [0.94-1.89]	2.58 [1.35-4.90]	393	1.61 [1.01-2.54]	3.69 [1.39-9.77]
High	186	1.28 [0.71-2.31]	2.81 [1.09-7.22]	38	-	-
Organic solvents	2499			1565		
Ref.	2097	1	1	1468	-	-
Exposed	402	0.91 [0.55-1.52]	1.16 [0.42-3.19]	97	-	-
Medium	356	1.05 [0.63-1.76]	1.33 [0.48-3.67]	93	-	-
High	46	-	-	4	-	-

Multinomial logistic regressions adjusted for age, sex, BMI and smoking habits

Exposure were evaluated by the OAsJEM (<http://oasjem.vjf.inserm.fr/>) : High: high probability of exposure and moderate to high intensity; Medium: low to moderate probability or low intensity of exposure

Table E6: Associations between occupational exposures and uncontrolled asthma in participants with current adult-onset asthma and asthma control in 2 categories (ACT<20 vs ACT≥20)

ACT	Ever exposure		Current exposure	
	n	ACT<20 Odds ratio (IC95%)	n	ACT<20 Odds ratio (IC95%)
HMW Sensitizers	263		148	
Ref.	164	1	104	1
Exposed	99	2.07 [1.08-3.94]	44	1.48 [0.49-4.44]
LMW Sensitizers	259		147	
Ref.	164	1	104	1
Exposed	95	1.84 [0.93-3.65]	43	1.19 [0.38-3.79]
Irritants	311		162	
Ref.	164	1	154	1
Exposed	147	2.10 [1.14-3.84]	58	2.21 [0.86-5.69]
DCP	266		152	
Ref.	164	1	104	1
Exposed	102	2.24 [1.18-4.26]	48	2.13 [0.79-5.71]
Organic solvents	194		109	
Ref.	164	1	104	1
Exposed	30	2.11 [0.69-6.45]	5	2.97 [0.20-43.80]

Multinomial logistic regressions adjusted for age, sex, BMI and smoking habits

High: high probability of exposure and moderate to high intensity

Medium: low to moderate probability or low intensity of exposure

HMW: High Molecular Weight

LMW: Low Molecular Weight

DCP: Disinfectants and Cleaning Products

Table E7: Associations between occupational exposures and asthma control in participants with current adult-onset asthma

Asthma Control Test	Ever exposure			Current exposure		
		ACT \geq 20	ACT<20		ACT \geq 20	ACT<20
	n	Odds ratio (IC95%)	Odds ratio (IC95%)	n	Odds ratio (IC95%)	Odds ratio (IC95%)
Irritants without LMW sensitizers*	3504			1926		
Ref.	2134	1	1	1497	1	1
Exposed	1370	1.13 [0.86-1.50]	2.37 [1.37-4.09]	429	1.50 [1.00-2.23]	4.57 [1.95-10.71]
Medium	1044	1.16 [0.83-1.53]	2.38 [1.32-4.27]	362	1.39 [0.90-2.15]	5.38 [2.29-12.65]
High	326	1.16 [0.74-1.81]	2.34 [1.07-5.17]	67	2.09 [0.96-4.59]	-

Multinomial logistic regressions adjusted for age, sex, BMI and smoking habits

High: high probability of exposure and moderate to high intensity; Medium: low to moderate probability or low intensity of exposure

*Irritant exposure excluding agents also classified as LMW sensitizers

Table E8: Associations stratified by BMI between occupational ever exposures and asthma control in participants with current adult-onset asthma

Asthma control	BMI≤25		BMI>25		p*
	n	Odds ratio (IC95%)	n	Odds ratio (IC95%)	
HMW Sensitizers	2016		991		
Ref.	1451	1	683	1	
Exposed	565	4.76 [2.00-11.32]	308	1.49 [0.66-3.33]	0.05
LMW Sensitizers	2039		1010		
Ref.	1451	1	683	1	
Exposed	588	4.05 [1.63-10.04]	327	1.28 [0.56-2.95]	0.07
Irritants	2378		1320		
Ref.	1451	1	683	1	
Exposed	927	4.23 [1.82-9.86]	637	1.40 [0.70-2.80]	0.06
DCP	2043		1030		
Ref.	1451	1	683	1	
Exposed	592	4.31 [1.79-10.37]	347	1.66 [0.79-3.51]	0.10
Organic solvents	1683		859		
Ref.	1451	1	683	1	
Exposed	232	4.17 [1.29-13.45]	176	-	-

Multinomial logistic regressions adjusted for age, sex and smoking habits

*Interaction p between exposure and BMI