



**HAL**  
open science

## **Pleural plaques and the role of exposure to mineral particles in the Asbestos Post-Exposure Survey**

Christophe Paris, Isabelle Thaon, Francois Laurent, Anastasia Saade, Pascal Andujar, Patrick Brochard, Julia Benoist, Benedicte Clin, Gilbert Ferretti, Antoine Gislard, et al.

► **To cite this version:**

Christophe Paris, Isabelle Thaon, Francois Laurent, Anastasia Saade, Pascal Andujar, et al.. Pleural plaques and the role of exposure to mineral particles in the Asbestos Post-Exposure Survey. *Chest*, 2023, 164 (1), pp.149-158. 10.1016/j.chest.2023.02.004 . hal-04034145

**HAL Id: hal-04034145**

**<https://hal.science/hal-04034145>**

Submitted on 21 Jul 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

# Pleural plaques and the role of exposure to mineral particles in the Asbestos Post-Exposure Survey

## Pleural plaques and exposure to mineral particles

Christophe Paris\* MD, PhD<sup>1,2</sup>, Isabelle Thaon<sup>3</sup>, François Laurent MD, PhD<sup>4,5</sup>, Anastasia Saade MD, PhD<sup>1,2</sup>, Pascal Andujar MD, PhD<sup>6,7</sup>, Patrick Brochard MD, PhD<sup>8</sup>, Julia Benoist<sup>7</sup>, Benedicte Clin MD,- PhD<sup>9,10,11</sup>, Gilbert Ferretti MD, PhD<sup>12,13</sup>, Antoine Gislard MD<sup>14</sup>, Cecile Gramond PhD<sup>8</sup>, Pascal Wild PhD<sup>15</sup>, Aude Lacourt PhD<sup>8</sup>, Fleur Delva MD, PhD<sup>8</sup>, Jean-Claude Pairon MD, PhD<sup>6,7</sup>.

1. Centre de Pathologies Professionnelles et environnementales, CHU Pontchaillou, F-35000 Rennes, France
2. INSERM, IRSET U1085, Equipe ESTER, F-35000 Rennes, France
3. CHRU de Nancy, Université de Lorraine, Centre de Consultation de Pathologies Professionnelles, F-54000 Nancy, France
4. Service d'imagerie médicale diagnostique et thérapeutique. Unité d'imagerie thoracique CHHU de Bordeaux groupe hospitalier Sud Avenue de Magellan F-33604 Pessac France
5. Centre de recherche cardiothoracique INSERM U1045 université de Bordeaux avenue Leo Saignat F-33000 Bordeaux, France
6. Univ Paris Est Créteil, INSERM, IMRB, Equipe GEIC20, F-94010 Creteil, France
7. Centre Hospitalier Intercommunal, Service de Pathologies professionnelles et de l'Environnement, Institut Santé-Travail Paris-Est, F-94000 Creteil, France
8. Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Epicene team, UMR 1219, F-33000 Bordeaux, France.
9. INSERM U1086 « ANTICIPE », F-14000 Caen, France
10. Université de Caen Normandie, F-14000 Caen, France
11. CHU Caen, Service de santé au travail et pathologie professionnelle, F-14000 Caen, France
12. Service de radiologie diagnostique et thérapeutique Hôpital Michallon CHU Grenoble Alpes F-38043 Grenoble, France
13. Université Grenoble Alpes Avenue des Maquis du Gresivaudan F-38700 La Tronche, France
14. Centre de Pathologies Professionnelles et environnementales, CHU Rouen, F-76000 Rouen, France
15. INRS, French Institute for Research and Safety, F-54055 Vandoeuvre-Les-Nancy, France

\*Corresponding author :

Pr Christophe Paris, MD, PhD,

Centre de Pathologies Professionnelles et Environnementales, CHRU Pontchaillou,

2 rue Henri Le Guilloux, F-35033 Cedex 9 Rennes, France

Email : [christophe.paris@inserm.fr](mailto:christophe.paris@inserm.fr)

**Fundings.** This work was supported by the French National Health Insurance (Occupational Risk Prevention Department), French Ministry of Labor and Social Relations, French Agency for Food, Environmental and Occupational Health and Safety (ANSES grant 07-CRD-51, EST 2006/1/43, EST 2009/68).

All authors declared no conflict of interest

### Acknowledgments

The authors would like to thank members of the asbestos post-exposure program for their contribution to study design or data collection of the ARDCo program: E. Abboud, J. Ameille, B. Aubert, Y. Badachi, J. Baron, C. Beigelman-Aubry, J. Benichou, A. Bergeret, A. Caillet, P. Catilina, G. Christ de Blasi, F. Conso, E. Guichard, A. Jankowski, V. Latrabe, N. Le Stang, M.

54 Letourneux, G. Limido, A Luc, P. Malherbe, M.F. Marquignon, M. Maurel, B. Millet, M.  
55 Montaudon, L. Mouchot, G. Ogier, M. Pinet, A. Porte, J.L. Rehel, P. Reungoat, R. Ribero, M.  
56 Savès, E. Schorle, A. Sobaszek, A. Stoufflet, V. Tainturier, F.X. Thomas, L. Thorel, the  
57 FRANCIM network, and the Calvados, Manche, Gironde and Isère cancer registries, and  
58 National Health Insurance personnel (Aquitaine, Haute-Normandie, Basse-Normandie, and  
59 Rhône-Alpes).

60

61 **Author Contributions :**

62 Study concept and design : CP, FL, PB, JCP, Acquisition of data : CP, IT, FL, PB, SC, BC, NF,  
63 GF, AG, Analysis and interpretation of data : CP, IT, FL, PA, PB, AG, AL, JCP, First draft of  
64 the manuscript : CP, JCP, Critical revision of the manuscript for important intellectual content :  
65 CP, IT, FL, AS, PA, PB, BC, NF, GF, PW, AL, JCP, statistical analysis : CP, CG, AL, Obtained  
66 funding : CP, JCP, Study supervision : CP, JCP, Full access to all data and final responsibility  
67 for the decision to submit for publication : CP, JCP

1 Key Words: asbestos, silica, refractory ceramic fibres, mineral wool fibres, pleural plaques,  
2 exposure, occupational, epidemiology  
3  
4 Abbreviation list  
5 RCF: Refractory Ceramic Fibers  
6 MWF: Mineral Wool Fibers  
7 PP: Pleural Plaques  
8 CT: Computed Tomodensitometry  
9 CEI: Cumulative Exposure Index  
10 JEM: Job-Exposure Matrix  
11 OR: Odds Ratio  
12  
13  
14

Journal Pre-proof

**15 Abstract**

16 Background. Previous studies have inconsistently reported associations between Refractory  
17 Ceramic Fibers (RCF) or Mineral Wool Fibers (MWF) and the presence of pleural plaques  
18 (PP). Moreover, all these studies were based on Chest X-Ray, known to be associated with a  
19 poor sensitivity for the diagnosis of PP.

20 Research question. Does the risk of pleural plaques increase with cumulative exposure to RCF,  
21 MWF and silica ? and if yes, do these dose-response relationships depend on the co-exposure  
22 to asbestos or conversely, are the dose-response relationships for asbestos modified by co-  
23 exposure to RCF, MWF and silica ?

24 Study design and Methods. Volunteer workers were invited to participate in a CT-scan  
25 screening program for asbestos-related diseases in France. Asbestos exposure was assessed by  
26 industrial hygienists and exposure to RCF, MWF and silica was determined by using Job-  
27 Exposure Matrices. A Cumulative Exposure Index (CEI) was then calculated for each subject  
28 and separately for each of the 4 mineral particle exposures. All available CT-scans were  
29 submitted to randomized, double reading by a panel of radiologists.

30 Results. In this cohort of 5,457 subjects, we found a significant dose-response relationships,  
31 after adjustment for asbestos exposure between CEI to RCF or MWF and the risk of PP (OR=  
32 1.29 [1.00-1.67] and OR= 1.84 [1.49-2.27] for the highest CEI quartile respectively). Moreover,  
33 significant interactions were found between asbestos on one side and respectively MWF or RCF  
34 on the other side.

35 Interpretation. This study suggests the existence of a significant association between exposure  
36 to RCF and MWF and the presence of PP in a large population previously exposed to asbestos  
37 and screened by CT-scan.

38 Although the relationship between exposure to asbestos and the prevalence of pleural plaques  
39 is well known <sup>1,2</sup>, the scientific evidence is weaker concerning the role of exposure to other  
40 fibers, including Mineral Wool Fibers (MWF) and Refractory Ceramic Fibers (RCF). Previous  
41 studies have inconsistently reported associations between RCF or MWF and the presence of  
42 pleural plaques <sup>3-5</sup>. In 1995, De Vuyst *et al.* concluded that there was no evidence that pleural  
43 plaques were associated with glass-, rock- or slag-wool exposures on the basis of the  
44 epidemiological literature <sup>6</sup>. Recently, more convincingly results were published by Le Masters  
45 *et al.* <sup>7</sup> reporting an association between pleural plaques and RCF, with significant dose-  
46 response curves, even in a sub-sample of subjects with no known asbestos exposure. However,  
47 all these studies were based on Chest X-Ray, which is well known to have poor sensitivity for  
48 the diagnosis of pleural plaques. Finally, in a previous study, Lacourt *et al.* <sup>8</sup> also reported a  
49 possible modifier effect of exposure to RCF on the dose-response relationships between  
50 mesothelioma and asbestos CEI. To our knowledge, no such possible effect has been studied  
51 between asbestos exposure and other fibers for pleural plaques. The aim of the present study  
52 was to study the association between RCF and MWF exposures and pleural plaques in a large  
53 cohort of subjects all previously exposed to asbestos and screened by CT-scan, and, if exists,  
54 the existence of a possible interaction with asbestos exposure, or conversely, a possible modifier  
55 effect of these exposures on the dose-response relationships between pleural plaques and  
56 asbestos exposure.

57 .

58

## 59 **Study Design & Methods**

### 60 **Study population**

61 A more complete description of the study design has been previously published <sup>9,10</sup>. Briefly, an  
62 asbestos-related diseases screening program was organized between October 2003 and

63 December 2005 in four regions of France (Lower and Upper Normandy, Aquitaine and Rhone-  
64 Alpes) in order to assess the usefulness and validity of CT-Scan in former asbestos-exposed  
65 populations. The volunteer subjects recruited in this program worked in various industrial  
66 sectors such as iron and steel manufacture, construction sector, cargo handling, metalworking,  
67 ship repair. All subjects had to have been exposed to asbestos to be included in the cohort. They  
68 received, according to a detailed design, a free medical check-up including chest CT-scan and  
69 pulmonary function tests. Subjects for whom a CT-scan was available for analysis at baseline  
70 constituted the Asbestos Post-Exposure Survey (APEXs) population. The present study  
71 included all male and female subjects of the APEXs with confirmed asbestos exposure.

## 72 **Occupational exposures and tobacco consumption**

73 All subjects completed their full work history by means of a “*cursus laboris*” and a standardised  
74 self-questionnaire. Asbestos exposure has been assessed by industrial hygienists <sup>11</sup>, as MWF,  
75 RCF and silica exposures have been estimated by Job-Exposure Matrices (JEM). Cumulative  
76 exposure index were computed for each mineral particle by the mean of the product of  
77 probability (of exposure) x duration x intensity level. All non-null probability of exposure were  
78 considered as exposed. Additional details on the method for making these measurements is  
79 provided in an online data supplement.

80 Smoking status was recorded at baseline (never smoker, former smoker for more than one-year,  
81 current smoker including former smoker having stopped smoking for less than one year).

82

## 83 **CT scanning**

84 The detailed protocol for CT-scan acquisition at inclusion and interpretation of CT-Scan has  
85 been previously described <sup>10</sup>. Interstitial or pleural abnormalities were registered on a  
86 standardized form according to the Fleischner Society glossary of terms <sup>12</sup>. Pleural plaques were  
87 defined as circumscribed, quadrangular, pleural elevations, with clearly demarcated borders

88 and tissue density, sometimes calcified, presenting a typical topography, at least on some of the  
89 images <sup>13</sup> (supplementary figure 1).

90

### 91 **Statistical analysis**

92 Subject characteristics (age, smoking status at inclusion, asbestos, MWF, RCF and silica  
93 exposure parameters) were compared between subjects with and without pleural plaques, by  
94 means of Chi2 or two-sided Fisher–Freeman–Halton test depending on the sample size for each  
95 of these mineral particles. Exposures to asbestos, MWF, RCF and silica were characterized by  
96 duration of exposure and CEI, expressed as quartiles or continuous variables. Statistical  
97 associations between pleural plaques and the various exposures were tested by using  
98 unconditional logistic regressions. Several models were fitted separately depending on the type  
99 of definition of exposure to the 4 mineral particles i.e. asbestos: CEI expressed as log (CEI +  
100 1) or by quartiles; MWF, RCF and silica: absence / presence, CEI expressed as log (CEI + 1)  
101 or by quartiles.

102 As all subjects were exposed to asbestos, we introduced interaction terms by dichotomising  
103 exposure variables: i) for studying the interaction of asbestos exposure on dose-response  
104 relationships between CEI of the 3 particles and pleural plaques, we first created an asbestos  
105 0/1 variable ( $<$  median value of CEI,  $\geq$  median value) and then computed the interaction term  
106 as  $\log(\text{CEI}_{\text{particles}} + 1) * \text{asbestos } 0/1 \text{ variable}$ . If this interaction was significant, we computed  
107  $\text{Log}(\text{CEI}_{\text{particles}} + 1)$  for each category of the asbestos 0/1 variable; ii) for the last research  
108 question, we computed the asbestos CEI respectively within non-exposed and exposed subjects  
109 to each of the other particles. Interaction terms were assessed in three separate models  
110 introducing asbestos CEI of subjects exposed to each of the 3 particles in a model including  
111 asbestos CEI for all subjects.

112



113 All multiple analyses were adjusted for age and smoking status, and depending on the analysis,  
114 cumulative exposure to asbestos.

115 Statistical analysis was carried out using SAS software version 9.4 (SAS Institute, Inc, Cary,  
116 NC). All statistical tests were two-sided, and the limit of statistical significance was defined as  
117  $p < 0.05$ .

118

## 119 **Results**

120 The study-population flow-chart is shown in Figure 1. Subject characteristics according to the  
121 presence of pleural plaques are presented in Table 1. Overall, the prevalence of pleural plaques  
122 in the 5,457 subjects (including 5,225 males) involved in the present study was 20.2% (n=1,102,  
123 of whom 1,078 males). Comparison of subjects with or without pleural plaques demonstrated  
124 that patients with pleural plaques were older (65.2 years vs 62.5 years,  $p < 0.0001$ ), and less often  
125 non-smokers (19.2% vs 27.7%,  $p < 0.0001$ ). The percentage of subjects exposed to MWF, RCF  
126 and silica were 70.1%, 27.7% and 57.4%, respectively considering a non-null probability of  
127 exposure by the JEM (Supplementary Table 1). Subjects with pleural plaques had significantly  
128 higher CEI to asbestos, MWF, RCF and silica than subjects without pleural plaques regardless  
129 of the exposure considered. In univariate analysis, dose-response effects were significant for  
130 the 4 types of mineral particles.

131 Adjusting for smoking status and age confirmed these dose-response relationships for MWF,  
132 RCF and silica (Table 2). However, also adjusting for CEI to asbestos resulted in significant  
133 dose-response effects only for MWF and a close significant one for RCF. Moreover,  
134 considering the CEI to these 4 agents (Table 3), only asbestos (OR = 1.37 [1.31-1.44]) and  
135 MWF (OR = 1.41 [1.30-1.54]) demonstrated a significant dose-response relationships after  
136 adjustment for age, smoking status and all other co-exposures. Dose-response relationships  
137 with MWF CEI was more pronounced when exposure to asbestos was greater than the CEI

138 median) with a significant interaction term. Significant dose-response relationships with CEI  
139 to asbestos were also observed for the 6 groups of subjects exposed or not exposed to the other  
140 3 mineral particles (Table 4). However, these results suggested a differential slope in subjects  
141 exposed to MWF, with an asbestos-related OR for the highest quartile relative to the lowest  
142 quartile of 3.68 [2.73-4.97] in subjects not exposed to MWF vs an asbestos-related OR of 5.28  
143 [4.24-6.59] in subjects exposed to MWF. A similar pattern, albeit less pronounced, was also  
144 observed for RCF, with an asbestos-related OR of 4.30 [3.43-5.39] and 6.28 [4.80-8.23], in  
145 subjects not exposed and exposed to RCF, respectively. These two interactions were significant  
146 but no such significant interaction was observed for silica (Table 5).

147

## 148 **Discussion**

149 Based on a large cohort of more than 5,000 subjects with CT-scan data, our study reported  
150 coherent positive effects of co-exposures to asbestos and MWF, and to a lesser extent, for RCF,  
151 but not with silica. A significant dose-response relationship was observed between the CEI to  
152 MWF and the presence of pleural plaques on CT-scan, after adjustment for age, smoking status,  
153 asbestos exposure and exposure to other mineral particles. Moreover a significant modifier  
154 effect was observed for co-exposure to asbestos and MWF or RCF compared to exposure to  
155 asbestos alone.

156 The major bias related to these types of analyses is the possibility of a residual effect of asbestos  
157 associated with other exposures despite adjustment, rather than an effect of co-exposures  
158 themselves. Simultaneous co-exposures to asbestos, MWF or RCF often occurred in industrial  
159 settings using these fibers, depending on several criteria such as historical evolution of  
160 processes, economic conditions, technical requirements, etc. The statistical consequences of  
161 analyses of such highly correlated variables have been extensively discussed by Lacourt *et al.*  
162 <sup>14</sup>. Briefly, using JEM for the assessment of exposure to MWF, RCF and silica is thought to

163 include non-differential misclassification and bias toward the null for OR estimates <sup>15</sup>.  
164 However, these three JEMs may also be correlated by construction, resulting in correlated  
165 misclassifications. In this case, distortion of estimates may be unstable, toward as well as away  
166 from the null <sup>16</sup>. It can then be hypothesized that significant associations observed in this study  
167 may simply reflect the effect of asbestos and not the effect to other fibers. However, two  
168 elements strongly argue against such an hypothesis. Firstly, asbestos exposure was estimated  
169 for each subject by an independent assessment based on recorded job tasks by industrial  
170 hygienists, while assessment of exposure to other agents, namely MWF, RCF and silica, was  
171 based on JEMs. We can therefore hypothesize that misclassifications of exposure between the  
172 hygienist's assessment of asbestos exposure and the JEM were limited and poorly correlated,  
173 which would contribute to avoiding bias in our results. Secondly, dose-response relationships  
174 between pleural plaques and exposures to RCF, MWF and silica were clearly different, as we  
175 observed no association for silica, and a significant association for the other two agents. Co-  
176 exposures to asbestos and silica are also a frequent event in industrial settings such as in  
177 foundries, mining or construction, and 57% of our subjects were exposed to both asbestos and  
178 silica (data not shown). In our data set, correlation coefficients between asbestos and the 3 CEI  
179 to mineral particles were all significant and relatively similar (supplementary Table 2) except  
180 for silica. In univariate analyses, we found a significant dose-response relationship between  
181 CEI to silica and the presence of pleural plaques but this association was not significant after  
182 adjustment for CEI to asbestos. Moreover, we found significant interactions between RCF and  
183 MWF exposure and asbestos-related slopes for the presence of pleural plaques, but not for silica  
184 exposure. These differential results between pleural plaques and co-exposures to asbestos,  
185 MWF, RCF and silica as well as statistical adjustments performed in our study support the  
186 hypothesis that the possible role of a confounding residual effect of asbestos exposure on our

187 results was low. However, such a hypothesis cannot be totally ruled out due to our  
188 epidemiological design and we cannot achieve definite conclusions.

189 The results of epidemiological studies on the role of Man-Made Mineral Fibers (MMMF) on  
190 pleural plaques are inconsistent and sparse. Pleural plaques have been clearly associated with  
191 the presence of asbestos fibers in the lungs, mainly due to occupational exposures <sup>1,9</sup>. In an  
192 autopsy study of 288 men <sup>3</sup>, Karjalainen *et al.* reported a significant association between the  
193 presence of pleural plaques and age, smoking, pulmonary concentration of asbestos but not with  
194 other inorganic fibers. However, the possible modifier effect of other inorganic fibers on the  
195 association between pleural plaques and pulmonary concentration of asbestos was not assessed  
196 in this study. The first study from the MMMF industry, including 1,028 subjects, with  
197 interpretable chest X-rays for 941 subjects, reported only a few pleural abnormalities (15  
198 subjects with pleural thickening, 1 with pleural calcification, 1 with pleural plaques), and did  
199 not provide more detailed analyses regarding the small number of abnormalities <sup>4</sup>. In the  
200 mineral wool industry, Jarvolm *et al.* reported a non-significant prevalence of pleural plaques  
201 among 933 workers and 865 referents (12 vs 3)<sup>5</sup>. In a study in the fiberglass industry, Kilburn  
202 *et al.* reported pleural abnormalities in 20/284 subjects, only 2 of whom had been previously  
203 exposed to asbestos <sup>17</sup>. The authors concluded that these pleural abnormalities could be  
204 explained by fiberglass exposure alone. New findings have emerged from the US-RCF industry  
205 studies. In a retrospective cohort and a nested case-control study, Lockey *et al.* reported a  
206 prevalence of pleural plaques in 20 cases among 652 workers <sup>18</sup>. Moreover, significant dose-  
207 response relationships were observed with duration, time since first exposure and cumulative  
208 exposure (fiber-month/mL) to RCF. Taking into account previous asbestos exposure in the  
209 nested case-control study did not modify these associations. A recent up-date confirmed these  
210 results with a significant dose-response association with cumulative exposure to RCF in the  
211 whole cohort (n=1341, OR = 6.9 [3.6-13.4] for Cumulative Exposure (CE) >135 relative to <15

212 fiber-month/mL) or in subjects without asbestos exposure (n=647, OR = 9.1 [2.5-33.6] for  
213 CE>135 relative to <15 fiber-month/mL)<sup>7</sup>. The results of the only other cohort from the  
214 European RCF industry were in accordance with these findings<sup>19</sup>. In 355 workers not exposed  
215 to asbestos (among 774 RCF exposed workers), the authors found a significant exposure-  
216 response for the prevalence of pleural plaques with time since first exposure to RCF (OR = 4.01  
217 [1.54-10.44]) in a non-age adjusted model. Our results, based on CT features, provide new  
218 findings compared to previous published series exclusively based on radiological data as we  
219 found a significant association between pleural plaques and RCF exposure, after adjustment for  
220 age, smoking and asbestos exposure (Table 3, OR = 1.29 [1.0-1.67] in the group with the  
221 highest quartile of CEI to RCF). However, this association was less pronounced than that  
222 observed for MWF exposure (Table 2, OR = 1.84 [1.49-2.27]). Moreover, in the full model,  
223 with adjustment for the various mineral particles (namely asbestos, RCF, MWF and silica),  
224 only the association with MWF persisted (Table 3, OR = 1.41 [1.30-1.54]). These discrepancies  
225 are difficult to explain. This last result (Table 3) could be explained by the correlation between  
226 RCF and MWF exposures assessed by JEM, as described above, or by over-adjustment.  
227 However, both the lower intensity level of exposure and the smaller number of subjects exposed  
228 to RCF (when compared to MWF exposed subjects) may also explain our absence of  
229 significant association of exposure to RCF with pleural plaques in this cohort.

230 To our knowledge, no association between pleural plaques and MWF exposure has been  
231 previously reported in the literature. However, as already mentioned, only a limited number of  
232 studies have been published and we did not identify any studies published after 1995. The  
233 available studies present a number of weaknesses (absence of control group, small number of  
234 subjects, use of chest X-rays) and these publications therefore cannot be used to reliably  
235 demonstrate the absence of such an association. Consequently, we consider that our findings,

236 based on a large cohort and using HRCT for the diagnosis of pleural plaques, support an  
237 association between RCF and MWF and the presence of pleural plaques.

238 Another interesting result is the effect of co-exposures to asbestos and RCF or MWF. The  
239 association between pleural plaques and asbestos CEI appeared to be significantly stronger in  
240 subjects both exposed to asbestos and one of these fibers than in subjects only exposed to  
241 asbestos. To our knowledge, this is the first time that this type of result has been published.  
242 Interestingly, in a case-control study conducted on other French regions, Lacourt *et al.* reported  
243 a possible modifier effect of RCF, MWF and to a lesser extent silica exposures on the  
244 association between asbestos exposure and pleural mesothelioma <sup>8,14</sup>.

245 Many studies have evaluated the toxicological characteristics of various fibers <sup>20</sup>. However,  
246 only rare studies have demonstrated the pleural effects of fibers other than asbestos, and most  
247 of them concerned RCF. In a subchronic inhalation study, Gelzleither demonstrated that RCF-  
248 1 caused pleural fibrosis in hamsters but not in rats <sup>21</sup>. Conversely, in a comparative study  
249 between rats and hamsters, Everitt showed that RCF induced pleural inflammation in both  
250 species <sup>22</sup>. In a chronic multidose RCF inhalation study in rats and hamsters, Mast also reported  
251 pleural fibrosis in both hamsters and rats <sup>23</sup>. Only one study reporting the effects of two different  
252 MWFs was found. This study reported pleural inflammation and fibrosis in hamsters only with  
253 one of the two fibers studied <sup>24</sup>. We also showed a modifier effect of co-exposure with asbestos  
254 and MWF or RCF. In an experimental model, Davis previously demonstrated that co-exposure  
255 to chrysotile or amosite and quartz may enhance the pulmonary fibrosis effect as well as the  
256 pleural inflammation induced by either of the two types of asbestos alone. In the same study,  
257 another compound, titanium oxide, mixed with amosite only enhanced pleural inflammation  
258 relative to the inflammation induced by amosite alone <sup>25</sup>. Bellmann *et al.* reported that the  
259 addition of non-fibrous particulates to a RCF sample, significantly enhanced lung inflammatory  
260 adverse effects of RCF alone <sup>26</sup>. Davis concluded that co-exposure to both non-fibrous and

261 fibrous particles may affect the biological effect of the fibers alone <sup>27</sup>. Several mechanisms  
262 have been proposed to explain these results: overload and direct inflammation, synergistic  
263 effects between inorganic substances and decreased clearance of fibers <sup>28</sup>.  
264 Finally, biopersistence has been described as one of the major determinants of the toxicology  
265 of fibers. In particular, biopersistence of fibers correlates with collagen deposition in the lung  
266 (as a surrogate for early fibrotic response). Biopersistence has also been described as a  
267 determinant of translocation of fibers from the lungs to the pleura <sup>29</sup>, although the mechanisms  
268 of translocation have not been elucidated. It has also been reported that long fibers translocate  
269 from interstitial spaces to pleural spaces via lymphatic stomata, resulting in black spots and  
270 possibly leading to benign and malignant local pleural changes modifications <sup>30,31</sup>. All short-  
271 term inhalation measurements on long fibers indicate that RCF is significantly less biopersistent  
272 than amphibole asbestos but more biopersistent than other (but not all) MWFs <sup>32</sup>. Some chronic  
273 inhalation studies have also reported longer biopersistence for RCF compared to most MWF,  
274 associated with the length of the fibers, although discordant results have been reported by  
275 various studies <sup>33</sup>. Finally, Lockey et al. also reported that RCF can persist in human lung tissue  
276 for up to 20 years in 7 formerly exposed subjects <sup>34</sup>. Despite the lack of studies, these  
277 experimental findings do not invalidate the possibility of either a specific association between  
278 RCF and MWF with pleural plaques or a possible modifier effect of asbestos alone, even if the  
279 evidence is weaker for MWF.

280

### 281 **Interpretation**

282 Our study reported dose-response relationships between exposure to RCF, MWF and the  
283 presence of pleural plaques, after controlling for asbestos exposure, in a large cohort of asbestos  
284 exposed workers assessed by CT-Scan. Moreover, we also suggest the existence of a modifier  
285 effect of these two mineral particles on the relationships between asbestos exposure and the risk

286 of pleural plaques. No such results were observed with silica. A review of the sparse literature  
287 also supports these two findings, from both the epidemiological or experimental points of view.  
288 However, co-exposure to asbestos among these subjects, did not allow us to have definite  
289 conclusions, despite advanced statistical analyses. If confirmed, our findings encourage  
290 clinicians to assess previous exposure to asbestos but also MWF or RCF, and consider diagnosis  
291 of pleural plaques, beside an asbestos exposure but also for the two others fibers, alone or in  
292 combination. Moreover, compensation for these patients have to be discussed.

293

294

Journal Pre-proof



295 **Acknowledgments**

296 The study was approved by the hospital ethics committee (CPPRB Paris-Cochin n°1946 (2002),  
297 CPP Ile De France III n°1946/11/02-02 (2010)). All participants received information about the  
298 study and gave their written informed consent.

299

300 Author Contributions:

301 Study concept and design : CP, FL, PB, JCP, Acquisition of data : CP, IT, FL, PB, SC, BC, NF,  
302 GF, AG, Analysis and interpretation of data : CP, IT, FL, PA, PB, AG, AL, JCP, First draft of  
303 the manuscript : CP, JCP, Critical revision of the manuscript for important intellectual content :  
304 CP, IT, FL, AS, PA, PB, BC, NF, GF, PW, AL, JCP, statistical analysis : CP, CG, AL, Obtained  
305 funding : CP, JCP, Study supervision : CP, JCP, Full access to all data and final responsibility  
306 for the decision to submit for publication : CP, JCP, guarantor of the content of the manuscript  
307 and data analysis: CP

308

309 All authors declared no conflict of interest

310

311 Take-home Points:

312

313 Study question: Does the risk of pleural plaques increase with cumulative exposure to RCF,  
314 MWF and silica ? and if yes, do these dose-response relationships depend on the co-exposure  
315 to asbestos or conversely, do the dose-response relationships for asbestos were modified by co-  
316 exposure to RCF, MWF and silica ?

317 Results: Exposure to RCF and MWF were associated with the prevalence of pleural plaques,  
318 after adjustment for asbestos exposure. A significant interaction was observed between  
319 exposure to RCF and MWF and exposure to asbestos, as well as a modifier effect of dose-  
320 response relationships between pleural plaques and asbestos in presence of an exposure to RCF  
321 and MWF.

322 Interpretation: If confirmed, our findings encourage clinicians to assess previous exposure to  
323 asbestos but also MWF or RCF, and consider diagnosis of pleural plaques, beside an asbestos  
324 exposure but also for the two others fibers, alone or in combination

325

326

327

328

Journal Pre-proof

329 **References**

- 330
- 331 1. Churg A. Asbestos fibers and pleural plaques in a general autopsy population. *Am J*  
332 *Pathol.* 1982;109(1):88-96.
- 333 2. Paris C, Thierry S, Brochard P, et al. Pleural plaques and asbestosis: dose- and time-  
334 response relationships based on HRCT data. *Eur Respir J.* 2009;34(1):72-79.
- 335 3. Karjalainen A, Karhunen PJ, Lalu K, et al. Pleural plaques and exposure to mineral  
336 fibres in a male urban necropsy population. *Occup Environ Med.* 1994;51(7):456-460.
- 337 4. Weill H, Hughes JM, Hammad YY, Glindmeyer HW, Sharon G, Jones RN.  
338 Respiratory health in workers exposed to man-made vitreous fibers. *Am Rev Respir*  
339 *Dis.* 1983;128(1):104-112.
- 340 5. Järholm B, Hillerdal G, Järliden AK, et al. Occurrence of pleural plaques in workers  
341 with exposure to mineral wool. *Int Arch Occup Environ Health.* 1995;67(5):343-346.
- 342 6. De Vuyst P, Dumortier P, Swaen GM, Pairon JC, Brochard P. Respiratory health  
343 effects of man-made vitreous (mineral) fibres. *Eur Respir J.* 1995;8(12):2149-2173.
- 344 7. LeMasters G, Lockey JE, Hilbert TJ, et al. A 30-year mortality and respiratory  
345 morbidity study of refractory ceramic fiber workers. *Inhal Toxicol.* 2017;29(10):462-  
346 470.
- 347 8. Lacourt A, Rinaldo M, Gramond C, et al. Co-exposure to refractory ceramic fibres and  
348 asbestos and risk of pleural mesothelioma. *Eur Respir J.* 2014;44(3):725-733.
- 349 9. Paris C, Thierry S, Brochard P, et al. Pleural plaques and asbestosis: dose- and time-  
350 response relationships based on HRCT data. *European Respiratory Journal.*  
351 2009;34(1):72-79.
- 352 10. Pairon JC, Laurent F, Rinaldo M, et al. Pleural plaques and the risk of pleural  
353 mesothelioma. *J Natl Cancer Inst.* 2013;105(4):293-301.
- 354 11. Ameille J, Letourneux M, Paris C, et al. Does Asbestos Exposure Cause Airway  
355 Obstruction, in the Absence of Confirmed Asbestosis? *American Journal of*  
356 *Respiratory and Critical Care Medicine.* 2010;182(4):526-530.
- 357 12. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J.  
358 Fleischner Society: glossary of terms for thoracic imaging. *Radiology.*  
359 2008;246(3):697-722.
- 360 13. Beigelman-Aubry C, Ferretti G, Mompont D, et al. [Computed tomographic atlas of  
361 benign asbestos related pathology]. *J Radiol.* 2007;88(6):845-862.
- 362 14. Lacourt A, Gramond C, Audignon S, et al. Pleural mesothelioma and occupational  
363 coexposure to asbestos, mineral wool, and silica. *Am J Respir Crit Care Med.*  
364 2013;187(9):977-982.
- 365 15. Bouyer J, Dardenne J, Hémon D. Performance of odds ratios obtained with a job-  
366 exposure matrix and individual exposure assessment with special reference to  
367 misclassification errors. *Scand J Work Environ Health.* 1995;21(4):265-271.
- 368 16. Michels KB, Bingham SA, Luben R, Welch AA, Day NE. The effect of correlated  
369 measurement error in multivariate models of diet. *Am J Epidemiol.* 2004;160(1):59-  
370 67.
- 371 17. Kilburn KH, Powers D, Warshaw RH. Pulmonary effects of exposure to fine  
372 fibreglass: irregular opacities and small airways obstruction. *Br J Ind Med.*  
373 1992;49(10):714-720.
- 374 18. Lockey J, Lemasters G, Rice C, et al. Refractory ceramic fiber exposure and pleural  
375 plaques. *Am J Respir Crit Care Med.* 1996;154(5):1405-1410.
- 376 19. Cowie HA, Wild P, Beck J, et al. An epidemiological study of the respiratory health of  
377 workers in the European refractory ceramic fibre industry. *Occup Environ Med.*  
378 2001;58(12):800-810.

- 379 20. Bernstein DM. Synthetic vitreous fibers: a review toxicology, epidemiology and  
380 regulations. *Crit Rev Toxicol.* 2007;37(10):839-886.
- 381 21. Gelzleichter TR, Bermudez E, Mangum JB, et al. Comparison of pulmonary and  
382 pleural responses of rats and hamsters to inhaled refractory ceramic fibers. *Toxicol Sci.*  
383 1999;49(1):93-101.
- 384 22. Everitt JI, Gelzleichter TR, Bermudez E, et al. Comparison of pleural responses of rats  
385 and hamsters to subchronic inhalation of refractory ceramic fibers. *Environ Health*  
386 *Perspect.* 1997;105 Suppl 5:1209-1213.
- 387 23. Mast RW, Hesterberg TW, Glass LR, McConnell EE, Anderson R, Bernstein DM.  
388 Chronic inhalation and biopersistence of refractory ceramic fiber in rats and hamsters.  
389 *Environ Health Perspect.* 1994;102 Suppl 5:207-209.
- 390 24. McConnell EE, Axten C, Hesterberg TW, et al. Studies on the inhalation toxicology of  
391 two fiberglasses and amosite asbestos in the Syrian golden hamster. Part II. Results of  
392 chronic exposure. *Inhal Toxicol.* 1999;11(9):785-835.
- 393 25. Davis JM, Jones AD, Miller BG. Experimental studies in rats on the effects of  
394 asbestos inhalation coupled with the inhalation of titanium dioxide or quartz. *Int J Exp*  
395 *Pathol.* 1991;72(5):501-525.
- 396 26. Bellmann B, Muhle H, Creutzenberg O, Ernst H, Brown RC, Sébastien P. Effects of  
397 nonfibrous particles on ceramic fiber (RCF1) toxicity in rats. *Inhal Toxicol.*  
398 2001;13(10):877-901.
- 399 27. Davis JM. Mixed fibrous and non-fibrous dust exposures and interactions between  
400 agents in fibre carcinogenesis. *IARC Sci Publ.* 1996(140):127-135.
- 401 28. Brown RC, Bellmann B, Muhle H, Davis JM, Maxim LD. Survey of the biological  
402 effects of refractory ceramic fibres: overload and its possible consequences. *Ann*  
403 *Occup Hyg.* 2005;49(4):295-307.
- 404 29. Broaddus VC, Everitt JI, Black B, Kane AB. Non-neoplastic and neoplastic pleural  
405 endpoints following fiber exposure. *J Toxicol Environ Health B Crit Rev.* 2011;14(1-  
406 4):153-178.
- 407 30. Boutin C, Dumortier P, Rey F, Viallat JR, De Vuyst P. Black spots concentrate  
408 oncogenic asbestos fibers in the parietal pleura. Thoracoscopic and mineralogic study.  
409 *Am J Respir Crit Care Med.* 1996;153(1):444-449.
- 410 31. Donaldson K, Murphy FA, Duffin R, Poland CA. Asbestos, carbon nanotubes and the  
411 pleural mesothelium: a review of the hypothesis regarding the role of long fibre  
412 retention in the parietal pleura, inflammation and mesothelioma. *Part Fibre Toxicol.*  
413 2010;7:5.
- 414 32. Utell MJ, Maxim LD. Refractory ceramic fiber (RCF) toxicity and epidemiology: a  
415 review. *Inhal Toxicol.* 2010;22(6):500-521.
- 416 33. IARC. *Man-Made Vitreous Fibres.* Vol 81. Lyon: IARC Press; 2002.
- 417 34. Lockey JE, Roggli VL, Hilbert TJ, et al. Biopersistence of refractory ceramic fiber in  
418 human lung tissue and a 20-year follow-up of radiographic pleural changes in  
419 workers. *J Occup Environ Med.* 2012;54(7):781-788.

420  
421

422

423 **Table 1.** General characteristics of subjects according to the presence of pleural plaques on CT-  
 424 scan (APExS, n=5,457)

	No pleural plaques (4355) n (%)	Pleural plaques (1102) n (%)	P value
Age (years) <sup>1</sup>	62.5 (5.6)	65.2 (6.1)	<0.0001
Gender			
Male	4147 (79.4)	1078 (20.6)	<0.0001
Female	208 (89.7)	24 (10.3)	
Smoking status			
Non smokers	1208 (85.1)	211 (14.9)	<0.0001
Former smokers	2495 (77.0)	747 (23.0)	
Smokers	306 (78.9)	82 (21.1)	
Unknown smoking status	346 (84.8)	62 (15.2)	

425 <sup>1</sup>: mean (SD)

426

**Table 2.** Risk of pleural plaques with absence/presence of Mineral Wool Fibers (MWF), Refractory Ceramic Fibers (RCF) and silica exposures, adjusted for smoking status and age (model a) and cumulative exposure to asbestos (model b) (APEXS, n=5,457, 1,102 with pleural plaques)

	Model a <sup>1</sup>		Model b <sup>2</sup>	
	OR [95% CI]	P value	OR [95% CI]	P value
<b>Asbestos</b>				
CEI (eq. f/mL.years) <sup>3,4</sup>				
Q1	reference			
Q2	1.38 [1.09-1.74]			
Q3	2.32 [1.87-2.88]			
Q4	4.75 [3.87-5.83]	<0.0001		
<b>MWF (f/mL.years) <sup>4,5</sup></b>				
Non-exposed	reference		reference	
Exposed (yes)	1.67 [1.42-1.96]	<0.0001	1.44 [1.22-1.70]	<0.0001
Q1	1.11 [0.89-1.39]		1.17 [0.93-1.48]	
Q2	1.40 [1.12-1.73]		1.25 [1.00-1.55]	
Q3	1.78 [1.45-2.19]		1.51 [1.22-1.86]	
Q4	2.59 [2.11-3.17]	<0.0001	1.84 [1.49-2.27]	<0.0001
<b>RCF (f/mL.years) <sup>4,5</sup></b>				
Non-exposed	reference		reference	
Exposed (yes)	1.34 [1.15-1.55]	<0.0001	1.11 [0.96-1.30]	0.170
Q1	0.80 [0.60-1.07]		0.80 [0.59-1.08]	
Q2	1.52 [1.20-1.94]		1.15 [0.90-1.47]	
Q3	1.40 [1.08-1.83]		1.22 [0.93-1.60]	
Q4	1.73 [1.35-2.22]	<0.0001	1.29 [1.00-1.67]	0.054
<b>Silica (mg/m<sup>3</sup>.years) <sup>4,5</sup></b>				
Non-exposed	reference		reference	
Exposed (yes)	1.13 [0.98-1.29]	0.091	1.16 [1.01-1.34]	0.037
Q1	1.06 [0.86-1.31]		1.06 [0.85-1.31]	
Q2	1.08 [0.88-1.34]		1.12 [0.90-1.39]	
Q3	1.26 [1.03-1.54]		1.32 [1.08-1.62]	
Q4	1.10 [0.90-1.35]	0.269	1.16 [0.94-1.44]	0.104

<sup>1</sup>: logistic regression models for each exposure to asbestos, RCF, MWF and silica, adjusted for age and smoking status. Category (yes/no or quartiles CEI) were analyzed separately

<sup>2</sup>: logistic regression models for each exposure to RCF, MWF and silica, adjusted for age, smoking status and asbestos exposure. Categories (yes/no or quartiles CEI) were analyzed separately

<sup>3</sup>: exposure assessed by industrial hygienists

<sup>4</sup>: Expressed as quartiles, for asbestos: Q1=[0-3.70], Q2=[3.70-26.73], Q3=[26.73-48.08], Q4=[≥48.08]; for MWF: Q1=[0-0.032], Q2=[0.032-0.231], Q3=[0.231-1.270], Q4=[≥1.270]; for RCF: Q1=[0-0.006], Q2=[0.006-0.035], Q3=[0.035-0.342], Q4=[≥0.342]; for silica: Q1=[0-0.081], Q2=[0.081-0.369], Q3=[0.369-1.435], Q4=[≥1.435].

<sup>5</sup>: exposure assessed by Job-Exposure Matrices; all non-null probability of exposure were considered as exposed

**Table 3.** Risk of pleural plaques according to cumulative exposure to asbestos, Mineral Wool Fibers (MWF), Refractory Ceramic Fibers (RCF) and silica (APEXS, n=5,457, 1,102 with pleural plaques)

	Model a <sup>1</sup>		Model b <sup>2</sup>	
	OR [95%CI] <sup>1</sup>	P value	OR [95%CI]	P value
Asbestos <sup>3</sup>				
Log (CEI + 1)	1.37 [1.31-1.44]	<0.0001	1.39 [1.33-1.45]	<0.0001
MWF <sup>4</sup>				
Log (CEI + 1)	1.41 [1.30-1.54]	<0.0001		
Log (CEI +1)a <sup>-5</sup>	-	-	0.98 [0.76-1.27]	0.893
Log (CEI +1)a <sup>+5</sup>	-	-	1.44 [1.32-1.57]	<0.0001
RCF <sup>4</sup>				
Log (CEI + 1)	0.83 [0.65-1.06]	0.131	0.97 [0.77-1.23]	0.796
Silica <sup>4</sup>				
Log (CEI +1)	1.11 [1.00-1.23]	0.054	1.10 [0.99-1.22]	0.069

<sup>1</sup>: logistic regression model, adjusted for age and smoking status and cumulative exposures to asbestos, MWF, RCF and silica

<sup>2</sup>: logistic regression models, adjusted for age, smoking status and cumulative exposures to asbestos, RCF, silica and MWF CEI according to asbestos CEI dichotomized on the median value; Interaction term P value = 0.002

<sup>3</sup>: exposure assessed by industrial hygienists

<sup>4</sup>: exposure assessed by Job-Exposure Matrices; all non-null probability of exposure were considered as exposed

<sup>5</sup> Log (CEI +1)a<sup>-</sup>: MWF CEI in subjects with an asbestos CEI < median value, Log (CEI +1)a<sup>+</sup>: MWF CEI in subjects with an asbestos CEI ≥ median value,

Table 4. Risk of pleural plaques according to cumulative exposure to asbestos, by category of exposure (no/yes) to Mineral Wool Fibers (MWF), Refractory Ceramic Fibers (RCF) and silica (APExS, n=5,457, 1,102 with pleural plaques)

	Non-exposed to MWF <sup>1</sup>		Exposed to MWF <sup>1</sup>	
	OR [95%CI] <sup>2</sup>	P value	OR [95%CI] <sup>2</sup>	P value
Asbestos CEI (eq. f/mL.years) <sup>3,4</sup>				
Q1	reference		reference	
Q2	1.08 [0.74-1.59]		1.48 [1.15-3.84]	
Q3	1.21 [0.81-1.79]		2.48 [1.95-3.07]	
Q4	3.68 [2.73-4.97]	<0.0001	5.28 [4.24-6.59]	<0.0001
	Non-exposed to RCF <sup>1</sup>		Exposed to RCF <sup>1</sup>	
	OR [95%CI] <sup>2</sup>	P value	OR [95%CI] <sup>2</sup>	P value
Asbestos CEI (eq. f/mL.years) <sup>3,4</sup>				
Q1	reference		reference	
Q2	1.38 [1.07-1.77]		1.38 [0.96-1.98]	
Q3	2.11 [1.64-2.70]		2.26 [1.72-2.95]	
Q4	4.30 [3.43-5.39]	<0.0001	6.28 [4.80-8.23]	<0.0001
	Non-exposed to Silica <sup>1</sup>		Exposed to Silica <sup>1</sup>	
	OR [95%CI] <sup>2</sup>	P value	OR [95%CI] <sup>2</sup>	P value
Asbestos CEI (eq. f/mL.years) <sup>3,4</sup>				
Q1	reference		reference	
Q2	1.19 [0.86-1.65]		1.47 [1.15-1.93]	
Q3	1.90 [1.42-2.56]		2.31 [1.82-2.93]	
Q4	4.57 [3.58-5.83]	<0.0001	5.10 [4.02-6.47]	<0.0001

<sup>1</sup>: exposure assessed by Job-Exposure Matrices; all non-null probability of exposure were considered as exposed

<sup>2</sup> logistic regression models, adjusted for age and smoking status

<sup>3</sup>: exposure assessed by industrial hygienists

<sup>4</sup>: Expressed as quartiles, for asbestos: Q1=]0-3.70], Q2=]3.70-26.73], Q3= ]26.73-48.08], Q4=]≥48.08];



Table 5. Risk of pleural plaques according to cumulative exposure to asbestos in the whole cohort and cumulative exposure to asbestos in subjects exposed to MWF, RCF or silica used as an interaction term (APExS, n=5,457, 1,102 with pleural plaques)

		Model <sup>1</sup>	
		OR [95%CI]	P value
MWF			
	Log (CEI <sub>a</sub> +1) <sup>2</sup>	1.34 [1.26-1.41]	<0.0001
	Log [(CEI <sub>a</sub> /MWF+)+1] <sup>3</sup>	1.11 [1.06-1.15]	<0.0001
RCF			
	Log (CEI <sub>a</sub> +1) <sup>2</sup>	1.41 [1.35-1.49]	<0.0001
	Log [(CEI <sub>a</sub> / RCF+)+1] <sup>3</sup>	1.05 [1.01-1.09]	0.018
Silica			
	Log (CEI <sub>a</sub> +1) <sup>2</sup>	1.42 [1.36-1.49]	<0.0001
	Log [(CEI <sub>a</sub> ) / Silica+)+1] <sup>3</sup>	1.03 [0.99-1.07]	0.132

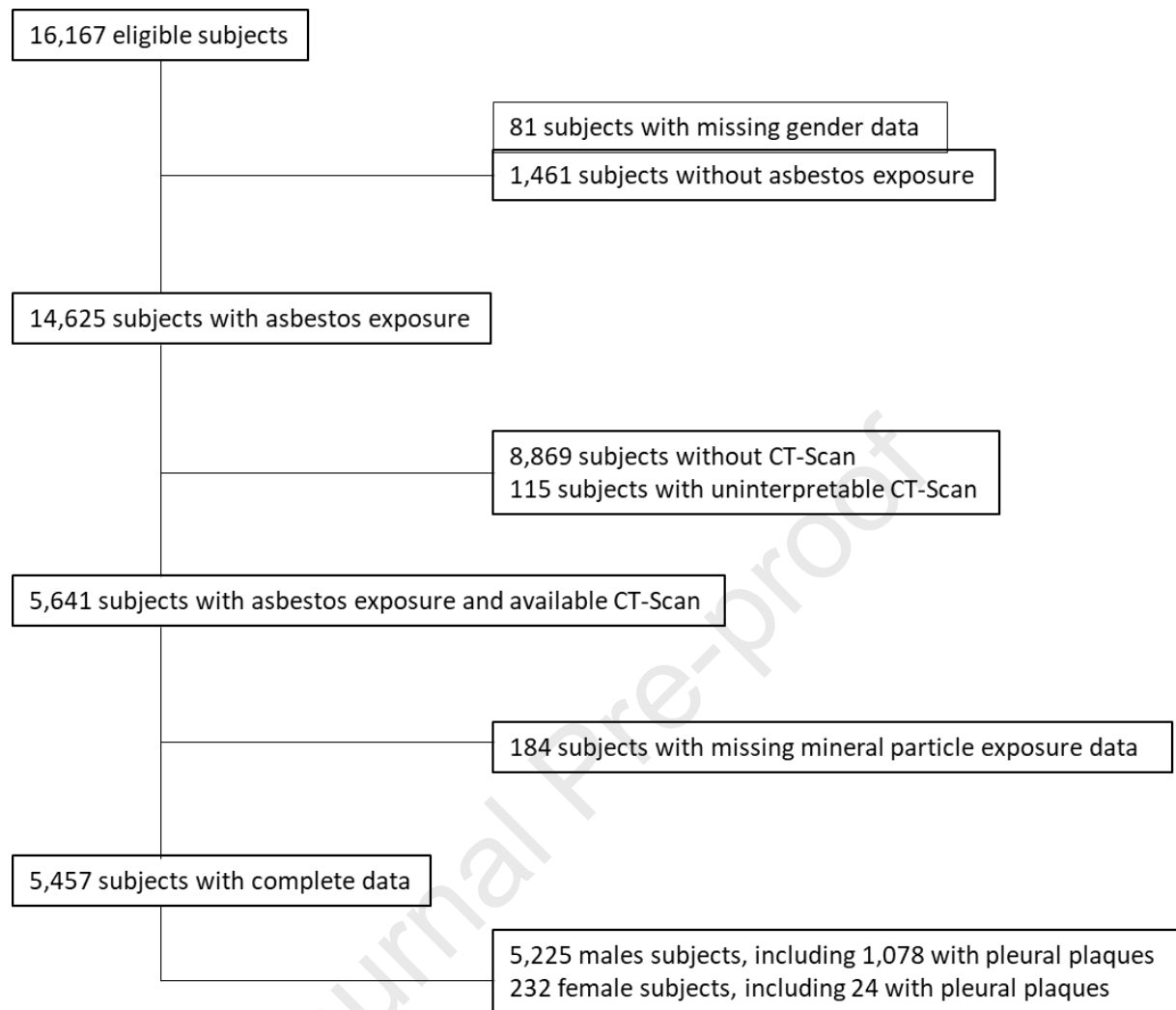
*CEI<sub>a</sub>: asbestos cumulative exposure index in the whole cohort; CEI<sub>a</sub> / MWF+: asbestos cumulative exposure index in subjects exposed to MWF; CEI<sub>a</sub> / RCF+: asbestos cumulative exposure index in subjects exposed to RCF; CEI<sub>a</sub> / Silica+: asbestos cumulative exposure index in subjects exposed to silica;*

<sup>1</sup>: Logistic regression models, adjusted for age and smoking status

<sup>2</sup>: exposure assessed by industrial hygienists

<sup>3</sup>: exposure assessed by Job-Exposure Matrices (JEM), probability of exposure  $\geq 1\%$

Journal Pre-proof

**Figure 1. Flow-chart of the study**

### **Conflict of interest**

Christophe Paris has nothing to disclose  
Isabelle Thaon has nothing to disclose  
François Laurent has nothing to disclose  
Anastasia Saade has nothing to disclose  
Pascal Andujar has nothing to disclose  
Patrick Brochard has nothing to disclose  
Julia Benoist has nothing to disclose  
Benedicte Clin has nothing to disclose  
Gilbert Ferretti has nothing to disclose  
Antoine Gislard has nothing to disclose  
Celine Gramond has nothing to disclose  
Pascal Wild has nothing to disclose  
Aude Lacourt has nothing to disclose  
Fleur Delva has nothing to disclose  
Jean-Claude Pairon has nothing to disclose

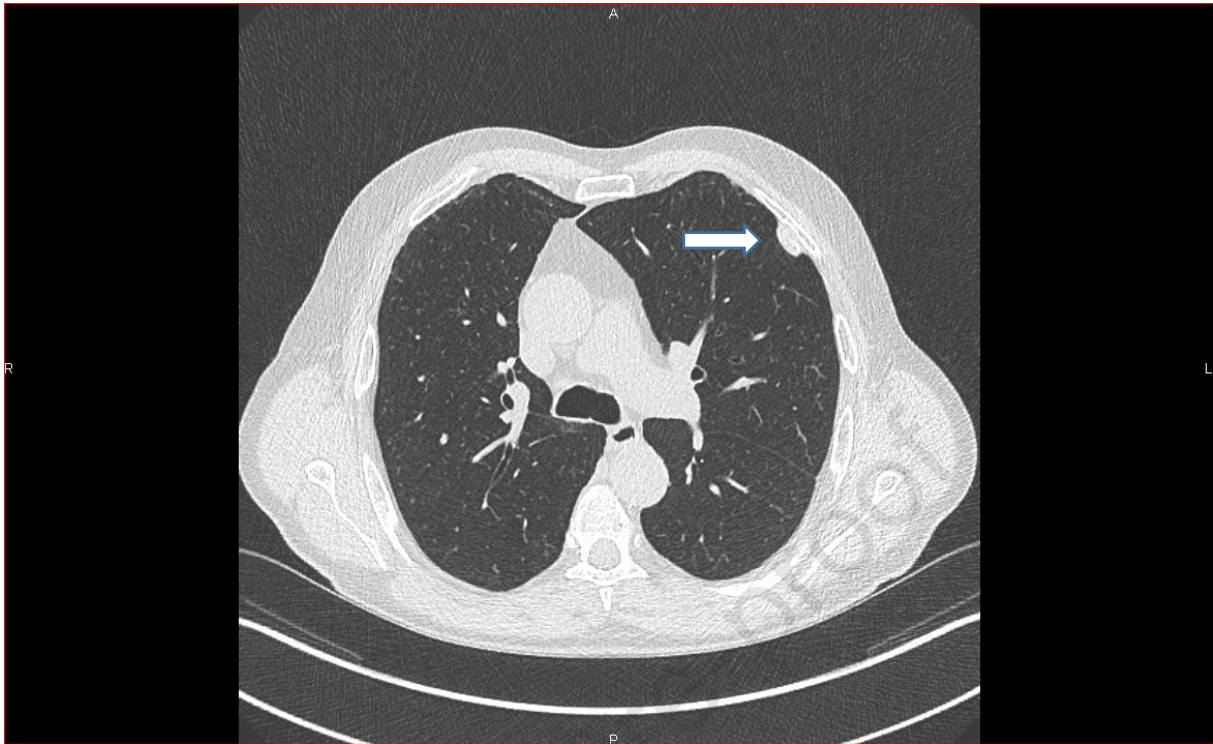
Journal Pre-proof

**Supplementary Methods.**

Using full work history, industrial hygienists coded the dates and duration (years) of exposure for each job associated with asbestos exposure. Intensity of asbestos exposure, expressed as equivalent fibers/mL, was then coded as low or passive exposure: 0.01; intermediate: 0.1; high intermediate: 1; high: 10). An individual cumulative exposure index (CEI) was then calculated as the sum of each duration x intensity product for each exposed job throughout each subject's working life. Owing to the absence of atmospheric measurements and the lack of detailed information on exposure frequency (percentage of working time), the asbestos CEI is expressed in equivalent  $f/ml \times years$  (eq.  $f/ml.y$ ).

Exposures to MWF and RCF as well as silica were assessed by using job-exposure matrices in the "MATGENE" program [35], after coding each occupation / activity pair by means of International Standard Classification of Occupations (ISCO) 1968 and "Nomenclature des Activités Françaises" (NAF) 2000 codes. A non-null probability of exposure was retained to define the presence of exposure to these three agents. Similarly to asbestos, a CEI was then calculated for each subject, based on the period, probability, estimated level and duration of exposure. These CEI were expressed as fibers/mL.years for MWF and RCF and as  $mg/m^3.years$  for silica.

## Supplementary Figure 1. Example of pleural plaque



Pleural plaques (arrow) were defined as circumscribed, quadrangular, pleural elevations, with clearly demarcated borders and tissue density, sometimes calcified, presenting a typical topography, at least on some of the images (see Beigelman-Aubry C, Ferretti G, Mompoin D, et al. Computed tomographic atlas of benign asbestos related pathology. *J Radiol.* 2007;88(6):845-862.

**Supplementary Table E1.** Characteristics of exposure to Asbestos, Mineral Wool Fibers (MWF), Refractory Ceramic Fibers (RCF) and silica according to the presence of pleural plaques on CT-scan (APEXS, n=5,457)

	Overall (5457)	No pleural plaques (4355) n (%)	Pleural plaques (1102) n (%)	P value
<b>Asbestos</b>				
Duration (years) <sup>1</sup>		34.8 (8.3)	36.2 (7.5)	<0.0001
CEI (eq. f/mL.years) <sup>2,3</sup>		55.8 (92.5)	111.0 (125.7)	<0.0001
Q1		1235 (89.6)	143 (10.4)	
Q2		1165 (86.2)	186 (13.8)	
Q3		1075 (78.8)	289 (21.2)	
Q4		880 (64.5)	484 (35.5)	<0.0001
<b>MWF</b>				
Exposure (yes)	3827 (70.1)	2958 (77.3)	869 (22.7)	<0.0001
Duration (years) <sup>1</sup>		24.1 (13.9)	26.8 (14.2)	<0.0001
CEI (f/mL.years) <sup>3,4</sup>		2.2 (11.4)	7.7 (25.5)	<0.0001
Non-Exposed		1397 (85.7)	233 (14.3)	
Q1		795 (83.3)	160 (16.7)	
Q2		770 (80.3)	189 (19.7)	
Q3		710 (74.2)	247 (25.8)	
Q4		683 (71.4)	273 (28.6)	<0.0001
<b>RCF</b>				
Exposure (yes)	1512 (27.7)	1166 (77.1)	346 (22.9)	0.002
Duration (years) <sup>1</sup>		13.4 (7.3)	11.8 (6.8)	0.0006
CEI (f/mL.years) <sup>3,4</sup>		0.51 (1.61)	0.82 (2.5)	0.006
Non-Exposed		3189 (80.8)	756 (19.2)	
Q1		319 (84.4)	59 (15.6)	
Q2		309 (74.5)	106 (25.5)	
Q3		258 (75.7)	83 (24.3)	
Q4		280 (74.1)	98 (25.9)	<0.0001
<b>Silica</b>				
Exposure (yes)	3130 (57.4)	2468 (78.9)	662 (21.1)	0.041
Duration (years) <sup>1</sup>		22.8 (14.3)	23.8 (14.6)	0.143
CEI (mg/m <sup>3</sup> .years) <sup>3,4</sup>		1.77 (4.6)	2.9 (9.2)	<0.0001
Non-Exposed		1887 (81.1)	440 (18.9)	
Q1		642 (81.5)	157 (19.5)	
Q2		615 (80.3)	151 (19.7)	
Q3		596 (76.1)	187 (23.9)	
Q4		615 (78.6)	167 (21.4)	0.040

<sup>1</sup>: mean (SD)<sup>2</sup> exposure assessed by industrial hygienists<sup>3</sup>: Expressed as quartiles, for asbestos: Q1=[0-3.70], Q2=[3.70-26.73], Q3=[26.73-48.08], Q4=[≥48.08]; for MWF: Q1=[0-0.032], Q2=[0.032-0.231], Q3=[0.231-1.270], Q4=[≥1.270]; for RCF: Q1=[0-0.006], Q2=[0.006-0.035], Q3=[0.035-0.342], Q4=[≥0.342]; for silica: Q1=[0-0.081], Q2=[0.081-0.369], Q3=[0.369-1.435], Q4=[≥1.435].

<sup>4</sup>: *exposure assessed by Job-Exposure Matrices; all non-null probability of exposure were considered as exposed*

Supplementary Table 2. Correlation coefficients between CEI to asbestos, MWF, RCF and silica

	Asbestos	MWF	RCF	Silica
Asbestos	1.00			
MWF	0.60	1.00		
RCF	0.58	0.58	1.00	
Silica	0.07	-0.02	0.88	1.00