



**HAL**  
open science

## **Occupational exposure to unintentionally emitted nanoscale particles and risk of cancer from lung to central nervous system - results from three French case-control studies**

Guyguy Manangama, Céline Gramond, Sabyne Audignon-Durand, Isabelle Baldi, Pascale Fabro-Peray, Annabelle Gilg Soit Ilg, Pascal Guénel, Pierre Lebailly, Danièle Luce, Isabelle Stücker, et al.

### ► **To cite this version:**

Guyguy Manangama, Céline Gramond, Sabyne Audignon-Durand, Isabelle Baldi, Pascale Fabro-Peray, et al.. Occupational exposure to unintentionally emitted nanoscale particles and risk of cancer from lung to central nervous system - results from three French case-control studies. *Environmental Research*, 2020, 191, pp.110024. 10.1016/j.envres.2020.110024 . hal-02930142

**HAL Id: hal-02930142**

**<https://hal.science/hal-02930142>**

Submitted on 11 Sep 2020

**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.

**Credit author statement**

Guyguy Manangama : Writing - Review & Editing

Céline Gramond : Formal analysis, Writing - Review & Editing

Sabyne Audignon-Durand : Resources, Writing - Review & Editing

Isabelle Baldi : Resources, Writing - Review & Editing

Pascale Fabro-Peray : Resources, Writing - Review & Editing

Annabelle Gilg Soit Ilg : Resources, Writing - Review & Editing

Pascal Guénel : Resources, Writing - Review & Editing

Pierre Lebailly : Resources, Writing - Review & Editing

Danièle Luce : Resources, Writing - Review & Editing

Isabelle Stücker : Resources, Writing - Review & Editing

Patrick Brochard : Conceptualization, Funding acquisition, Writing - Review & Editing

Aude Lacourt : Conceptualization, Methodology, Supervision, Writing - Original Draft,

Writing - Review & Editing

1 **Occupational exposure to unintentionally emitted nanoscale particles and risk of cancer: from**  
2 **lung to central nervous system - results from three French case-control studies**

3 Guyguy Manangama<sup>1</sup>, Céline Gramond<sup>1</sup>, Sabyne Audignon-Durand<sup>1</sup>, Isabelle Baldi<sup>1</sup>, Pascale Fabro-  
4 Peray<sup>2</sup>, Annabelle Gilg Soit Ilg<sup>3</sup>, Pascal Guénel<sup>4</sup>, Pierre Lebailly<sup>5</sup>, Danièle Luce<sup>6</sup>, Isabelle Stücker<sup>4</sup>,  
5 Patrick Brochard<sup>1</sup>, Aude Lacourt<sup>1\*</sup>

6 <sup>1</sup> Univ. Bordeaux, Inserm, Bordeaux Population Health Research Center, Epicene team, UMR 1219,  
7 F-33000 Bordeaux, France

8 <sup>2</sup> CHU Nîmes, BESPIM, F-30029 Nîmes, France

9 <sup>3</sup> Santé publique France, Direction Santé Travail, F-94415, Saint-Maurice cedex, France

10 <sup>4</sup> Centre de recherche en Epidémiologie et Santé des Populations (CESP), Cancer and Environment  
11 team, Université Paris-Sud, Université Paris-Saclay, F-94800, Villejuif, France

12 <sup>5</sup> ANTICIPE, U1086 INSERM, Université de Caen Normandie, and Centre de Lutte Contre le Cancer  
13 François Baclesse, F-14000 Caen, France

14 <sup>6</sup> Université de Rennes, Inserm, EHESP, Irset (Institut de Recherche en Santé, Environnement et  
15 Travail) - UMR\_S 1085, Pointe-à-Pitre, France

16 **CORRESPONDING AUTHOR**

17 Aude Lacourt

18 Tel: +33 5 57 57 16 23

19 Fax: +33 5 57 57 47 33

20 aude.lacourt@inserm.fr

21

1 **ABSTRACT**

2 **Objectives:** Nanoscale particles (1-100 nm) can be of natural origin, and either intentionally or  
3 unintentionally produced by human activities. Toxicological data have suggested a possible  
4 carcinogenic effect of such particles. The aim of this study was to estimate the association between  
5 occupational exposure to nanoscale particles and risk of lung cancer, pleural mesothelioma and brain  
6 tumors in adults.

7 **Methods:** Three French population-based case-control studies were analyzed: 1) the ICARE study  
8 including 2,029 lung cancer cases and 2,591 controls; 2) the PNSM study including 371 pleural  
9 mesothelioma cases and 730 controls and 3) the CERENAT study including 257 brain tumor cases and  
10 511 controls. Occupational exposure to unintentionally emitted nanoscale particles (UNPs) was  
11 retrospectively assessed by a job exposure matrix providing a probability and a frequency of exposure.

12 **Results:** In adjusted analyses among men, significant associations between occupational exposure to  
13 UNPs and lung cancer (OR=1.51; 95% CI: 1.22-1.86 and brain tumors (OR=1.69; 95% CI: 1.17-2.44)  
14 were observed. No increased OR was observed for pleural mesothelioma (OR=0.78; 95% CI: 0.46-  
15 1.33).

16 **Conclusion:** This is the first study showing positive associations between occupational exposure to  
17 UNPs and increased risk of lung cancer and brain tumors. These preliminary results should encourage  
18 further epidemiological research.

19

20 **Keywords:** cancer; lung; central nervous system; occupational exposure; unintentionally emitted  
21 nanoscale particles.

22

23

1

2

3 Funding sources: INCA – grant number SHSESP11-061

4

5

Journal Pre-proof

## 1        1. Introduction

2        Particulate matter (mainly PM<sub>2.5</sub>) in outdoor air pollution has been classified by IARC (the  
3        International Agency for Research on Cancer) as carcinogenic to humans, with sufficient evidence for  
4        lung cancer (Loomis et al., 2014). The composition of particulate matter aerosol is complex in terms  
5        of particle size range and chemical composition and it is still unclear whether the observed adverse  
6        human's health effect should be attributed to a specific particle size range (Stone et al., 2017;  
7        Wichmann et al., 2000).

8        Among more complex definition, nanoscale particles (NPs) may be defined as particles with at least  
9        one dimension in the size range 1 nm-100 nm. They may be naturally occurring (from volcano ashes,  
10        wild fires), unintentionally produced from anthropogenic processes (combustions, welding, diesel  
11        engine exhaust) or intentionally produced for commercial purposes due to their physico-chemical  
12        properties (medicine, automobile industry, cosmetic industry, food processing industry, etc.)  
13        (Oberdorster et al., 2005).

14        Regarding their potential adverse health effects, NPs have demonstrated a higher toxicity and an  
15        increased biological reactivity compared to micron-sized particles of identical chemical composition  
16        and for an equivalent mass concentration (Stone et al., 2017). In terms of cancer endpoints, the  
17        toxicological mechanisms described have led to the hypothesis of a potential association between  
18        exposure to NPs and cancer occurrence (Donaldson and Poland, 2012). Indeed, once inhaled into the  
19        lungs, NPs trigger an inflammatory response within the lung but also a systematic response through  
20        the release of inflammatory mediators into the blood stream (Oberdorster et al., 2005). Besides  
21        inflammation, genotoxic effects have been documented following exposure to NPs, either directly  
22        through direct interaction with DNA or mitotic spindle apparatus or indirectly through oxidative  
23        damages (Donaldson et al., 2010b; Magaye et al., 2012; Magdolenova et al., 2014; Moller et al., 2014;  
24        Toyokuni, 2013). From carcinogenicity studies, the lung cancer hypothesis as well as the  
25        mesothelioma hypothesis have been put forward, especially those linked to multiwalled carbon  
26        nanotubes (Ju et al., 2017; Suzui et al., 2016). Finally, NPs may also translocate from the lungs to

1 different organs, including the brain, due to their capability to cross biological barriers, for instance the  
2 alveolar capillary barrier, placental barrier and the blood-brain barrier (Campagnolo et al., 2017; Elder  
3 and Oberdorster, 2006; Nakane, 2012; Nemmar et al., 2001; Oberdorster et al., 2005, 2002).  
4 Additionally, NPs may also reach the brain through the olfactory nerve (Oberdorster et al., 2009).

5 While epidemiological evidence of the carcinogenicity of NPs has been derived from particulate  
6 matter in outdoor air pollution studies (Beelen et al., 2014; Goldberg et al., 2017; Ostro et al., 2015;  
7 Weichenthal et al., 2020, 2017a, 2017b) or diesel exhaust engine emission studies (classified by IARC  
8 as carcinogenic to humans due to sufficient evidence for lung cancer), little is known regarding  
9 occupational exposures to nanoscale particles. Liou et al reviewed the first epidemiological studies  
10 related to nanomaterials and concluded that there was a lack of consistency between studies;  
11 nonetheless, the results suggested that occupational exposure to nanomaterials may have detrimental  
12 effects on human health (Liou et al., 2015). Same conclusions were drawn by Schulte et al in 2019  
13 (Schulte et al., 2019).

14 In addition, in the occupational setting, workers may be exposed to unintentionally emitted nanoscale  
15 particles in high concentrations, as compared to particulate matter exposure from outdoor air pollution  
16 among the general population, possibly conferring a high risk of cancer to certain occupational groups.  
17 We thus undertook the present analysis to assess the association between occupational exposure to  
18 unintentionally emitted nanoscale particles (UNPs) and cancer occurrence, and more specifically lung  
19 cancer, pleural mesothelioma and brain tumors.

## 20 2. Methods

### 21 2.1. Study populations

22 We analyzed three datasets from three population-based case-control studies which aimed at  
23 identifying environmental risk factors for lung cancer, pleural mesothelioma and brain tumors.

24 The lung cancer study (ICARE) was conducted between 2001 and 2007 in 10 French ‘departments’  
25 (administrative areas) and has been described in detail previously (Luce et al., 2011). In total, 2926

1 incident cases of histologically confirmed lung cancer (C33-C34 ICD-O) in consenting patients aged  
2 18 to 75 years were included in the study. Controls, frequency-matched to cases by sex, age (<40  
3 years, 40-54, 55-64,>65 years) and 'departments' of residence, were selected by list-assisted random  
4 digit dialing according to the incidence density sampling method.

5 The pleural mesothelioma study (PNSM), also previously described in detail (Rolland et al., 2010),  
6 included patients with incident pleural mesothelioma, following a standardized procedure for  
7 pathological and clinical confirmation of the diagnosis, between 1998 and 2002 in 19 'departments' of  
8 France. Two population controls were randomly selected from electoral lists and matched to each case  
9 for sex, age (+/- 5 years) and 'department' of residence.

10 Finally, the brain tumor study (CERENAT), previously described by Coureau et al. (Coureau et al.,  
11 2014), was conducted between 2004 and 2006 in four French 'departments'. Patients diagnosed with  
12 an incident benign or malignant CNS tumor were exhaustively identified from population-based  
13 cancer registries. Histological types were grouped into categories: gliomas, meningiomas, lymphomas  
14 and other unspecified primary brain tumors. For each case, two controls were randomly selected from  
15 the general population based on the electoral lists. Cases and controls were individually matched on  
16 age (+/- 2 years), sex and department of residence.

## 17 2.2. Data collection

18 Socio-demographic characteristics, residential history, personal and familial history of cancer, and  
19 detailed occupational history were collected in the three studies. Lifestyle characteristics (including  
20 detailed smoking history, alcohol consumption) were collected in the ICARE and CERENAT studies  
21 but not in the PNSM. Each study collected additional specific information related to the particular  
22 objectives of each study.

23 In all studies, lifetime occupational history was collected, including each job held for at least 6 months  
24 (one month for the ICARE study). As a minimum, the following information was recorded: job title,  
25 industrial branch, start year and end year, and description of main tasks.



### 2.3. Exposure assessment

Lifetime occupational exposure to UNPs was retrospectively assessed using a specific job exposure matrix (JEM) for unintentionally emitted nanoscale particles, the MatPUF JEM, developed by industrial hygienists between 2010 and 2014. Each step in the construction of this JEM, described below, was validated by a multidisciplinary panel of 23 experts from various disciplines (3 aerosol metrologists, 3 chemists, 7 industrial hygienists or risk assessment specialists, 8 occupational physicians and, or both toxicologists and 2 epidemiologists) who together had the necessary specific knowledge to understand UFP exposure assessments. In this JEM, UNPs were defined as 1-100 nm solid particles, unintentionally produced by human activities at work (Audignon-Durand S, Gramond C, Ducamp S, Manangama G, Garrigou A, Delva F, Brochard P, Lacourt A. Annals of work exposures and health. under review).”

Through an extensive literature review (more than 300 published articles dealing with metrological data, See supplementary table 1 for more details), sources of emissions at the workplace of UNPs were identified. These emission sources were linked to work processes that may have an impact on materials commonly worked with and which may lead to the emission of NPs. These work processes involved high temperatures, combustion, and mechanical processes with high energies. Overall, 57 work processes grouped into 9 major categories were considered as emitting UNPs (See supplementary table 2 for details).

For each work process, the chemical families of UNPs were categorized into 7 classes: 1-Metallic particles; 2- Mineral particles; 3-Carbon particles; 4-Polycyclic Aromatic Hydrocarbon (PAH) particles; 5-Polymer particles, mainly plastics; 6-Wood particles; 7-Other organic particles.

For each occupational code in the international standard classification of occupations, edition 1968 (ISCO-68), the industrial hygienists determined whether they involved at least one of the 57 previously defined work processes. Exposure parameters in terms of probability and frequency of exposure were then assessed for each combination of an occupation and a work process:

1 - The probability of exposure was defined as the proportion of workers who might be exposed to  
2 UNPs through the implementation of the work process among workers involved in that occupation.  
3 The probability of exposure was defined on a semi-quantitative scale and numerical values  
4 corresponding to the class center were assigned to each class (Table1).

5 - The frequency of exposure was defined as the proportion of working time during which the exposure  
6 occurred through the implementation of the work process in a typical 8-hr working day and in a  
7 typical working year. The frequency of exposure was defined on a semi-quantitative scale and  
8 numerical values corresponding to the class center were assigned (Table 1).

9 Due to the heterogeneity of quantitative data in terms of measurement protocols as well as  
10 concentration units (mass concentration, number concentration, surface area concentration) and the  
11 lack of quantitative data for a large number of work processes at the time the JEM was built, the  
12 experts were unable to assess the 'intensity of exposure' parameter.

13 Finally, the probability and frequency of exposure were computed at the occupation level by  
14 summarizing the exposure parameters assessed at the occupational code-work processes level (Table  
15 1). For some specific occupational code/work process combinations, the industrial branch (based on  
16 the activities of the French classification NAF edition 2000), was considered in the exposure  
17 assessment.

#### 18 2.4. Potential confounders

19 For lung cancer, smoking, occupational asbestos exposure and occupational silica exposure were  
20 considered as potential confounders. Lifetime smoking history was assessed by the comprehensive  
21 smoking index (CSI) (Leffondre et al., 2006). Lifetime occupational exposures to asbestos and to  
22 silica in the ICARE study were assessed by two specific job-exposure matrices and summarized  
23 through cumulative exposure indices (Guida et al., 2013).

1 For pleural mesothelioma, only lifetime occupational asbestos exposure was considered as a potential  
2 confounder. It was retrospectively assessed by experts and summarized through a cumulative index of  
3 exposure (Lacourt et al., 2017).

4 Finally, for CNS tumors, lifelong pesticide exposure as well as cumulative duration of mobile phone  
5 calls were considered.

## 6 2.5. Statistical analysis

### 7 2.5.1. Main analysis

8 Subjects were defined as “probably exposed” to UNPs if they had held at least one job with a  
9 probability of exposure of at least 50%. Subjects who had held jobs with a probability of exposure less  
10 than 50% but greater than 0% were considered to be “possibly exposed” to UNPs.

11 For each exposed subject, we derived the total duration of exposure in years and the total weighted  
12 duration of exposure, which was the sum of durations of exposure for each job held by a subject  
13 weighted by the frequency of exposure. For subjects who had held more than one job over the same  
14 year, we counted 6 months for each job in the calculation of the duration of exposure.

15 Odds ratios of lung cancer associated with UNPs were estimated using unconditional logistic  
16 regression adjusted for age (using fractional polynomial of degree 2 with powers  $p=-2$  and  $q=-2$ ),  
17 department of residence, comprehensive smoking index (CSI), the cumulative index of exposure to  
18 asbestos (using fractional polynomial of degree 1 with powers  $p=-1$ ) and the cumulative index of  
19 exposure to silica (using fractional polynomial of degree 1 with powers  $p=-1$ ).

20 Associations between UNPs and pleural mesothelioma or CNS tumors were estimated using  
21 conditional logistic regression stratified by age (5-year categories) and district of residence and further  
22 adjusted for age as a continuous variable (in order to remove any residual confounding due to age in  
23 the strata definition). For pleural mesothelioma, models were further adjusted for the cumulative index  
24 of exposure to asbestos (using fractional polynomial of degree 2 with powers  $p=-2$  and  $q=0.5$ ). For

1 CNS tumors, analyses were carried for all histological types and for neuroepithelial tumors and  
2 meningiomas separately.

3 Analyses were conducted on men and women separately.

#### 4 2.5.2. Sensitivity analyses

5 In addition, sensitivity analyses were performed for CNS tumors by adjusting for pesticide exposure  
6 (binary variable) and the cumulative duration of calls (hours) categorized into light-medium or heavy  
7 users.

### 8 3. Results

9 Some characteristics of cases and controls included in the three studies are presented in supplementary  
10 file (Supplementary tables 3 and 4) and have been described in detail elsewhere (Coureau et al., 2014;  
11 Luce et al., 2011; Rolland et al., 2010).

12 Table 2 presents the 20 most frequent occupations held by subjects in the three studies (36 occupations  
13 in total) which have led to occupational exposure to UNPs (corresponding to the “probable exposure”  
14 criterion). For the ICARE study, lorry and van driver occupations were held by 9.7% of cases and  
15 8.2% of controls and were considered as occupationally exposed to carbonaceous and PAH UNPs  
16 through the combustion engine process. In the PNSM study, sheet-metal workers accounted for 8.1%  
17 of cases and 2.1% of controls and entailed occupational exposure to metallic and carbonaceous UNPs  
18 through the machining, welding and thermal cutting processes. Finally, in the CERENAT study, the  
19 most frequently exposed occupations were farmers, who accounted for 11.3% of cases and 9.2% of  
20 controls.

21 Table 3 presents the adjusted associations between UNPs and lung cancer or pleural mesothelioma  
22 among men. When comparing probably exposed subjects with never exposed subjects, the OR was  
23 1.51 (95% CI: 1.22-1.86) for lung cancer. When considering the probability of exposure, the OR was  
24 1.59 (95% CI: 1.25-2.02) for subjects exposed with a probability of exposure between 50% to 90% and

1 1.46 (95% CI: 1.17-1.83) for subjects exposed with a probability greater than 90% compared to non-  
2 exposed. When restricting the analyses to probably exposed subjects, the OR associated with a one-  
3 year increase in the total weighted duration of exposure was 1.09 (95% CI: 0.99-1.20) and 1.06  
4 (95% CI: 0.99-1.13) for the duration of exposure (unweighted by frequency). For pleural  
5 mesothelioma, the adjusted OR was 0.78 (95% CI: 0.46-1.33) for subjects probably exposed to UNPs  
6 compared to non-exposed subjects.

7 Table 4 presents the adjusted associations between UNPs and CNS tumors among men, overall and for  
8 neuroepithelial tumors and meningiomas separately. Considering all CNS tumors, the OR comparing  
9 probably exposed subjects to non-exposed subjects was significantly increased (OR=1.69; 95% CI:  
10 1.17-2.44) and ORs tended to be greater for meningiomas than for neuroepithelial tumors (OR=2.19;  
11 95% CI: 0.96-5.01 and OR=1.47; 95% CI: 0.91-2.36, respectively for probably exposed vs non-  
12 exposed subjects). There was no clear trend for either the probability of exposure or the total weighted  
13 duration of exposure or the unweighted duration among exposed subjects.

14 Finally, Table 5 presents adjusted associations between UNP chemical families and lung cancer in  
15 men. It was unclear whether the magnitude of the ORs was associated with a specific chemical family  
16 or a mixture of chemical families. For example, the OR comparing subjects exposed concomitantly to  
17 metallic, mineral, carbonaceous and wood UNPs to non-exposed subjects was 1.40 (95% CI: 1.03-  
18 1.90), but it was also of the same magnitude for subjects exposed only to carbon UNPs (OR=1.41;  
19 95% CI: 1.06-1.87) or only to wood UNPs (OR=1.44; 95% CI: 0.74-2.81). It was impossible to  
20 perform such analyses for pleural mesothelioma and CNS tumors due to the small sample sizes.

21 No significant associations were observed among exposed women (OR=1.07; 95% 0.79-1.46 for the  
22 ICARE study; OR=1.89; 95% CI: 0.93-3.85 for PNSM study and OR=0.78; 95% CI: 0.54-1.13 for the  
23 CERENAT study) (See supplementary material tables 5 and 6).

24 For CNS, although we thought *a priori* that pesticide and mobile phone exposures were not  
25 confounding factors in the relationship between UNPs and CNS tumors, we performed a set of

1 sensitivity analyses by adjusting for those two factors. Estimated ORs was similar to those presented  
2 in the main analyses (Supplementary table 7).

#### 3 4. Discussion

4 Our results reveal a positive association between occupational exposure to UNPs and lung cancer and  
5 CNS tumors, while this association was not observed for pleural mesothelioma. For lung cancer, all  
6 analyses were adjusted for the main potential confounders (smoking, asbestos and silica exposure).  
7 For smoking, we used the comprehensive smoking index which has been shown to perform well in  
8 adjusting for smoking in lung cancer studies (Leffondre et al., 2006). Given that occupational  
9 exposure to asbestos is strongly associated with pleural mesothelioma and ORs are close to the null  
10 regarding the relationship between UNPs and pleural mesothelioma, with the inclusion of asbestos  
11 exposure data in the analyses as a confounding factor, it is unlikely that the ORs observed for lung  
12 cancer are due to residual confounding from asbestos exposure. However, we were not able to  
13 consider exposure to PM<sub>2.5</sub> from outdoor air pollution, a well-established lung carcinogen (IARC  
14 group 1), since PM<sub>2.5</sub> exposure monitoring was implemented in France since 2010 only. Although  
15 confounding from outdoor air pollution is not likely to explain the whole association between  
16 occupational exposure to nanoscale particles and lung cancer, we acknowledge that this is a limitation  
17 of our study.

18 For CNS tumors, except for ionizing radiation, which is a well-established risk factor, the etiology of  
19 these tumors is largely unknown, with some environmental exposures being investigated such as  
20 mobile phone use or pesticide exposure (McNeill, 2016). Since the sensitivity analyses that we  
21 performed by further adjusting for mobile phone use or pesticide exposure did not significantly change  
22 the estimated ORs, we thus believe that the likelihood that our results were confounded by a third  
23 factor is low.

24 Clinical controlled exposure (mainly to PM<sub>2.5</sub> or diesel exhaust particles) studies have demonstrated  
25 airway inflammation in healthy subjects (Ghio et al., 2012; Xu et al., 2017), exacerbation of pre-  
26 existing conditions such as asthma (McCreanor et al., 2007; Patel et al., 2013) and respiratory and

1 cardiovascular responses to traffic-related aerosol (Sinharay et al., 2018) Furthermore, exposure to  
2 ultrafine particles from ambient air pollution is associated with numerous pre-clinical or clinical  
3 cardiovascular endpoints (Bourdrel et al., 2017; Weichenthal, 2012).

4 The brain hypothesis has been put forward following observation of neurological impairment  
5 following exposure to PM in highly polluted Mexico cities (Calderon-Garciduenas et al., 2016).  
6 Following that, numerous studies have implicated NPs in the development of several neurological  
7 disorders such as Parkinson's disease, Alzheimer's disease and sclerosis, as well as behavioral  
8 changes and cognitive developments (Heusinkveld et al., 2016). Indeed, UNPs may translocate into  
9 the brain through the brain-blood barrier passage following inhalation, deposition and translocation  
10 into the bloodstream or via the olfactory nerves (Oberdorster et al., 2009). In vivo studies have  
11 demonstrated that nanoscale particle exposure is associated with indicators of neural inflammation,  
12 either directly from particles which enter into the brain or through the systemic inflammation  
13 generated (Campbell et al., 2005; Hopkins et al., 2018).

14 Due to their small size, UNPs may penetrate deep into the lungs (Oberdorster et al., 2005). Moreover,  
15 their small size prevents macrophages from effectively taking them up, which generate oxidative stress  
16 and inflammatory responses (Val et al., 2009). Finally, UNPs may translocate outside the lungs and  
17 enter into the blood stream and thus accumulate in secondary organs (Stone et al., 2017).

18 Regarding epidemiological data, most knowledge related to UNPs is derived from ambient air  
19 pollution studies. While UNPs do not contribute to the mass concentration of particulate matter  
20 exposure to the same extent as coarse particles, UNPs are predominant in terms of particle numbers  
21 and have been incriminated in the observed adverse health effects (Delfino et al., 2005). Despite rather  
22 inconclusive results from previous studies regarding lung cancer and exposure to nanoscale particles  
23 from outdoor air pollution (Ostro et al., 2015; Weichenthal et al., 2017a), Weichenthal et al, have  
24 recently showed a positive association between nanoscale particles from outdoor air pollution and  
25 brain tumors which was not explained by other air pollutants such as PM<sub>2.5</sub> mass concentrations  
26 (Weichenthal et al., 2020).

1 Regarding the occupational setting, a recent literature review has identified all occupational cohorts  
2 related to engineered nanomaterials workers. While this review has reinforced the UNPs hypothesis,  
3 with most studies demonstrating short-term effects such as a reduction in pulmonary function or  
4 inflammatory responses, it has also pointed out the limited epidemiological data and the need for  
5 longitudinal epidemiological studies (Schulte et al., 2019) as others (Ohlwein et al., 2019). UNPs  
6 aerosol composition is complex, in terms of both chemical composition and particle size distribution.  
7 Despite the difference between UNPs aerosols and nanomaterial aerosols, they share numerous  
8 physicochemical and toxicological properties, which may be used to extrapolate results from one  
9 exposure to the other (Stone et al., 2017).

10 The main challenge regarding UNPs exposure is related to retrospective exposure assessment. In this  
11 study, we used a JEM to retrospectively assess occupational exposure to UNPs. Such methods prevent  
12 recall bias regarding exposure if cases do not recall their occupational career as accurately as controls.  
13 Previous studies have shown a good validity of self-reported work history without systematic errors  
14 between cases and controls (Schlaefer et al., 2009; Teschke et al., 2002).

15 Besides the limitations of the job-exposure matrix in general, the MatPUF JEM only provides a  
16 probability and a frequency of exposure parameters. Indeed, at the time of construction of the MatPUF  
17 JEM, it was impossible to *a priori* estimate an intensity of exposure parameter from the available  
18 metrological data due to the heterogeneity of published data in terms of measurement methods as well  
19 as the units used to express UNPs concentration (mass concentration vs particulate number vs surface  
20 area) (Brouwer et al., 2012). Without an intensity of exposure parameter, it is impossible to estimate  
21 dose-response relationships. We tried to approximate this parameter by analyzing the total weighted  
22 duration of exposure. Most results were inconclusive with ORs being around the null. Analyses with  
23 the duration of exposure (unweighted by frequency) showed similar results. Since UNPs exposure is  
24 ubiquitous at the workplace, it is highly probable that the longest duration of exposure categories may  
25 include subjects with high intensity of exposure as well as those with low or very low intensity of  
26 exposure, leading to ORs close to 1. To overcome this main limitation, we are currently working on a  
27 new version of the MatPUF JEM that will integrate the intensity of exposure parameter.



1 In analyses conducted in women, we did not find significant associations in the three studies. This  
2 could be explained on the one hand by the low number of cases among women and on the other hand  
3 by the method used to characterize the exposure. The use of JEM in female populations shows  
4 limitations related to their sensitivity that may lead to underestimations of association measures. It has  
5 been shown that women and men with the same job title do not perform the same tasks. Women are  
6 expected to have lower occupational exposure than men with the same job title (Bertin et al., 2018;  
7 Messing et al., 1994).

8 Regarding the results for pleural mesothelioma, in accordance with the hypotheses discussed by  
9 Donaldson (Donaldson et al., 2013) for the toxicity of elongated insoluble fine particles, the absence  
10 of excess risk (in relation to non-elongated nanoscale particles) is not very surprising. Indeed, he  
11 describes how only carbon nanotubes that are sufficiently long and bio persistent may translocate to  
12 the pleura, where they can be retained and cause inflammation and oxidative stress. In the overall  
13 occupational situation described in the JEM, the probability of being exposed to elongated carbon  
14 nanotubes during the job histories of participants in our study is negligible. In addition, regarding  
15 exposure to asbestos, which is an elongated particle, an adjustment has been made to take this  
16 confounding factor into account. Given that the relationship between asbestos exposure and pleural  
17 mesothelioma is much stronger among men, it is unlikely that our analyses might be confounded by a  
18 third factor.

19 The three studies analyzed were population-based case-control studies which included incident cases  
20 during the study recruitment period and randomly selected controls from the general population  
21 (Coureau et al., 2014; Luce et al., 2011; Rolland et al., 2010). Analyzing already-constituted case-  
22 control studies which have gathered the entire occupational history of subjects might be a way to  
23 obtain additional knowledge on the association between occupational exposure to nanoscale particles  
24 and cancer.

25 In total, despite the use of the JEM, which could lead to a classification error and thus to an  
26 underestimation of associations, we were able to confirm the existing hypothesis of an over-risk of

1 lung cancer associated with work situations exposing subjects to specific ultrafine particles (such as  
2 diesel exhaust and welding fumes) (Loomis et al., 2014). Indeed, our data are consistent with the  
3 probable contribution of the whole spectra of ultrafine particles to lung cancer risk. We were also able  
4 to confirm the biologically plausible association between particle exposure and brain tumors, based on  
5 toxicological data (Oberdorster et al., 2009). Finally, our study allowed us to rule out an association  
6 between exposure to UNPs and pleural mesothelioma, which, based on toxicological data describing  
7 the translocation mechanisms of non-elongated particles, appears less plausible (Donaldson et al.,  
8 2010a).

## 9 5. Conclusion

10 To the best of our knowledge, this is the first study to show positive associations between occupational  
11 exposure to UNPs and increased risk of lung cancer and CNS tumors. A large number of people are  
12 potentially exposed to the UNPs, so their impact in terms of public health may not be negligible. Even  
13 though these preliminary results should be confirmed by other analyses including intensity of  
14 exposure, these results should encourage further epidemiological research on nanoscale particles and  
15 cancer.

16

## 17 **Competing financial interests declaration**

18 All authors declare they have no actual or potential competing financial interest.

## 19 **Contributors**

20 AL performed the literature review, planned the statistical analysis, and drafted the first version of this  
21 manuscript

22 GM performed the literature review and wrote the final version of the manuscript, taking into account  
23 the inputs of each co-author

- 1 CG performed all statistical analyses presented in the manuscript
- 2 SA performed the literature review on exposure data and built the job-exposure matrix PB supervised
- 3 all aspects of this manuscript
- 4 All co-authors participated in the editing and correction of the final text
- 5

## 6 REFERENCES

- 7 Beelen, R., Raaschou-Nielsen, O., Stafoggia, M., Andersen, Z.J., Weinmayr, G., Hoffmann, B., Wolf,  
8 K., Samoli, E., Fischer, P., Nieuwenhuijsen, M., Vineis, P., Xun, W.W., Katsouyanni, K.,  
9 Dimakopoulou, K., Oudin, A., Forsberg, B., Modig, L., Havulinna, A.S., Lanki, T., Turunen,  
10 A., Oftedal, B., Nystad, W., Nafstad, P., De Faire, U., Pedersen, N.L., Ostenson, C.G.,  
11 Fratiglioni, L., Penell, J., Korek, M., Pershagen, G., Eriksen, K.T., Overvad, K., Ellermann,  
12 T., Eeftens, M., Peeters, P.H., Meliefste, K., Wang, M., Bueno-de-Mesquita, B., Sugiri, D.,  
13 Kramer, U., Heinrich, J., de Hoogh, K., Key, T., Peters, A., Hampel, R., Concin, H., Nagel,  
14 G., Ineichen, A., Schaffner, E., Probst-Hensch, N., Kunzli, N., Schindler, C., Schikowski, T.,  
15 Adam, M., Phuleria, H., Vilier, A., Clavel-Chapelon, F., Declercq, C., Grioni, S., Krogh, V.,  
16 Tsai, M.Y., Ricceri, F., Sacerdote, C., Galassi, C., Migliore, E., Ranzi, A., Cesaroni, G.,  
17 Badaloni, C., Forastiere, F., Tamayo, I., Amiano, P., Dorransoro, M., Katsoulis, M.,  
18 Trichopoulou, A., Brunekreef, B., Hoek, G., 2014. Effects of long-term exposure to air  
19 pollution on natural-cause mortality: an analysis of 22 European cohorts within the  
20 multicentre ESCAPE project. *Lancet* 383, 785–95.
- 21 Bertin, M., Thebaud-Mony, A., Counil, E., Giscop93 study, group, 2018. Do Women and Men Have  
22 the Same Patterns of Multiple Occupational Carcinogenic Exposures? Results from a Cohort  
23 of Cancer Patients. *Ann Work Expo Health* 62, 450–464.
- 24 Bourdrel, T., Bind, M.A., Bejot, Y., Morel, O., Argacha, J.F., 2017. Cardiovascular effects of air  
25 pollution. *Arch Cardiovasc Dis* 110, 634–642.
- 26 Brouwer, D., Berges, M., Virji, M.A., Fransman, W., Bello, D., Hodson, L., Gabriel, S., Tielemans, E.,  
27 2012. Harmonization of measurement strategies for exposure to manufactured nano-objects;  
28 report of a workshop. *Ann Occup Hyg* 56, 1–9.
- 29 Calderon-Garciduenas, L., Leray, E., Heydarpour, P., Torres-Jardon, R., Reis, J., 2016. Air pollution, a  
30 rising environmental risk factor for cognition, neuroinflammation and neurodegeneration: The  
31 clinical impact on children and beyond. *Rev Neurol (Paris)* 172, 69–80.
- 32 Campagnolo, L., Massimiani, M., Vecchione, L., Piccirilli, D., Toschi, N., Magrini, A., Bonanno, E.,  
33 Scimeca, M., Castagnozzi, L., Buonanno, G., Stabile, L., Cubadda, F., Aureli, F., Fokkens,  
34 P.H., Kreyling, W.G., Cassee, F.R., Pietroiusti, A., 2017. Silver nanoparticles inhaled during  
35 pregnancy reach and affect the placenta and the foetus. *Nanotoxicology* 11, 687–698.
- 36 Campbell, A., Oldham, M., Becaria, A., Bondy, S.C., Meacher, D., Sioutas, C., Misra, C., Mendez,  
37 L.B., Kleinman, M., 2005. Particulate matter in polluted air may increase biomarkers of  
38 inflammation in mouse brain. *Neurotoxicology* 26, 133–40.

- 1 Coureau, G., Bouvier, G., Lebailly, P., Fabbro-Peray, P., Gruber, A., Leffondre, K., Guillamo, J.S.,  
2 Loiseau, H., Mathoulin-Pelissier, S., Salamon, R., Baldi, I., 2014. Mobile phone use and brain  
3 tumours in the CERENAT case-control study. *Occup Environ Med* 71, 514–22.
- 4 Delfino, R.J., Sioutas, C., Malik, S., 2005. Potential role of ultrafine particles in associations between  
5 airborne particle mass and cardiovascular health. *Environ Health Perspect* 113, 934–46.
- 6 Donaldson, K., Murphy, F.A., Duffin, R., Poland, C.A., 2010a. Asbestos, carbon nanotubes and the  
7 pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in  
8 the parietal pleura, inflammation and mesothelioma. *Part Fibre Toxicol* 7, 5.
- 9 Donaldson, K., Poland, C.A., 2012. Inhaled nanoparticles and lung cancer - what we can learn from  
10 conventional particle toxicology. *Swiss Med Wkly* 142, w13547.
- 11 Donaldson, K., Poland, C.A., Murphy, F.A., MacFarlane, M., Chernova, T., Schinwald, A., 2013.  
12 Pulmonary toxicity of carbon nanotubes and asbestos - similarities and differences. *Adv Drug*  
13 *Deliv Rev* 65, 2078–86.
- 14 Donaldson, K., Poland, C.A., Schins, R.P., 2010b. Possible genotoxic mechanisms of nanoparticles:  
15 criteria for improved test strategies. *Nanotoxicology* 4, 414–20.
- 16 Elder, A., Oberdorster, G., 2006. Translocation and effects of ultrafine particles outside of the lung.  
17 *Clin Occup Environ Med* 5, 785–96.
- 18 Ghio, A.J., Sobus, J.R., Pleil, J.D., Madden, M.C., 2012. Controlled human exposures to diesel  
19 exhaust. *Swiss Med Wkly* 142, w13597.
- 20 Goldberg, M.S., Labreche, F., Weichenthal, S., Lavigne, E., Valois, M.F., Hatzopoulou, M., Van  
21 Ryswyk, K., Shekarrizfard, M., Villeneuve, P.J., Crouse, D., Parent, M.E., 2017. The  
22 association between the incidence of postmenopausal breast cancer and concentrations at  
23 street-level of nitrogen dioxide and ultrafine particles. *Environ Res* 158, 7–15.
- 24 Guida, F., Paget-Bailly, S., Lamkarkach, F., Gaye, O., Ducamp, S., Menvielle, G., Papadopoulos, A.,  
25 Matrat, M., Fevotte, J., Cenee, S., Cyr, D., Schmaus, A., Carton, M., Radoi, L., Lapotre-  
26 Ledoux, B., Molinie, F., Luce, D., Stucker, I., 2013. Risk of lung cancer associated with  
27 occupational exposure to mineral wools: updating knowledge from a french population-based  
28 case-control study, the ICARE study. *J Occup Environ Med* 55, 786–95.
- 29 Heusinkveld, H.J., Wahle, T., Campbell, A., Westerink, R.H.S., Tran, L., Johnston, H., Stone, V.,  
30 Cassee, F.R., Schins, R.P.F., 2016. Neurodegenerative and neurological disorders by small  
31 inhaled particles. *Neurotoxicology* 56, 94–106.
- 32 Hopkins, L.E., Laing, E.A., Peake, J.L., Uyeminami, D., Mack, S.M., Li, X., Smiley-Jewell, S.,  
33 Pinkerton, K.E., 2018. Repeated Iron-Soot Exposure and Nose-to-brain Transport of Inhaled  
34 Ultrafine Particles. *Toxicol Pathol* 46, 75–84.
- 35 Ju, L., Wu, W., Yu, M., Lou, J., Wu, H., Yin, X., Jia, Z., Xiao, Y., Zhu, L., Yang, J., 2017. Different  
36 Cellular Response of Human Mesothelial Cell MeT-5A to Short-Term and Long-Term  
37 Multiwalled Carbon Nanotubes Exposure. *Biomed Res Int*.
- 38 Lacourt, A., Leveque, E., Guichard, E., Gilg Soit Ilg, A., Sylvestre, M.P., Leffondre, K., 2017. Dose-  
39 time-response association between occupational asbestos exposure and pleural mesothelioma.  
40 *Occup Environ Med* 74, 691–697.
- 41 Leffondre, K., Abrahamowicz, M., Xiao, Y., Siemiatycki, J., 2006. Modelling smoking history using a  
42 comprehensive smoking index: application to lung cancer. *Stat Med* 25, 4132–46.

- 1 Liou, S.H., Tsai, C.S., Pelclova, D., Schubauer-Berigan, M.K., Schulte, P.A., 2015. Assessing the first  
2 wave of epidemiological studies of nanomaterial workers. *J Nanopart Res* 17, 413.
- 3 Loomis, D., Huang, W., Chen, G., 2014. The International Agency for Research on Cancer (IARC)  
4 evaluation of the carcinogenicity of outdoor air pollution: focus on China. *Chin J Cancer* 33,  
5 189–96.
- 6 Luce, D., Stucker, I., Group, I.S., 2011. Investigation of occupational and environmental causes of  
7 respiratory cancers (ICARE): a multicenter, population-based case-control study in France.  
8 *BMC Public Health* 11, 928.
- 9 Magaye, R., Zhao, J., Bowman, L., Ding, M., 2012. Genotoxicity and carcinogenicity of cobalt-,  
10 nickel- and copper-based nanoparticles. *Exp Ther Med* 4, 551–561.
- 11 Magdolenova, Z., Collins, A., Kumar, A., Dhawan, A., Stone, V., Dusinska, M., 2014. Mechanisms of  
12 genotoxicity. A review of in vitro and in vivo studies with engineered nanoparticles.  
13 *Nanotoxicology* 8, 233–78.
- 14 McCreanor, J., Cullinan, P., Nieuwenhuijsen, M.J., Stewart-Evans, J., Malliarou, E., Jarup, L.,  
15 Harrington, R., Svartengren, M., Han, I.K., Ohman-Strickland, P., Chung, K.F., Zhang, J.,  
16 2007. Respiratory effects of exposure to diesel traffic in persons with asthma. *N Engl J Med*  
17 357, 2348–58.
- 18 McNeill, K.A., 2016. Epidemiology of Brain Tumors. *Neurol Clin* 34, 981–998.
- 19 Messing, K., Dumais, L., Courville, J., Seifert, A.M., Boucher, M., 1994. Evaluation of exposure data  
20 from men and women with the same job title. *J Occup Med* 36, 913–7.
- 21 Moller, P., Danielsen, P.H., Karottki, D.G., Jantzen, K., Roursgaard, M., Klingberg, H., Jensen, D.M.,  
22 Christophersen, D.V., Hemmingsen, J.G., Cao, Y., Loft, S., 2014. Oxidative stress and  
23 inflammation generated DNA damage by exposure to air pollution particles. *Mutat Res Rev*  
24 *Mutat Res* 762, 133–66.
- 25 Nakane, H., 2012. Translocation of particles deposited in the respiratory system: a systematic review  
26 and statistical analysis. *Environ Health Prev Med* 17, 263–74.
- 27 Nemmar, A., Vanbilloen, H., Hoylaerts, M.F., Hoet, P.H., Verbruggen, A., Nemery, B., 2001. Passage  
28 of intratracheally instilled ultrafine particles from the lung into the systemic circulation in  
29 hamster. *Am J Respir Crit Care Med* 164, 1665–8.
- 30 Oberdorster, G., Elder, A., Rinderknecht, A., 2009. Nanoparticles and the brain: cause for concern? *J*  
31 *Nanosci Nanotechnol* 9, 4996–5007.
- 32 Oberdorster, G., Oberdorster, E., Oberdorster, J., 2005. Nanotoxicology: an emerging discipline  
33 evolving from studies of ultrafine particles. *Environ Health Perspect* 113, 823–39.
- 34 Oberdorster, G., Sharp, Z., Atudorei, V., Elder, A., Gelein, R., Lunts, A., Kreyling, W., Cox, C., 2002.  
35 Extrapulmonary translocation of ultrafine carbon particles following whole-body inhalation  
36 exposure of rats. *J Toxicol Environ Health A* 65, 1531–43.
- 37 Ohlwein, S., Kappeler, R., Kutlar Joss, M., Kunzli, N., Hoffmann, B., 2019. Health effects of ultrafine  
38 particles: a systematic literature review update of epidemiological evidence. *Int J Public*  
39 *Health* 64, 547–559.
- 40 Ostro, B., Hu, J., Goldberg, D., Reynolds, P., Hertz, A., Bernstein, L., Kleman, M.J., 2015.  
41 Associations of mortality with long-term exposures to fine and ultrafine particles, species and

- 1 sources: results from the California Teachers Study Cohort. *Environ Health Perspect* 123,  
2 549–56.
- 3 Patel, M., Pilcher, J., Pritchard, A., Perrin, K., Travers, J., Shaw, D., Holt, S., Harwood, M., Black, P.,  
4 Weatherall, M., Beasley, R., Group, S.S., 2013. Efficacy and safety of maintenance and  
5 reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe  
6 exacerbations: a randomised controlled trial. *Lancet Respir Med* 1, 32–42.
- 7 Rolland, P., Gramond, C., Lacourt, A., Astoul, P., Chamming's, S., Ducamp, S., Frenay, C., Galateau-  
8 Salle, F., Ilg, A.G., Imbernon, E., Le Stang, N., Paireon, J.C., Goldberg, M., Brochard, P.,  
9 Group, P.S., 2010. Occupations and industries in France at high risk for pleural mesothelioma:  
10 A population-based case-control study (1998-2002). *Am J Ind Med* 53, 1207–19.
- 11 Schlaefer, K., Schlehofer, B., Schuz, J., 2009. Validity of self-reported occupational noise exposure.  
12 *Eur J Epidemiol* 24, 469–75.
- 13 Schulte, P.A., Leso, V., Niang, M., Iavicoli, I., 2019. Current state of knowledge on the health effects  
14 of engineered nanomaterials in workers: a systematic review of human studies and  
15 epidemiological investigations. *Scand J Work Environ Health* 45, 217–238.
- 16 Sinharay, R., Gong, J., Barratt, B., Ohman-Strickland, P., Ernst, S., Kelly, F.J., Zhang, J.J., Collins, P.,  
17 Cullinan, P., Chung, K.F., 2018. Respiratory and cardiovascular responses to walking down a  
18 traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years  
19 and older with chronic lung or heart disease and age-matched healthy controls: a randomised,  
20 crossover study. *Lancet* 391, 339–349.
- 21 Stone, V., Miller, M.R., Clift, M.J.D., Elder, A., Mills, N.L., Moller, P., Schins, R.P.F., Vogel, U.,  
22 Kreyling, W.G., Alstrup Jensen, K., Kuhlbusch, T.A.J., Schwarze, P.E., Hoet, P., Pietroiusti,  
23 A., De Vizcaya-Ruiz, A., Baeza-Squiban, A., Teixeira, J.P., Tran, C.L., Cassee, F.R., 2017.  
24 Nanomaterials Versus Ambient Ultrafine Particles: An Opportunity to Exchange Toxicology  
25 Knowledge. *Environ Health Perspect* 125, 106002.
- 26 Suzui, M., Futakuchi, M., Fukamachi, K., Numano, T., Abdelgied, M., Takahashi, S., Ohnishi, M.,  
27 Omori, T., Tsuruoka, S., Hirose, A., Kanno, J., Sakamoto, Y., Alexander, D.B., Alexander,  
28 W.T., Jiegou, X., Tsuda, H., 2016. Multiwalled carbon nanotubes intratracheally instilled into  
29 the rat lung induce development of pleural malignant mesothelioma and lung tumors. *Cancer*  
30 *Sci* 107, 924–35.
- 31 Teschke, K., Olshan, A.F., Daniels, J.L., De Roos, A.J., Parks, C.G., Schulz, M., Vaughan, T.L., 2002.  
32 Occupational exposure assessment in case-control studies: opportunities for improvement.  
33 *Occup Environ Med* 59, 575–93; discussion 594.
- 34 Toyokuni, S., 2013. Genotoxicity and carcinogenicity risk of carbon nanotubes. *Adv Drug Deliv Rev*  
35 65, 2098–110.
- 36 Val, S., Hussain, S., Boland, S., Hamel, R., Baeza-Squiban, A., Marano, F., 2009. Carbon black and  
37 titanium dioxide nanoparticles induce pro-inflammatory responses in bronchial epithelial cells:  
38 need for multiparametric evaluation due to adsorption artifacts. *Inhal Toxicol* 21 Suppl 1,  
39 115–22.
- 40 Weichenthal, S., 2012. Selected physiological effects of ultrafine particles in acute cardiovascular  
41 morbidity. *Environ Res* 115, 26–36.
- 42 Weichenthal, S., Bai, L., Hatzopoulou, M., Van Ryswyk, K., Kwong, J.C., Jerrett, M., van Donkelaar,  
43 A., Martin, R.V., Burnett, R.T., Lu, H., Chen, H., 2017a. Long-term exposure to ambient

- 1 ultrafine particles and respiratory disease incidence in Toronto, Canada: a cohort study.  
2 Environ Health 16, 64.
- 3 Weichenthal, S., Lavigne, E., Valois, M.F., Hatzopoulou, M., Van Ryswyk, K., Shekarrizfard, M.,  
4 Villeneuve, P.J., Goldberg, M.S., Parent, M.E., 2017b. Spatial variations in ambient ultrafine  
5 particle concentrations and the risk of incident prostate cancer: A case-control study. Environ  
6 Res 156, 374–380.
- 7 Weichenthal, S., Olaniyan, T., Christidis, T., Lavigne, E., Hatzopoulou, M., Van Ryswyk, K.,  
8 Tjepkema, M., Burnett, R., 2020. Within-city Spatial Variations in Ambient Ultrafine Particle  
9 Concentrations and Incident Brain Tumors in Adults. Epidemiology 31, 177–183.
- 10 Wichmann, H.E., Spix, C., Tuch, T., Wolke, G., Peters, A., Heinrich, J., Kreyling, W.G., Heyder, J.,  
11 2000. Daily mortality and fine and ultrafine particles in Erfurt, Germany part I: role of particle  
12 number and particle mass. Res Rep Health Eff Inst 5–86; discussion 87-94.
- 13 Xu, H., Ho, S.S., Cao, J., Guinot, B., Kan, H., Shen, Z., Ho, K.F., Liu, S., Zhao, Z., Li, J., Zhang, N.,  
14 Zhu, C., Zhang, Q., Huang, R., 2017. A 10-year observation of PM<sub>2.5</sub>-bound nickel in Xi'an,  
15 China: Effects of source control on its trend and associated health risks. Sci Rep 7, 41132.
- 16

Table 1: Exposure parameters assessed in the MatPuf job-exposure matrix according the level of assessment

Assessment level	Probability of exposure	Frequency of exposure	Intensity of exposure																	
<b>Occupational code* × work process</b>	% of exposed workers through the implementation of the work process <sup>†</sup> <i>j</i> among workers involved the occupational code <i>i</i>	% of working time during which the exposure occurred through the implementation of the work process <i>j</i> in occupational code <i>i</i> on a 8h typical working day and on a typical working year	Not assessed due to heterogeneity of quantitative data																	
	<table border="1"> <thead> <tr> <th>Categorization</th> <th>Numerical value</th> </tr> </thead> <tbody> <tr> <td>Possible: &gt;0-10%</td> <td>0.05</td> </tr> <tr> <td>Probable: &gt;10-50%</td> <td>0.30</td> </tr> <tr> <td>Highly probable: &gt; 50%</td> <td>0.75</td> </tr> </tbody> </table>	Categorization	Numerical value	Possible: >0-10%	0.05	Probable: >10-50%	0.30	Highly probable: > 50%	0.75	<table border="1"> <thead> <tr> <th>Categorization</th> <th>Numerical value</th> </tr> </thead> <tbody> <tr> <td>Sporadic: &gt;0-5%</td> <td>0.025</td> </tr> <tr> <td>Occasional: &gt;5-30%</td> <td>0.175</td> </tr> <tr> <td>Frequent: &gt;30-70%</td> <td>0.50</td> </tr> <tr> <td>Permanent: &gt;70%</td> <td>0.85</td> </tr> </tbody> </table>	Categorization	Numerical value	Sporadic: >0-5%	0.025	Occasional: >5-30%	0.175	Frequent: >30-70%	0.50	Permanent: >70%	0.85
Categorization	Numerical value																			
Possible: >0-10%	0.05																			
Probable: >10-50%	0.30																			
Highly probable: > 50%	0.75																			
Categorization	Numerical value																			
Sporadic: >0-5%	0.025																			
Occasional: >5-30%	0.175																			
Frequent: >30-70%	0.50																			
Permanent: >70%	0.85																			
<b>Occupational code</b>	% of exposed workers among workers involved in the occupation <i>i</i>	% of working time during which the exposure occurred in occupation I on a 8h typical																		



working day and on a typical working year

$$1 - \prod_{i=1}^n \left( 1 - \text{Probability}_{\text{occupational code } i \times \text{work process } j} \right) \quad 1 - \prod_{i=1}^n \left[ 1 - \left( \text{Probability}_{\text{occupational code } i \times \text{work process } j} \times \text{Frequency}_{\text{occupational code } i \times \text{work process } j} \right) \right]$$

n: number of work processes assessed for the occupation  $i$

n: number of work processes assessed for the occupation  $i$

\* Occupational code defining according to the International Standard Classification of Occupations, Revised Edition 1968

† From a list of 57 pre-defined work processes assessed as unintentionally-emitting nanoscale particles

Journal Pre-proof

Table 2 : Most represented occupations exposed to nanoscale particles with a probability of exposure greater than 50% among men, French case-control studies on lung cancer (ICARE study, 2001-2007), pleural mesothelioma ((PNSM study, 1998-2002) and central nervous system tumors (CERENAT study, 2004-2006).

	rank	Cases		Controls		Me	Mi n	C	H	W
		n	%	n	%					
ICARE Study										
9-85.50 Lorry and Van Driver (Local Transport)	1	93	4.6	129	5.0			X	X	
9-85.60 Lorry and Van Driver (Long-Distance Transport)	2	104	5.1	82	3.2			X	X	
4-32.20 Commercial Traveller	3	71	3.5	108	4.2			X	X	
8-43.20 Automobile Mechanic	4	78	3.8	100	3.9	X		X	X	
6-21.05 Farm Worker (General)	5	59	2.9	112	4.3		X	X	X	
6-25.10 Dairy Farm Worker (General)	6	52	2.6	82	3.2		X	X	X	
9-31.20 Building Painter	7	81	4.0	48	1.9		X			
9-59.10 Housebuilder (General)	8	71	3.5	57	2.2	X	X			X
8-55.20 Building Electrician	9	41	2.0	65	2.5		X			
8-71.05 Plumber (General)	10	59	2.9	47	1.8	X		X	X	
9-59.90 Other Construction Workers	11	61	3.0	41	1.6	X	X			X
6-11.10 General Farmer	12	45	2.2	52	2.0		X	X	X	
7-00.75 Supervisor and General Foreman (Construction Work)	13	28	1.4	68	2.6	X	X	X	X	X
9-85.90 Other Motor-Vehicle Drivers	14	45	2.2	51	2.0			X	X	
8-49.10 Machinery Mechanic (General)	15	38	1.9	55	2.1	X	X	X	X	

6-21.10 Farm Helper (General)	16	36	1.8	57	2.2	X	X	X
4-31.20 Technical Salesman	17	41	2.0	48	1.9		X	X
9-99.10 Labourer	18	52	2.6	37	1.4	X	X	X
5-31.30 Cook, except Private Service	19	41	2.0	45	1.7		X	X
8-73.10 Sheet-Metal Worker, General	20	43	2.1	37	1.4	X	X	X

## PNSM study

9-85.50 Lorry and Van Driver (Local Transport)	1	13	3.5	40	5.5		X	X		
6-21.05 Farm Worker (General)	2	11	3.0	36	4.9	X	X	X		
8-73.10 Sheet-Metal Worker, General	3	30	8.1	15	2.1	X	X	X		
4-32.20 Commercial Traveller	4	9	2.4	30	4.1		X	X		
6-11.10 General Farmer	5	2	0.5	37	5.1	X	X	X		
8-43.20 Automobile Mechanic	6	13	3.5	22	3.0	X	X	X		
9-99.10 Labourer	7	15	4.0	13	1.8	X	X	X		
6-21.10 Farm Helper (General)	8	4	1.1	24	3.3	X	X	X		
9-51.20 Bricklayer (Construction)	9	10	2.7	17	2.3	X				
7-00.50 Supervisor and General Foreman (Manufacturing of Machinery and Metal Product)	10	12	3.2	12	1.6	X	X	X		
7-00.75 Supervisor and General Foreman (Construction Work)	11	12	3.2	11	1.5	X	X	X	X	X
8-49.10 Machinery Mechanic (General)	12	12	3.2	11	1.5	X	X	X	X	
8-71.05 Plumber (General)	13	15	4.0	7	1.0	X	X	X		
8-71.10 Pipe Fitter (General)	14	20	5.4	1	0.1	X	X	X		
8-49.70 Plant Maintenance Mechanic	15	13	3.5	8	1.1	X	X	X	X	X
8-34.20 Lathe Operator	16	8	2.2	13	1.8	X	X	X		

8-72.10 Gas and Electronic Welder (General)	17	12	3.2	7	1.0	X	X	X
4-31.20 Technical Salesman	18	6	1.6	13	1.8		X	X
9-54.20 Construction Joiner	19	9	2.4	9	1.2			X
7-76.20 Bread Baker	20	5	1.3	13	1.8		X	X

## CERENAT study

6-21.05 Farm Worker (General)	1	17	6.6	26	5.1	X	X	X		
6-11.10 General Farmer	2	12	4.7	21	4.1	X	X	X		
9-85.50 Lorry and Van Driver (Local Transport)	3	9	3.5	18	3.5		X	X		
6-12.30 Orchard, Vineyard and Related Tree and Shrub Crop Farmer	4	10	3.9	16	3.1		X	X		
8-43.20 Automobile Mechanic	5	10	3.9	15	2.9	X	X	X		
4-32.20 Commercial Traveller	6	8	3.1	17	3.3		X	X		
8-71.05 Plumber (General)	7	8	3.1	16	3.1	X	X	X		
6-23.30 Vineyard Worker	8	7	2.7	9	1.8		X	X		
9-31.20 Building Painter	9	9	3.5	6	1.2	X				
9-51.90 Other Bricklayers, Stonemasons and Tile Setters	10	6	2.3	9	1.8	X				
9-54.10 Carpenter, General	11	4	1.6	11	2.2			X		
7-76.20 Bread Baker	12	9	3.5	5	1.0		X	X		
8-72.20 Electric Arc Welder (Hand)	13	7	2.7	7	1.4	X				
4-31.20 Technical Salesman	14	4	1.6	10	2.0		X	X		
7-00.75 Supervisor and General Foreman (Construction Work)	15	4	1.6	9	1.8	X	X	X	X	X
8-55.20 Building Electrician	16	5	1.9	7	1.4	X				
0-34.90 Other Electrical and Electronics	17	2	0.8	10	2.0	X				

## Engineering Technicians

6-25.10 Dairy Farm Worker (General)	18	6	2.3	5	1.0	X	X	X
8-49.10 Machinery Mechanic (General)	19	5	1.9	6	1.2	X	X	X
4-52.30 Canvasser	20	6	2.3	4	0.8		X	X

---

Me : Metallic particles ; Min : mineral particles ; C : Carbon particles ; H : polycyclic aromatic hydrocarbon particles ; W : wood particles

Table 3: Association between occupational exposure to nanoscale particles and respiratory cancers (lung cancer and pleural mesothelioma) among men, French case-control studies on lung cancer (ICARE study, 2001-2007) and pleural mesothelioma (PNSM study, 1998-2002).

	ICARE Study (Lung cancer study)						PNSM study (Pleural mesothelioma study)					
	Cases		Controls		OR*	95% CI	Cases		Controls		OR <sup>†</sup>	95% CI
	(N=2,029)		(N=2,591)				(N=371)		(N=730)			
	n	%	n	%			n	%	n	%		
Not exposed	263	13.0	582	22.5	1.00		35	9.4	171	23.4	1.00	
<i>Uncertain</i> <sup>‡</sup>	154	7.6	210	8.1	1.50	1.09-2.06	22	5.9	87	11.9	0.62	0.32-1.23
<b>Exposed</b> <sup>§</sup>	<b>1612</b>	<b>76.4</b>	<b>1799</b>	<b>69.4</b>	<b>1.51</b>	<b>1.22-1.86</b>	<b>314</b>	<b>84.7</b>	<b>472</b>	<b>64.7</b>	<b>0.78</b>	<b>0.46-1.33</b>
Highest probability of exposure (%)												
> 50-90	487	24.0	526	20.3	1.59	1.25-2.02	62	16.7	144	22.4	0.75	0.42-1.36
> 90	1125	55.4	1273	49.1	1.46	1.17-1.83	252	67.9	328	51.0	0.80	0.46-1.39
Duration of exposure (years) <sup>§</sup>					1.06	0.99—1.13			1.01	0.99-1.02		
Mean (SD)	27.2 (14.3)		25.2 (14.3)				28.1 (11.8)		25.9 (14.2)			
Min-Max	0.5-56		0.25-56				1-56		1-53			

---

Total weighted duration of exposure (years) <sup>¶</sup>			1.09	0.99-1.20		1.03	1.01-1.05
Mean (SD)	12.3 (9.6)	10.8 (9.0)			15.9 (11.1)	11.1 (9.3)	
Min-Max	0.1-47.5	0.0-44.1			0.2-48.2	0.0-43.8	

---

\* Odds ratio estimated from unconditional logistic regression adjusted for age (using fractional polynomial of degree 2 with powers  $p=-2$  and  $q=-2$ ), district of residence, smoking comprehensive index, the cumulative index of exposure to asbestos (using fractional polynomial of degree 1 with powers  $p=-1$ ) and the cumulative index of exposure to silica (using fractional polynomial of degree 1 with powers  $p=-1$ ).

† Odds ratio estimated from conditional logistic regression stratified by age (5-years categories), district of residence and further adjusted for age as a continuous variable and the cumulative index of exposure to asbestos (using fractional polynomial of degree 2 with powers  $p=-2$  and  $q=0.5$ ).

‡ Highest probability of exposure  $\leq 50\%$  but greater than 0%.

§ Highest probability of exposure  $> 50\%$ .

¶ Analyses restricted to ever exposed only.



Table 4: Association between occupational exposure to nanoscale particles and central nervous system tumors among men (CERENAT study, 2004-2006).

	Overall CNS tumors						Neuroepithelial tumors						Meningiomas					
	Cases		Controls		OR	95% CI	Cases		Controls		OR	95% CI	Cases		Controls		OR	95% CI
	(N=257)		(N=511)				(N=155)		(N=310)				(N=155)		(N=310)			
	n	%	n	%	*	n	%	n	%	*	n	%	n	%	*	n	%	
Not exposed	55	21.4	154	30.1	1.00	-	37	23.6	92	29.5	1.00	-	10	19.2	34	32.7	1.00	-
<i>Uncertain</i> <sup>†</sup>	24	9.3	55	10.8	1.23	0.70-2.16	17	10.8	36	11.5	1.25	0.63-2.49	3	5.8	9	8.7	0.98	0.23-4.29
<b>Exposed</b> <sup>‡</sup>	<b>178</b>	<b>69.3</b>	<b>302</b>	<b>59.1</b>	<b>1.69</b>	<b>1.17-2.44</b>	<b>103</b>	<b>65.6</b>	<b>184</b>	<b>59.0</b>	<b>1.47</b>	<b>0.91-2.36</b>	<b>39</b>	<b>75.0</b>	<b>61</b>	<b>58.7</b>	<b>2.19</b>	<b>0.96-5.01</b>
Highest probability of exposure (%)																		
> 50-90	72	28.0	100	19.6	2.02	1.30-3.11	40	25.5	63	20.2	1.67	0.94-2.94	14	26.9	20	19.2	2.31	0.88-6.02
> 90	106	41.3	202	39.5	1.48	0.99-2.23	63	40.1	121	38.8	1.34	0.79-2.27	25	48.1	41	39.4	2.12	0.87-5.15
Duration of exposure (years) <sup>§</sup>					1.00	0.99-1.02					0.99	0.98-1.02					1.02	0.99-1.06
Mean (SD)	24.6		22.9				22.3		20.9				29.9		26.7			
	(15.2)		(14.7)				(15.4)		(15.0)				(13.7)		(13.7)			

Min-Max	1-65	1-55	1-56	1-55	2-65	2-54		
Total weighted duration of exposure (years) <sup>§</sup>		0.98	0.96-1.01		0.98	0.95-1.02	0.99	0.95-1.04
Mean (SD)	8.8 (7.4)	9.8 (9.4)	8.5 (7.1)	9.1 (9.5)	9.8 (8.0)	10.9 (9.5)		
Min-Max	0.1-38.1	0.1-46.5	0.1-29.1	0.1-46.5	0.2-34.7	0.2-37.4		

\* Odds ratio estimated from conditional logistic regression models stratified by age (5-years categories), district of residence and further adjusted for age as a continuous variable.

† Highest probability of exposure  $\leq 50\%$  but greater than 0%.

‡ Highest probability of exposure  $> 50\%$ .

§ Analyses restricted to ever exposed only.

Table 5: Association between occupational exposure to main chemical families of nanoscale particles and respiratory cancers (lung cancer and pleural mesothelioma) among men, French case-control studies on lung cancer (ICARE study, 2001-2007) and on pleural mesothelioma (PNSM study, 1998-2002).

	Lung cancer study					
	Cases (N=1,875)		Controls (N=2,381)		OR*	95% CI
	n	%	n	%		
Not exposed	263	14.1	582	24.4	1.00	
Exposed						
<b>4 families of UNPs</b>						
Metallic + Mineral+ Carbon + Wood	354	18.9	318	13.4	1.40	1.03-1.90
<b>3 families of UNPs</b>						
Metallic + Mineral + Carbon	179	9.5	209	8.8	1.29	0.93-1.79
Metallic + Mineral + Wood	4	0.2	3	0.1	1.47	0.29-7.55
Metallic + Carbon + Wood	52	2.8	50	2.1	2.10	1.24-3.55
Mineral + Carbon + Wood	39	2.1	18	0.8	2.93	1.38-6.23
<b>2 families of UNPs</b>						
Metallic + Mineral	22	1.2	23	1.0	1.66	0.78-3.50
Metallic + Carbon	392	20.9	461	19.4	1.58	1.23-2.03
Metallic + Wood	3	0.2	2	0.1	0.89	0.13-6.12
Mineral + Carbon	248	13.2	341	14.3	1.56	1.17-2.08
Mineral + Wood	6	0.3	3	0.1	1.83	0.38-8.79
Carbon + Wood	21	1.1	31	1.3	1.67	0.85-3.29
<b>1 family of UNPs only</b>						

---

Metallic only	10	0.5	12	0.5	2.19	0.77-6.23
Mineral only	29	1.5	15	0.6	1.26	0.57-2.82
Carbon only	231	12.3	272	11.4	1.41	1.06-1.87
Wood only	22	1.2	41	1.7	1.44	0.74-2.81

---

\* Odds ratio estimated from unconditional logistic regression adjusted for age (using fractional polynomial of degree 2 with powers  $p=-2$  and  $q=-2$ ), district of residence, smoking comprehensive index, the cumulative index of exposure to asbestos (using fractional polynomial of degree 1 with powers  $p=-1$ ) and the cumulative index of exposure to silica (using fractional polynomial of degree 1 with powers  $p=-1$ ).

**Highlights**

- nanoscale particles may have a carcinogenic effect on humans
- Positive association between lung cancer, brain tumors and nanoscale particles
- Retrospective exposure assessment of nanoscale particles by a job-exposure matrix

Journal Pre-proof

**Declaration of interests**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Journal Pre-proof