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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**

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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.

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1 1. Introduction

2 Particulate matter (mainly PM_{2.5}) 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_{2.5} from outdoor air pollution, a well-established lung carcinogen (IARC
14 group 1), since PM_{2.5} 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_{2.5} 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_{2.5} 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

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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																
Occupational code* × work process	% of exposed workers through the implementation of the work process [†] <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: >0-10%</td> <td>0.05</td> </tr> <tr> <td>Probable: >10-50%</td> <td>0.30</td> </tr> <tr> <td>Highly probable: > 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: >0-5%</td> <td>0.025</td> </tr> <tr> <td>Occasional: >5-30%</td> <td>0.175</td> </tr> <tr> <td>Frequent: >30-70%</td> <td>0.50</td> </tr> <tr> <td>Permanent: >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%
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Occupational code	% 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

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* 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

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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
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 [†]	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> [‡]	154	7.6	210	8.1	1.50	1.09-2.06	22	5.9	87	11.9	0.62	0.32-1.23	
Exposed [§]	1612	76.4	1799	69.4	1.51	1.22-1.86	314	84.7	472	64.7	0.78	0.46-1.33	
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) [§]					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) [¶]			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> [†]	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
Exposed [‡]	178	69.3	302	59.1	1.69	1.17-2.44	103	65.6	184	59.0	1.47	0.91-2.36	39	75.0	61	58.7	2.19	0.96-5.01
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) [§]					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) [§]		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						
4 families of UNPs						
Metallic + Mineral+ Carbon + Wood	354	18.9	318	13.4	1.40	1.03-1.90
3 families of UNPs						
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
2 families of UNPs						
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
1 family of UNPs only						

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

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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:

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