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# Occupational Exposure to Silica Nanoparticles: Evaluation of Emission Fingerprints by Laboratory Simulations

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**Abstract:** Silica nanoparticles ($SiO_2$ NPs), due to their chemical-physical properties, are among the most widely produced nanomaterials (NMs) in the world, and therefore used in a wide range of industries. Such widespread use, however, draws attention to the health of workers during the production of such NMs and the need for techniques to assess occupational exposure. In the present study, laboratory simulation techniques were used to reproduce a critical work activity in a controlled environment in order to identify emission profiles useful for studying exposure during NM handling in the workplace. Weighing activity inside a glove box isolated from the external environment background and any pollutants was simulated. Real-time instrumentation was used to calculate the concentration, size distribution and surface area of the particles generated during the simulation, and time-integrated instrumentation was used to collect dust for off-line analysis.

**Keywords:** nanomaterials; silica nanoparticles; exposure monitoring; occupational safety and health; laboratory simulations



**Citation:** Natale, C.; Ferrante, R.; Boccuni, F.; Tombolini, F.; Sarto, M.S.; Iavicoli, S. Occupational Exposure to Silica Nanoparticles: Evaluation of Emission Fingerprints by Laboratory Simulations. *Sustainability* **2022**, *14*, 10251. https://doi.org/10.3390/su141610251

Academic Editor: Lucian-Ionel Cioca

Received: 13 July 2022
Accepted: 8 August 2022
Published: 18 August 2022



## 1. Introduction

In recent years, nanotechnologies (NTs) and nanomaterials (NMs) have shown a rapid development in a wide range of sectors such as pharmaceutical, medical, electrical, etc. [1]. NTs have been included among the six key enabling technologies (KETs) considered as a key tool in the European Commission's Horizon 2020 programme [2]. NMs have been defined by the International Organization for Standardization (ISO) as materials with any external dimension in the nanoscale (dimensions between 1 and 100 nanometers) [3].

Parallel to the innovative properties and enormous potential shown by NMs, the scientific community has also examined the potential effects of manufactured NMs on human health [4,5], with specific focus on the health and safety of workers, who produce, use, transport or handle NMs, and could be therefore exposed during their entire life cycle [6]. In particular, handling of nano-powders has been recognized as one of the critical phases for workers exposed in production processes [7]. The handling and transfer of nano-powders, including weighting, bag emptying, dumping, pouring and scooping activities may generate aerosols during the downstream use of produced NMs [8–10].

The parameters that can influence toxicity and therefore need to be taken into account for a comprehensive risk characterization in the study of occupational exposure to NMs include: size distribution, particle mass and number concentration, lung deposited surface area, chemical and morphological composition [11,12].

A key research challenge is to quantify these parameters under real exposure conditions in order to provide useful information for a proper occupational risk analysis. In this regard, monitoring techniques play a key role in the workplace. Based on the analysis of the scientific literature, the technical guidelines published by the Organization for Economic Co-operation and Development (OECD) recommend a harmonized tiered approach that involves three levels of investigation [13,14]: the first level consists in gathering information about materials, processes and the exposure scenario, the second level includes preliminary background and basic exposure assessment and the third level proposes a comprehensive exposure assessment with the addition of chemical/morphological off-line analyses.

The distinction of background from manufactured NMs emission specifically related to the process plays a key role in the analysis of workers' exposure. In fact, the background can be influenced by sources of ultrafine particles coming from the outdoor environment or other indoor activities (e.g., polycyclic aromatic hydrocarbons, pollutants from vehicular traffic, anthropogenic activities, photochemical smog, use of chemical agents, moisture or steam) and these can create difficulties in identifying the emission of produced NMs. Bekker et al. [10], for example, found low concentrations during low-energy activities, but the high background level recorded in the workplace may have corrected emissions from activities. For this reason, it is essential to characterize the background according to the main approaches frequently used in exposure measurement studies [14,15].

In this framework, laboratory simulations represent an added value to reproduce critical NMs handling activities in a controlled environment with extremely low background levels, representing an important source of information for the assessment of occupational exposure to NMs [16]. Indeed, the study of critical activities in an environment isolated from external emissive sources and with very low background levels allows the identification of potential sources of exposure. Some scientific studies [17–19], for example, evaluated emission of nanoparticles (NPs) from spray products and laser printers and showed the effectiveness of such simulations in analyzing occupational risk. On the other hand, Gomez et al. [20] highlighted the importance of using a controlled environment in order to determine the emission source.

The present study shows the results obtained by laboratory simulations of handling activities with $SiO_2$ NPs. Such NMs have become one of the most produced in the world since 2013 and are used in a wide range of sectors including agriculture, food, cosmetics and pigments [21]. However, this large use has led to an increased risk of exposure in workplaces [22,23] raising a global concern regarding the safety and potential adverse health effects. For this reason, we reproduced working activities in a glove box with low levels of background to identify emission profiles useful for the exposure assessment during the production of $SiO_2$ NPs. The study was carried out within the research project "NanoKey" developed by the Italian Workers' Compensation Authority (INAIL) in cooperation with the Italian Institute of Technology (IIT) with the aim to study occupational exposure to different types of NMs.

## 2. Materials and Methods

$SiO_2$ NPs, the subject matter of the research, have an average size of 25 nm and they are produced by liquid synthesis followed by lyophilization in order to obtain the product in powder form [24,25]. Detailed information on the material is reported in Table 1.

Weighing activity was simulated in the laboratory using an isolated and controlled environment (glove-box) in order to minimize background levels and highlight airborne NPs.

The glove box (mod. 14302, ITECO Engineering Srl, Castebolognese (RA), Italy) is isolated from outside influences by a HEPA filter, has a volume of 0.5 $m^3$, a stirring fan measuring 135 × 135 × 40 mm in thickness and 8 ports incorporated to withdraw samples for analytical measurements. Three weightings were carried out, using an analytical scale (Mettler Toledo XS 105 Dual Range, Max 41 g–d = 0.01 mg), each of 5 mg of $SiO_2$ NP.

The measurement instruments used are (Table 2):

- Condensation Particle Counter (CPC mod. 3007, TSI Inc., Shoreview, MN, USA) in order to measure the particle number concentration (PNC);
- Fast Mobility Particle Sizer (FMPS mod. 3091, TSI Inc., Shoreview, MN, USA) that provides the particle size distribution (PSD) over 32 channels and simultaneously also the PNC;
- Electrical Low Pressure Impactor (ELPI mod. Dekati Ltd., Kangasala, Finland) to measure real-time total PNC and PSD in the size range 6–10,000 nm and to collect on plates size classified particles for off-line analysis. Sampling supports are in aluminum (Al) with 25 mm size;
- Nanoparticle surface area monitor (NSAM mod. 3550, TSI Inc, Shoreview, MN, USA) for the measurement of lung deposition surface area (LDSA) of particles, which is an important occupational parameter, corresponding to the active surface area calculated as the product of the particle area for the probability density of deposition in the different zones of the respiratory tract (A, alveolar or TB, tracheobronchial), according to the model published by the ICRP [26].

**Table 1.** $SiO_2$ physicochemical characteristics declared by the manufacturer.

| Technical Name | Silica Nanoparticles ($SiO_2$ NPs) |
|---|---|
| Chemical composition | Silicon dioxide |
| Physical form and shape | Zero-dimensional (0-D) amorphous nanoparticles |
| Common form | Water solution or powder (white) |
| Density | Average bulk Density: 2.648 g/cm$^3$ |
| Size | 25 ± 1 nm |
| Particle Surface area | 1962.5 nm$^2$ |

**Table 2.** Main features of the instruments during simulations. TB = tracheobronchial, A = alveolar.

| Instrument | Class | Principle of Operation | Output | Size Range (nm) | Time Resolution (s) | Aspiration Flow (L/min) |
|---|---|---|---|---|---|---|
| CPC TSI Inc. Mod.3007 | Real-time | Optical detection | PNC (#/cm$^3$) | 10–1000 | 1 | 0.7 |
| FMPS TSI Inc. Mod.3091 | Real-time | Electrical mobility | PNC (#/cm$^3$) Size distribution | 5.6–560 | 1 | 10 |
| NSAM TSI Inc. Mod.3550 | Real-time | Diffusion charging | LDSA (μm$^2$/cm$^3$) and total (μm$^2$) for alveolar fraction | 10–1000 | 1 | 2.5 |
| HR-ELPI | Real-time/ Time-integrated | Electrical cascade impactor | PNC (#/cm$^3$) Size distribution Samples for off-line analysis | 6–10,000 | 0.1 | 10 |

Morphological analyses have been performed on materials collected by ELPI using a High-Resolution Field Emission Scanning Electron Microscope (HR-SEM) Ultra Plus (ZEISS) equipped with an Energy Dispersive X-ray Spectroscopy (EDS, Oxford Instruments INCA). For SEM characterization two different kinds of samples were considered. The first was the "trial sample" obtained by the manufacturer at the end of the production phases; the second, the "ELPI samples", were the samples collected on the ELPI filters during the handling phases simulation. The trial sample was dispersed in 2-propanol and sonicated for 15 min. The suspension was drop-cast on a stub covered with an aluminum filter.

These instruments were connected to the glove box, as shown in the Figure 1.

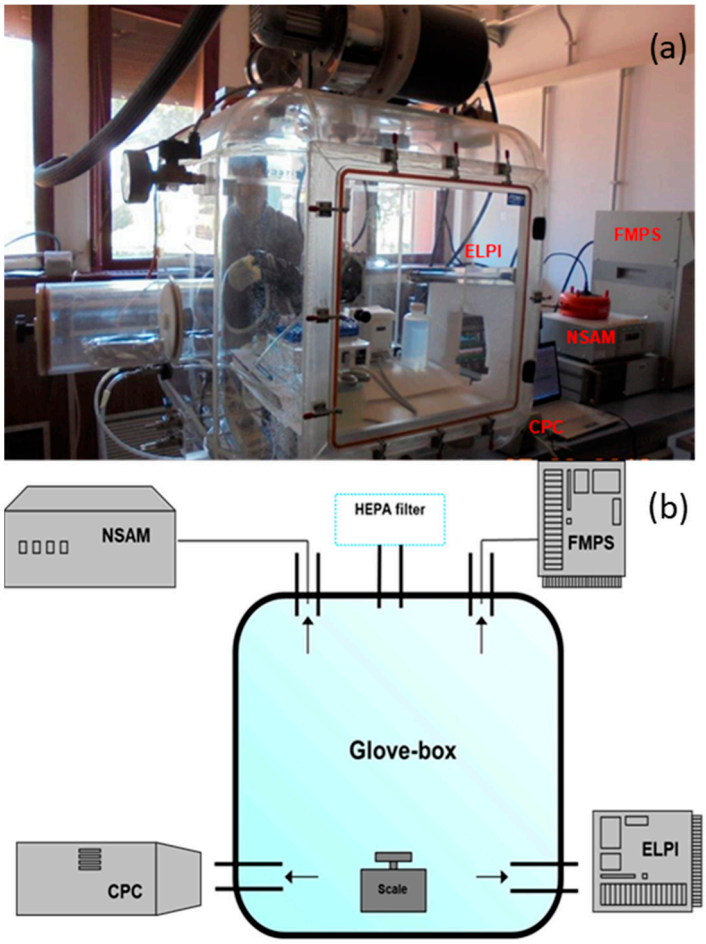


**Figure 1.** (**a**) Glove box and instruments used during simulations and (**b**) diagram of the instrumental set-up for glove box measurements.

## 3. Results and Discussion

Real-time background values were measured using the CPC for 15 min before the simulations started. Results show that inside the chamber the concentration of the particles was very low (mean value is 38 #/cm$^3$ and standard deviation is 6 #/cm$^3$) (Figure 2a).

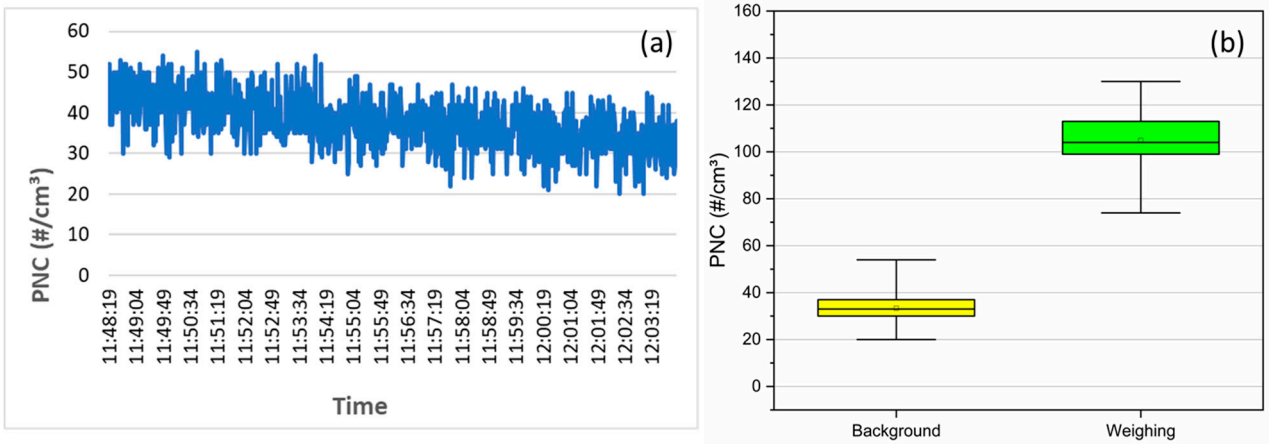


**Figure 2.** (**a**) PNC time series for the background and (**b**) box plot of PNC in the background (yellow) and in the weighing phase (green).

During the simulation of the weighing phase, the three instruments recorded simultaneously, thanks to their high acquisition rate (1 Hz), a very clear event of short duration (Figure 3).

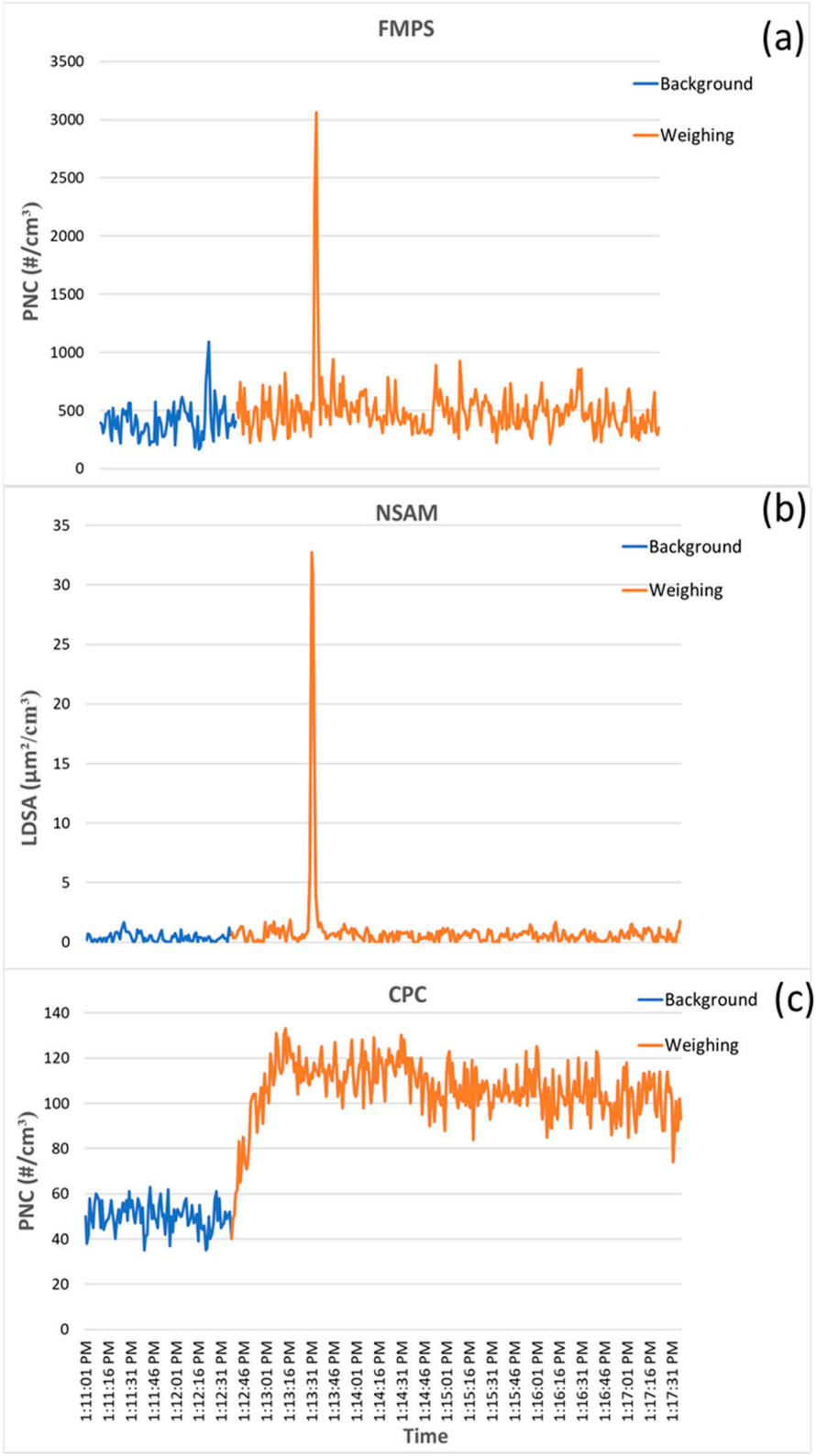


**Figure 3.** (**a**,**c**) PNC time series measured by FMPS and CPC and (**b**) LDSA time series measured by NSAM during simulation.

The distance of the sampling points from the emission source was significant in both the timing and in the intensity of the acquisition signals. In fact, while the FMPS and NSAM were positioned above the scale and in the middle of the glove box, the CPC's position was lateral and close to the work surface where the scale was placed. This probably caused a time delay (about 1 min) of the two instruments positioned in the middle of the test chamber and further away from the emissive source, but a higher signal intensity due to the extreme volatility of the particles used in the simulation (25 nm), which tend to diffuse upwards rather than downwards (conc. peak FMPS 3060 #/cm$^3$-conc. peak CPC 133 #/cm$^3$).

Box plots comparison between background and weighing phase (4 min) are reported in Figure 2b where the lowest edge of the box indicates the 25th percentile, the line inside the box marks the median and the top of the box indicates the 75th percentile. Whiskers above and below indicate the lowest and highest values. The corresponding mean values are 33 #/cm$^3$ and 105 #/cm$^3$ for the background and weighting phase, respectively. The box plot height is 7 #/cm$^3$ for the background and 14 #/cm$^3$ for the weighing. These results show higher variability and a higher median value during the weighing activity. This is due to a lack of homogeneity of plume diffusion within the glove box.

For the identification of the characteristic emission profiles, we represent the size distribution as a relative percentage, i.e., the percentage contribution of each single size channel with respect to the total concentration acquired during the simulation. This makes it possible to clearly identify which size range can be attributed the greatest contribution during the entire monitoring period. In Figure 4, the relative percentages concerning the background and the weighing phase have been compared. The two-dimensional distributions are represented by two main contributions that show a substantially bimodal distribution. The first contribution, common to both distributions, is in the 6–10 nm range, known in the literature as the nucleation mode fraction, which is characteristic of chemical reactions between elements such as $NO_x$, $SO_2$, $O_3$, $NH_3$, VOCs [27] present in the atmosphere, while the second contribution stands out in the two size profiles. In the background it falls out of the 60–100 nm range and it may be attributed to the outdoor emissions contribution due to vehicular traffic and in particular to the fraction concerning the accumulation mode [27,28]. In the weighing phase, instead, the second contribution falls out of the 25–34 nm range. In this case the emission is in the dimensional range characteristic of the $SiO_2$ test material (25 + 1 nm) and confirms that potential exposure during this phase of the production may happen. During the weighing phase, the lower percentage contribution in the 6–8 nm range from 8% to 19%, compared to the background (13–23%) shows that the emission in the 25–34 nm range has a significantly higher influence than the background, in which particles are mainly distributed in the 60–100 nm range. Furthermore, in the weighing phase, the contribution between 9 nm and 22 nm shows the presence in the test material of smaller size fractions than those declared by the manufacturer.

Finally, the LDSA has been identified, which represents the active surface area of airborne particles, i.e., the alveolar surface area of the particles inhaled by the operator that deposit in the lung [26]. This is an occupational parameter that identifies a biologically relevant dose metric for spherical nano-objects that explains about 80% of the observed variability in acute lung toxicity [29]. Figure 5 shows the signal detected by the NSAM during the weighing phase; it can be seen that at the time of the spill the total surface area increases from 15 μm$^2$ to more than 20 μm$^2$, showing a large increase in the occupied alveolar surface area, due to the small size of the particulate matter released into the environment.

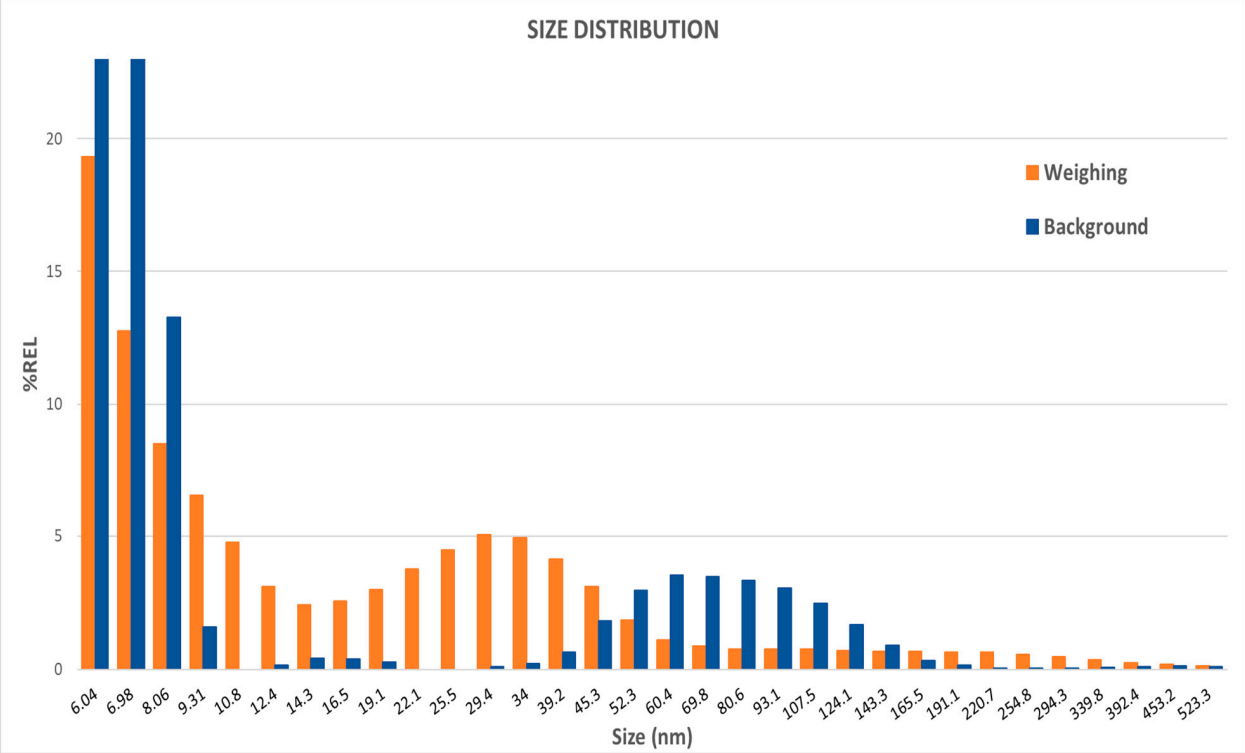


**Figure 4.** Relative percentage contribution of size distribution during weighing and background.

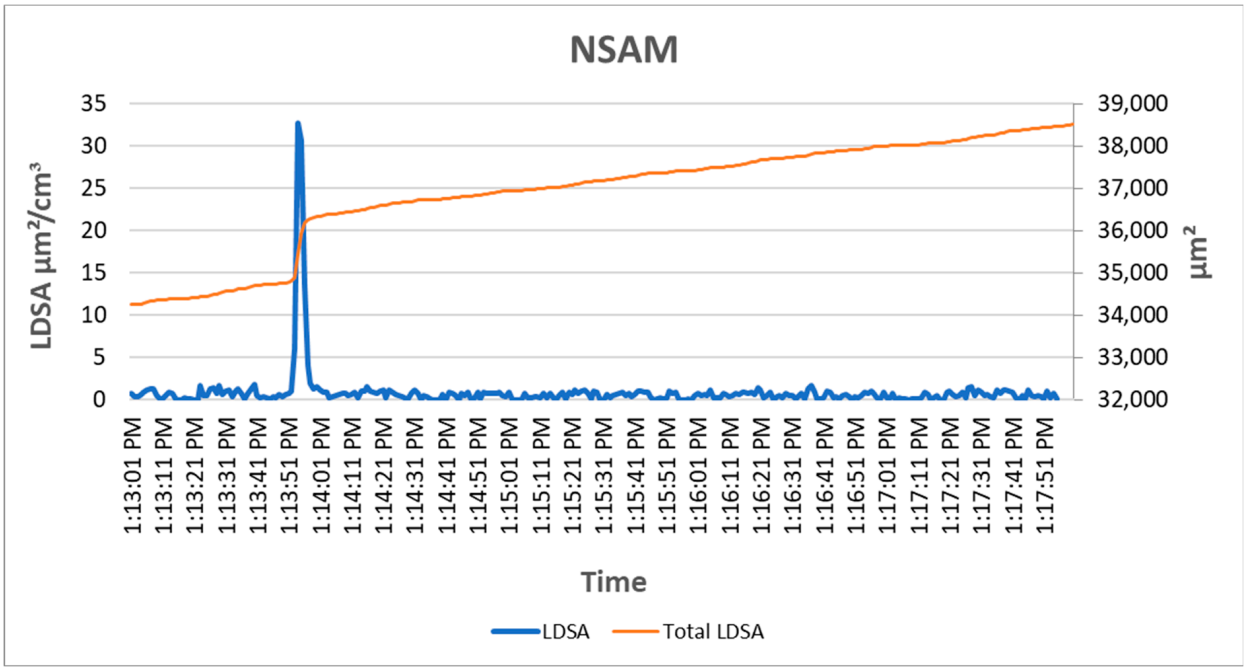


**Figure 5.** Cumulative surface area (orange) and second per second (blue) measured by the NSAM.

High resolution SEM images, Figure 6, show the $SiO_2$ NPs [24] used in the laboratory simulations of the present study; they occur as aggregates consisting of either two or three units (a,d) or even a higher number of particles (b,c), but also as single particles with a diameter of 25 nm (d). The shape and size of the aggregates are very different from each other and their dimensions vary, starting from a minimum of about 50 nm, i.e., two particles side by side (Figure 6d), to several hundred nanometers (Figure 6a–c).

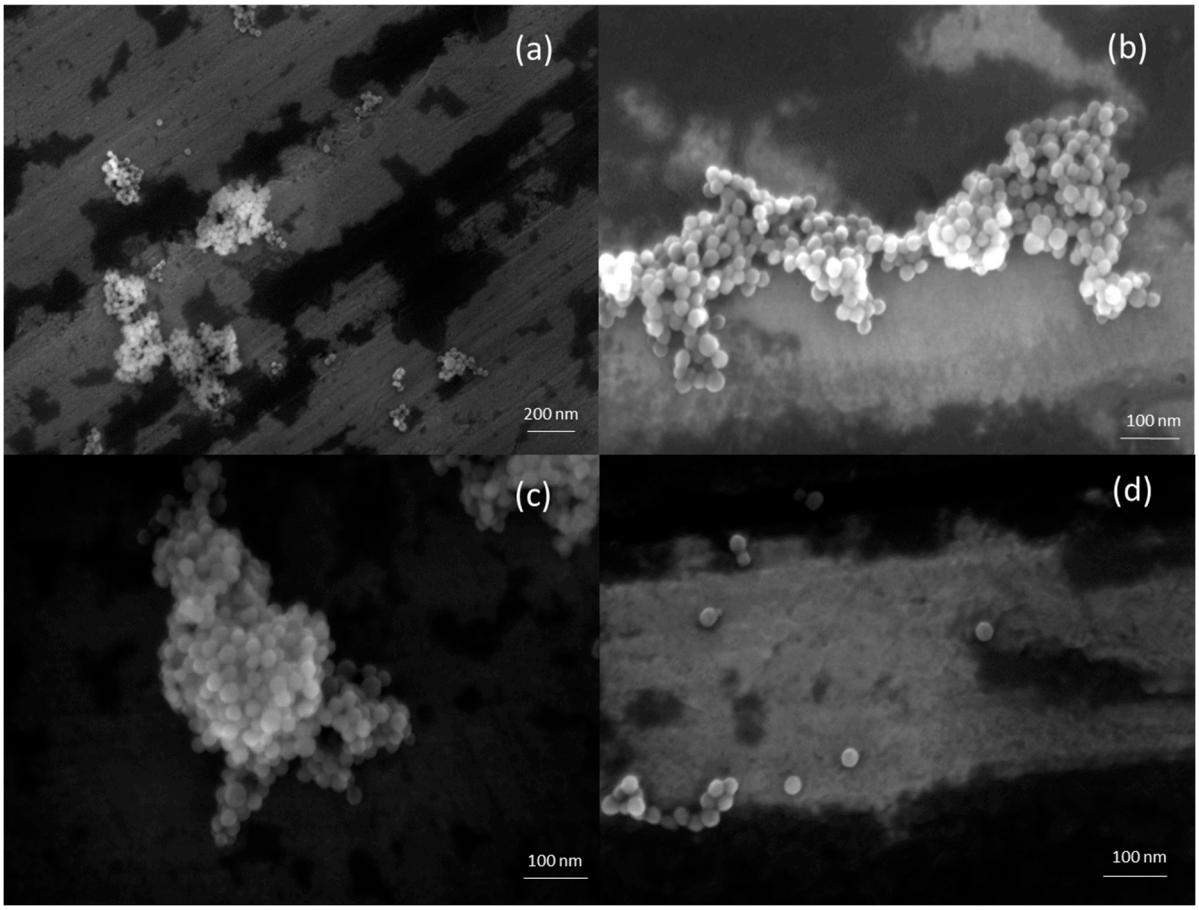


**Figure 6.** High resolution SEM images of $SiO_2$ trial sample. (**a**–**c**) aggregates of nanoparticles and (**d**) single NPs.

The particles diameter distribution was obtained measuring the diameters of 300 NPs and the corresponding histogram is shown in Figure 7. The distribution is Gaussian with the mean value at 25 nm and the standard deviation of 4 nm, according to the physiochemical properties given by the manufacturer [24].

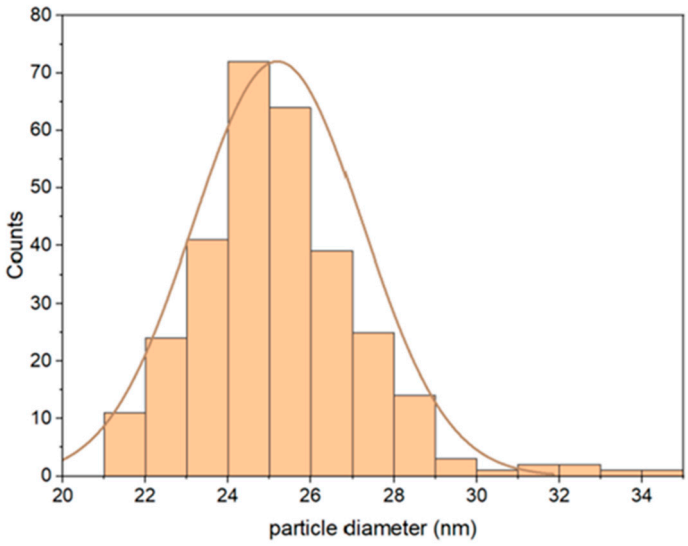


**Figure 7.** Histogram of particles diameter ($n$ = 300) and the corresponding Gaussian distribution curve (brown line).

High resolution SEM images of airborne $SiO_2$ NPs collected on ELPI filters in the glove box are shown in Figure 8. In the black boxes of Figure 8b the $SiO_2$ NPs diameters, of about 25 nm, collected during the simulation, are highlighted.

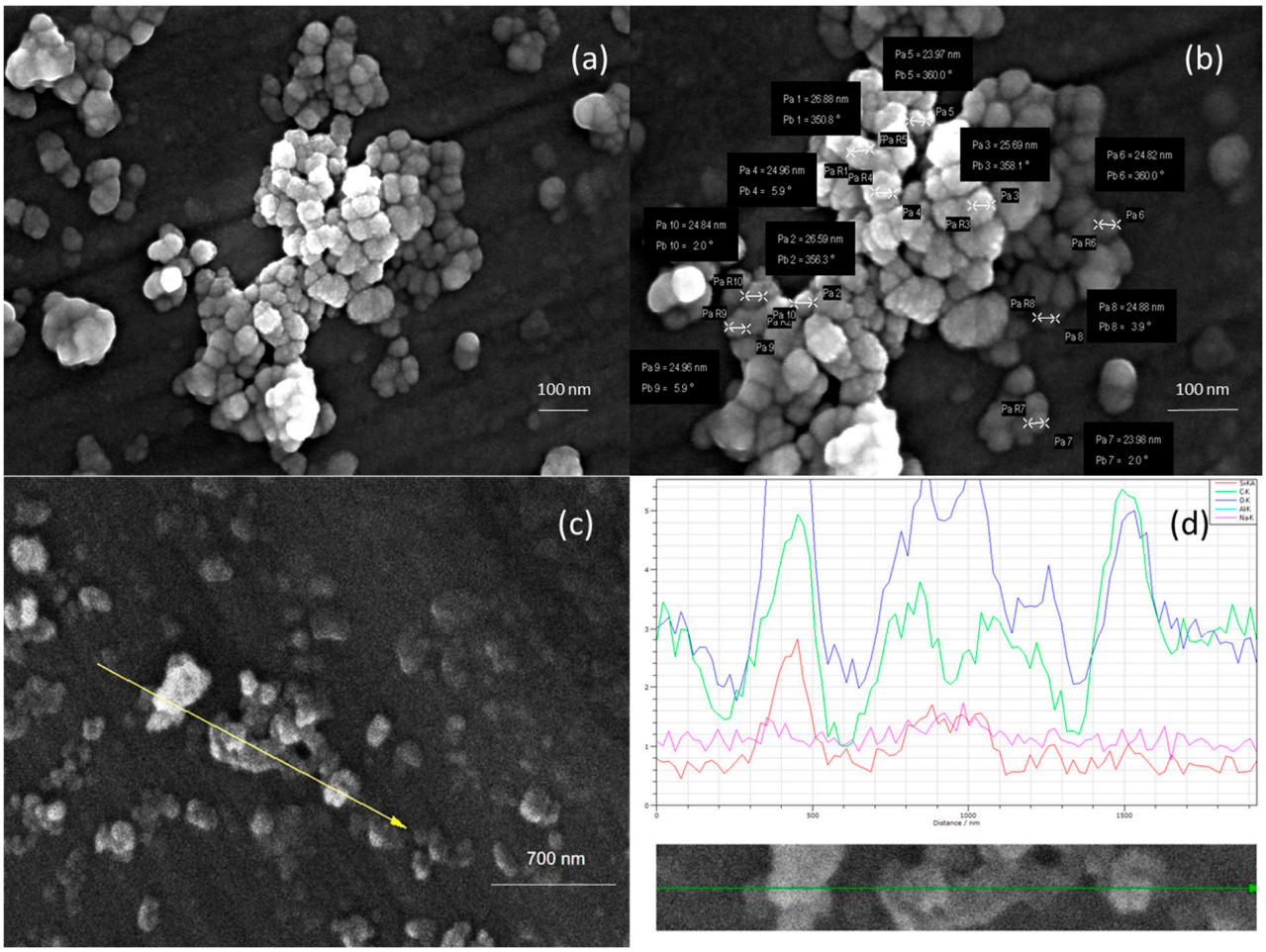


**Figure 8.** (**a**,**b**) High resolution SEM images of $SiO_2$ collected on the ELPI filters and (**c**) the EDS line scan mode acquisition following the yellow arrow, on which were acquired (**d**) the corresponding k-edge signals (silicon, red line; carbon, green line; oxygen, blue line; sodium, pink line). The symbol x-x in (**b**) indicates the length of the $SiO_2$ NPs diameter that is reported in the corresponding black boxes.

Morphological analysis of $SiO_2$ NPs sampled in the glove box (Figure 8) are in agreement with those sampled in the workplace during their production as reported in Boccuni et al. [30].

The EDS acquired in linescan mode (Figure 8c) shows that only the carbon signal (green line) and oxygen signal (blue line) are present on the substrate (range between 0 and 200 nm on the green line, Figure 8d). On the other hand, the silicon signal (red line), although low, is measured on an aggregate located between 500 and 1000 nm on the green line. To sum up, the morphology and the chemical composition of the collected NPs trace back to the airborne $SiO_2$ NPs generated during the weighing phases simulation in the glove box.

The observed results represent the fingerprint of the studied $SiO_2$ NPs which may allow their identification in workplace air under real exposure conditions.

## 4. Conclusions

In this study, laboratory simulations of $SiO_2$ NPs handling activities were carried out. The weighing activity was simulated in a controlled environment (glove box) without any influence of external emissive sources, using real-time and time-integrated instruments for the measurement of multiple parameters, in order to obtain the fingerprint of the studied NM.

Thanks to the very low background average values reached inside the test chamber (38 #/$cm^3$), it was possible to isolate the emission of $SiO_2$ NPs produced during the weighing phase, determining the related PNC, size distribution and LDSA. All instruments recorded a very clear event of short duration, with a strong increase in both PNC and LDSA. For this reason the study highlighted the need to use instrumentation with high-frequency measurements capable of detecting short-lived spills typical of production processes with short exposure phases. The comparison between the size distribution of the background and the weighing activity shows that potential exposure can occur during this activity. Furthermore, SEM characterization of the collected airborne material during the weighing phases show the typical morphology, particle size and chemical composition of handled $SiO_2$ NPs. Results showed that the simulation of the different production phases potentially at risk is a very important tool to understand the size distribution and behavior of NMs in the working environment. This makes it possible to plan monitoring and sampling and represents an important source of information for assessing and managing occupational exposure to engineered NMs.

**Author Contributions:** Conceptualization, C.N., R.F., F.B., F.T., M.S.S. and S.I.; Data curation, C.N., R.F., F.B. and F.T.; Formal analysis, C.N., R.F., F.B. and F.T.; Funding acquisition, M.S.S. and S.I.; Investigation, C.N., R.F., F.B. and F.T.; Methodology, C.N., R.F., F.B. and F.T.; Project administration, M.S.S. and S.I.; Resources, M.S.S. and S.I.; Software, C.N., R.F., F.B. and F.T.; Supervision, M.S.S. and S.I.; Validation, C.N., R.F., F.B., F.T., M.S.S. and S.I.; Visualization, C.N., R.F., F.B. and F.T.; Writing—review and editing, C.N., R.F., F.B., F.T., M.S.S. and S.I. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Italian Workers' Compensation Authority (INAIL) and coordinated in cooperation between the INAIL Department of Occupational and Environmental Medicine Epidemiology and Hygiene, and the Italian Institute of Technology (IIT). The findings and conclusions in this publication are those of the authors and do not necessarily represent the views of the employing organizations.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

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