Nanoparticle exposure and hazard in the ceramic industry: an overview of potential sources, toxicity and health effects

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Abstract

The ceramic industry is an industrial sector of great impact in the global economy that has been benefitting from advances in materials and processing technologies. Ceramic manufacturing has a strong potential for airborne particle formation and emission, namely of ultrafine particles (UFP) and nanoparticles (NP), meaning that workers of those industries are risk of potential exposure to these particles. At present, little is known on the impact of engineered nanoparticles (ENP) on the environment and human health and no established Occupational Exposure Limits (OEL) or specific regulations to airborne nanoparticles (ANP) exposure exist raising concerns about the possible consequences of such exposure. In this paper, we provide an overview of the current knowledge on occupational exposure to NP in the ceramic industry and their impact on human health. Possible sources and exposure scenarios, a summary of the existing methods for evaluation and monitoring of ANP in the workplace environment and proposed Nano Reference Values (NRV) for different classes of NP are presented. Case studies on occupational exposure to ANP generated at different stages of the ceramic manufacturing process are described. Finally, the toxicological potential of intentional and unintentional ANP that have been identified in the ceramic industry workplace environment is discussed based on the existing evidence from *in vitro* and *in vivo* inhalation toxicity studies.

Keywords: ceramic industry; occupational exposure; airborne nanoparticles; toxicity; human health

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1. Introduction

Throughout history to the present, the ceramic industry has been offering a wide range of materials with great impact on our daily lives. Broadly, a ceramic material can be defined as an inorganic, heat-resistant material composed by both metallic and non-metallic compounds. Ceramics have a broad application from construction to consumer goods and are used in several industrial processes and cutting-edge technologies. Bricks, ceramic tiles, drainage pipes, sanitaryware, household appliances, table- and ornamentalware are some of their most well-known applications. Due to their durability, strength, non-corrosive properties and ability to withstand very high temperatures, ceramics are also employed for specific uses (e.g. as enamels, abrasives and refractories) required in metallurgical processes, glass production and many other key processes across all industries (Pampuch, 2014). Advanced ceramics with unique mechanical, electrical and thermal properties emerged in the 80's having a huge impact in cutting-edge technologies. They are used to produce a variety of materials such as cutting tools, coatings, body armour, electrical and electronic equipment, engine parts and medical products (Marinescu, 2006; Munz and Fett, 2013). A significant number of the world's ceramic industries are located in European Union (EU) countries, with over 200,000 workers and an estimated production value of 28 billion euros per year (Cerame-Unie, 2012). Overall, EU ceramic industries account for 23% of the worldwide production, playing a significant role in the global economy (Cerame-Unie, 2012; Cerame-Unie, 2015; European Commission, 2007).

In general, the main process of ceramics manufacturing is quite straightforward. **Figure 1** depicts major steps of the general manufacturing process of a ceramic product, starting with the preparation of the raw material (including addition of auxiliary agents, if needed), followed by shaping, drying, surface treatment (when applicable), firing, product finishing/sorting and packaging. As shown in **Table 1**, a wide range of raw materials (oxide-based and non-oxide-based), in bulk and nanoforms, are currently utilized in the ceramic industry for different purposes. Nanotechnology has already reached the ceramic sector. For many years, nanoscale ceramic materials have been used in the biomedical field as orthopaedic implants (Traykova et al., 2006). At the same time, many nanomaterials (NM) have been applied in numerous ceramic processes. The specific nanoscale features of NM (size range 1 nm - 100 nm) (European Commission, 2011) offer the opportunity to explore novel property combinations or improved tribological, mechanical or corrosion properties for nanoceramics and nanopowders (**Table 1**). Indeed, NM such as graphene, carbon nanotubes (CNT) and carbon black are used in the ceramic industry for their reinforcing ability (Ahmad et al., 2015; Liu et al., 2016; Wakamatsu and Salomao, 2010). Titania (TiO_2) NP are also used for ceramic glaze, in tiles or as stiffening fillers (Cain and Morrell, 2001; da Silva et al., 2017; Manivasakan et al., 2010). Alumina (Al_2O_3) NP are used for making cutting tools and are often included as polishing agents just like ceria (CeO_2)

NP (Cain and Morrell, 2001). Silica (SiO_2) NP have also been incorporated in insulating ceramics due to their coolant, light transmission and fire-resistant properties in the materials (Lee et al., 2010). On the other hand, nano-sized clays have been used as catalysis, in perforation, nanocomposites and inks (Wakamatsu and Salomao, 2010). Over the last years, great attention has been given to ceramic nanocomposites due to their capacity to improve mechanical, thermal and electrical properties comparing with the conventional ceramic matrix composites (Palmero, 2015; Rathod et al., 2017). Ceramic oxides such as Al_2O_3, ZrO_2, TiO_2, Cr_2O_3 and SiO_2 are widely used as surface coating materials due to their capacity to improve resistance to wear, erosion, cavitation, fretting and corrosion (Knuuttila et al., 1998; Wang et al., 2009). Several processes for ceramics coating can be employed, for instance glazing, spraying, inkjet printing, laser-based processes and deposition techniques. These techniques often involve the injection of nanopowders that may lead to release and deposition of coarse and fine particulate matter (PM) (Fonseca et al., 2015a; Viana et al., 2017).

During the ceramic manufacturing process, the raw materials used can go through various transformation stages (**Figure 1**), that may pose different risks from the environmental point of view (Monfort et al., 2014). For instance, air emissions in the ceramic industry represent a major environmental concern due to the release of PM or dust during handling and processing of raw materials, as well as from gaseous compounds released during drying, calcination and firing of the raw materials (Barros et al., 2007; Bozsin, 1974). On the other hand, water emissions arise especially from manufacture of traditional ceramics and the resulting wastewater may contain insoluble PM, inorganic or organic materials and, in some cases, heavy metals (European Commission, 2007).

The development and exponential growth of nanotechnology-based industries, with an estimation of 6 million workers in 2020 (Roco, 2011), has raised concerns in the potential health risks of exposure to engineered (ENP) or airborne nanoparticles (ANP) (Woskie, 2010). Indeed, over the last years, NP have been regarded as emerging occupational hazards (Dolez and Debia, 2015). Yet, no official estimate of the number of workers involved in the use and manipulation of NP in the ceramic industry is currently available. This industrial sector is a relevant case of ENP and airborne particle exposure due to the increased likelihood of personal exposure to potentially hazardous materials during processing of raw materials and product manufacturing, where a wide range of nano- and bulk materials are used (Salmatonidis et al., 2019b).

The identification and characterization of NP exposure scenarios dictates the first stage of the workplace exposure assessment to these substances (Seipenbusch et al., 2014). The risk of occupational exposure to ANP strongly depends on its emissions levels, dispersion into the work environment and its eventual transformation within emission and exposure (Maynard and Kuempel, 2005). So far, it has not yet been possible to comprehensively assess the toxicity and establish the hazard of ENP and ANP, in particular, those derived from industrial ceramic

processes. Nevertheless, there are several studies in the literature evidencing adverse effects of ANP exposure on human health in occupational settings. In fact, both airborne ultrafine particles (UFP; <100 nm) and NP have been associated with cardiopulmonary health effects through a series of key biological mechanisms (Stone et al., 2017).

This review provides a broad overview of the current knowledge on the workplace exposure to ENP and ANP in the ceramic industry and their potential adverse effects to the human health. Thus, this paper outlines possible NP sources and exposure scenarios in ceramic industrial settings, illustrated by a group of published case studies. A summary description of the existing methods for ANP's workplace exposure measurement, as well as the current legislation, i.e. occupational exposure limits (OEL) and existing Nano Reference Values (NRV), will also be provided and discussed. The present work will also bring together the current knowledge of the biological and adverse health effects from exposure to some NP, in particular those that are used as input materials and/or are representative of chemical elements found in the ceramic occupational setting. The literature search was conducted across two electronic databases: NCBI (Pubmed) and Science Direct. Gray literature was identified using internet-wide search engines (Google and Google Scholar). The following search terms were used: occupational health, occupational exposure, nanoparticles emissions, ultrafine particles emissions, ceramic, industrial settings and indoor air.

2. Nanomaterials in the context of the ceramic industry

2.1. Occupational exposure to airborne nanoparticles

2.1.1. Sources and possible exposure scenarios

Occupational exposure to NP can occur from a number of different sources including: (1) production/synthesis, (2) handling/transport, (3) use/application, (4) fracturing and abrasion and (5) waste recycling/disposal (Schneider et al., 2011). The risk of aerosol particle exposure is dependent on the type of source, rate of particle transport and its removal or accumulation in the work environment, which is greatly influenced by factors such as indoor and outdoor activities, ventilation system, room design, among others (Hämeri et al., 2009; Salmatonidis et al., 2019b). The most common scenarios of aerosol NP emissions at industrial workplaces are often associated with mechanical (e.g. high-energy drilling) and combustion/heating processes (e.g. firing), thermal coating techniques (e.g. thermal spray coating), flame-based powder generation and indoor air quality-related aerosols (e.g. office machinery, cleaning fluids, infiltration of ambient nanoaerosols) (Hämeri et al., 2009). Additionally, the use of nanopowders as input materials is obviously a risk factor for the presence of ANP in the workplace air. In this context, exposure scenarios related to the manufacture and use of fullerenes, CNT, metal and metal oxide NP have been already identified and reported by Aitken et al. (2004).

Inhalation is considered the predominant route of exposure to ANP in occupational settings. However, ingestion and skin absorption exposure are also possible routes for NP during the manufacturing, use and disposal (Oberdorster et al., 2005). The smaller the particles the deeper they can penetrate into the lung (Heal et al., 2012; Oberdörster, 2000), eventually reaching the bloodstream and translocating to other organs (Fröhlich and Salar-Behzadi, 2014; Magdolenova et al., 2012; Vallyathan and Gwinn, 2006). Due to the high potential for fine and UFP release associated with the input materials and processes employed in ceramic industries, workers are likely exposed to these agents, which raise concerns on worker's health related to the poor indoor air quality (Aitken et al., 2004; Hristozov and Malsch, 2009).

At present, few studies on NP exposure in the ceramic industry exist. Most of ceramic raw materials are in the powder form. Therefore, when processing these materials, particularly in handling, transport, storage and mechanical treatment operations, fine particulate suspensions are generated in the air (Monfort et al., 2006). Moreover, high-energy processes such as laser ablation (LA), laser sintering (LS), physical vapour deposition (PVD), inkjet printing, plasma thermal spraying and glazing have a high potential for airborne particle formation and release to the workplace air (Fonseca et al., 2016; Fonseca et al., 2015b; Salmatonidis et al., 2019a; Salmatonidis et al., 2018; Viana et al., 2017). Machining processes (e.g. cutting, drilling, grinding) also possess a great potential for ANP release to the workplace environment as illustrated by manufacture of functionally graded materials by friction stir processing to produce aluminium (Al) alloys reinforced with SiC particles (Gandra et al., 2011). Fire and combustion processes are also highly associated with dispersion of combustible NP in the air, representing a greater risk (Hodson et al., 2009). For instance, NP containing metal oxide such as Al, cadmium (Cd), chromium (Cr), and copper (Cu) have been associated with welding processes (Donaldson et al., 2005).

To sum up, the two major potential sources that may contribute to workplace exposure to ANP in the ceramic industry includes the use of nanopowders as input materials for ceramics production and airborne, process-generated NP released during the manufacture of ceramics as the result of the employed industrial processes and equipment (**Figure 2**). Due to the limited information on the ANP occupational exposure, these materials cannot be considered safe without thorough investigation regarding their exposure levels and toxicity, which is a current research gap. In the section 2.1.3. will be explained in detail the available studies found in the literature regarding ANP occupational exposure in the ceramic industry.

2.1.2. Methods for workplace exposure evaluation

To identify and characterize workplace exposure scenarios, two approaches can be adopted: studies at real workplaces or laboratory simulations of workplaces/work processes. The advantage of the first approach is to obtain data under real work conditions, however, is a time-consuming

approach due to the numerous background aerosols. On the other hand, simulated workplace environments allow a clear differentiation of the aerosol's source, i.e. between background or particles unintentionally produced during the manufacturing process (Kuhlbusch et al., 2011). Measurement of worker's exposure to ANP can be performed using traditional industrial hygiene approaches that include: i) static (area) sampling, where samplers are placed at the source location, and ii) personal sampling, where samplers are fixed in the worker's breathing zone (Hodson et al., 2009). Accordingly, the available instrumentation for ANP exposure assessment can be divided into stationary, portable and personal (**Table 2**). Stationary equipment is the most accurate, however it only gives information at a single location at time. On the other hand, portable equipment, though easy to transport has lower accuracy and particle size resolution than the stationary equipment. In turn, personal equipment allows to monitor exposure levels in worker's breathing zone and are small and lightweight enough to be carried over an eight-hour shift, without compromising any activity carried out by the worker (Asbach et al., 2017; Tsai et al., 2012). Generally, personal sampling is considered the preferred method since it provides an accurate representation of the worker's exposure regarding inhalable, thoracic or respirable particle fractions (Stebounova et al., 2018). **Table 2** presents a general overview of the existing methods and available instrumentation for ANP quantification. Time-resolving instruments (direct-reading) allow real-time determinations of parameters such as particle number concentration, particle size distribution or lung deposited surface area (LDSA) concentration, while time-integrating equipments are used for sampling material onto substrates and filters for posterior analysis on particle chemical composition and/or morphology (Kuhlbusch et al., 2011; O'Shaughnessy, 2013). The main drawback of direct-reading measurements is the limited instrument sensitivity to detect small particles (Asbach et al., 2017; Todea et al., 2015). Thus, the type of assessment (ambient *vs* worker-oriented monitoring) and equipment used will greatly condition parameters to be assessed and quality of the obtained data. However, regardless the selected method for exposure monitoring, sampling conditions (start time, duration and frequency) are also critical for an accurate and reliable assessment of workers exposure. Furthermore, exposure measurements must take place before and during production and/or processing in order to understand the variation between ANP background levels and those found during the manufacturing activities (Hodson et al., 2009).

Despite exposure and air quality standards for particles being based on mass, when it comes to ANP or UFP, mass might not be the most meaningful metric due to the poor accuracy for measuring low mass concentrations in comparison with coarser particles (Oberdörster, 2010). At the same time, there is also an ongoing debate around NP dose metrics to be used in toxicological studies (Oberdörster et al., 2005; Oberdörster et al., 2007; Paur et al., 2011; Riediker et al., 2019; Wittmaack, 2006; Wittmaack, 2007). Features such as surface area, morphology and chemical composition have been found to play a relevant role in the responses to inhaled UFP and ANP

(Oberdörster et al., 2005; Stone et al., 2017). While some hold the view that NP-induced effects seem to be more strongly associated with size than mass (Oberdörster, 2010; Singh, 2015), other authors postulate that depending on NP physicochemical features and mode of action, particle surface area might be the most biologically-relevant metric (Schmid and Stoeger, 2016). At present, there is no available instrument capable of measuring the ANP surface area. However, LDSA concentration is a surface-area related parameter that can be determined that corresponds to the fraction of the airborne particle surface area concentration deposited in the lung (Todea et al., 2015) that is more easily measured than total surface area (Geiss et al., 2016). The particle lung deposition estimated by LDSA is an important aspect to take into consideration in occupational assessment, being influenced by parameters such as particle size, surface chemistry, distribution, breathing pattern and lung morphology rather than particle mass concentration (Reche et al., 2015).

Measurement of workplace exposure is thus essential to identify ANP sources and exposure levels, to implement control measures to efficiently reduce the exposure, contributing for the prevention of potential risks for worker's health. In this regard, mathematical/computational modelling can also be helpful to estimate exposure assessment through the analysis of the transport and fate of particles within the workplace environment (Schneider et al., 2011). Control banding (CB) is also of interest to manage workplace risks associated with occupational exposure to NM. Considering NM particularities, specific CB tools for NM have been developed (e.g. Stoffenmanager Nano, Nanosafer, CB Nanotool), with exposure assessments and derived risk levels (bands) based on different concepts and assumptions, and outputs in different formats (Liguori et al., 2016; Schulte et al., 2010; van Broekhuizen et al., 2012a).

2.1.3. Occupational exposure limits (OEL)

Occupational exposure limits (OEL) aim to protect from levels of exposure to airborne chemicals and particles that may endanger human health (Schenk and Johanson, 2010; Schulte et al., 2010). These are mostly derived from extrapolation of animal data to human, with all the related uncertainties and limitations of this estimate. A common procedure towards the definition of OEL in case of uncertain and insufficient data is the use of uncertainty factors (Schenk and Johanson, 2010). Currently, no official OEL for NP have been establish by any regulatory agency (Mihalache et al., 2017), mostly due to the uncertainty of ANP impact on human health (van Broekhuizen et al., 2012b). Notwithstanding, some organizations have provided guidance on benchmark levels. The Dutch Social and Economic Council has proposed Nano Reference Values (NRV) as a provisional substitute for OEL (**Table 3**) and preventive measures to control exposure to NP in the workplace environment. NRV are calculated based on the background-corrected number of NP with the diameter of 100 nm and a mass of 0.1 mg/m^3 (Mihalache et al., 2017) and not derived from any toxicological and epidemiological data. Accordingly, they constitute a

precautionary risk management tool for NM handling or processing in the workplace, but they do not guarantee that exposures below those values are safe as they are built on presumable health effects (van Broekhuizen et al., 2012a).

Pietroiusti and colleagues have compiled a number of proposed OEL for several ENP recommended by different institutions worldwide (Pietroiusti and Magrini, 2014; Pietroiusti, 2018). The World Health Organization (WHO) has also released guidance on protection of workers health from manufactured NP exposure based on the existing evidence of NP effects on human health, where a list of proposed OEL is also presented (World Health Organization, 2017). Altogether, these compilations demonstrate the efforts and progresses made over the past years to establish and define concrete and coherent OEL for NP. Nevertheless, there is still much work ahead, particularly in defining ANP-derived OEL in the context of industrial activities such as in the ceramic sector. The ongoing discussions on the metrics to be used for future "nano-OEL", i.e. mass-based or particle number-based, is also making difficult their successful implementation. While mass-based OEL are suitable for bulk materials, values for materials at the nanoscale seem to be rather high (Schulte et al., 2010). An additional limitation for the creation of nano-OEL is that NM are usually measured as primary NP and these are frequently presented in the workplace environments as micro-sized agglomerates, which may impar the correct classification for these OEL (Mihalache et al., 2017).

2.2. Airborne nanoparticle release and exposure in the ceramic industry: case studies

Just in recent years, studies on workplace exposure to ANP in ceramic industry settings began to emerge in the literature. This chapter focus on the existing case studies of ultrafine and ANP emissions during different stages of the ceramic manufacturing process, which are summarized in **Table 4**.

2.2.1. Firing process

The pioneering work of Voliotis et al. (2014) investigated the size, concentration and elemental composition of particles emitted during the different stages of the ceramic firing process, i.e. before and after ceramics painting and glazing, in a traditional small-sized pottery studio. This study showed that when the kiln reached temperatures above 600°C most of the emitted particles were in the nanometer range. The size of the emitted ANP varied between 30-70 nm during the first stage of the firing process, where the ceramics were unpainted and unglazed, with a peak concentration around 6.5×10^5 particles/cm^3. In the second stage of the firing process, where the ceramics were painted and glazed, the mean particle size ranged from 15 to 40 nm and their particle number concentration peaked at 1.2×10^6/cm^3. Elemental analysis by Energy-Dispersive X-ray (EDX) spectroscopy of individual particles collected during the two firing stages revealed

that the main element found was Si, emitted by the clay, whereas the second firing stage mostly generated particles containing Pb and Cu derived from the pigments used for glazing (Voliotis et al., 2014).

2.2.2. Surface treatment processes

In the ceramic industry, the use of laser-based techniques to improve ceramics surface properties is becoming widespread. The high-energy nature of these lasers may entail some risks of NP generation and emission. Fonseca and co-workers have investigated particle emissions during two processes using laser technology, laser sintering (LS) and laser ablation (LA) of ceramic tiles. In the first study, particle measurements were performed at laboratory scale both at the emission source, a three meters long pilot plant-scale furnace, and at the worker's breathing zone (Fonseca et al., 2015b). ANP emissions were found to be highly dependent on temperature and tile chemical composition and induced by thermal and nucleation processes. Primary ANP emissions with a particle mean diameter of 18 nm reached concentrations up to 6.7×10^6 particles/cm^3. In the indoor area (breathing zone), particles decreased in number, mass and LDSA concentration but they were still present at high concentrations and in a size range of 13 to 27 nm. In the workers' breathing zone, the collected particles presented diameters larger than in the furnace but smaller than the background air. The highest concentrations of metals including Zn, Pb, Cu, Cr, As and Ti have been found in the UFP fraction (Fonseca et al., 2015b). In a second study, the authors addressed ANP formation and release mechanisms from tile sintering using high power CO_2 lasers but at industrial scale in a seven meters long industrial furnace (Fonseca et al., 2016). They have underlined the difficulty to directly extrapolate particle emissions obtained at laboratory scale to industrial scale due to three main reasons: (1) Fuel: laboratory furnaces are electric, while industrial furnaces are gas-powered; (2) Gas flow: inside industrial furnaces it is much higher than in laboratory furnaces; and (3) Area: a larger working area is expected in industrial than in laboratory settings resulting in a higher particle dispersion and consequently lower particle concentrations in the breathing zone. According to this workplace exposure evaluation, new particle formation from gaseous precursors occurred during thermal treatments in both red clay and porcelain ceramic materials. This phenomenon was independent of the laser treatment. Generation and emission of ultrafine and nano-sized airborne particles occurred during the sintering process of the ceramic facility under study, and the measured exposure concentrations exceeded NRV (Fonseca et al., 2016).

Salmatonidis et al. (2018) investigated the mechanisms behind ANP formation and emission during pulsed LA of four types of ceramic tiles, using two different laser setups: near-infrared laser widely used for engraving, and mid-infrared laser generally employed for cutting and welding. These authors considered the influence of the ceramic material properties, process parameters and lasers wavelength on the formation and release of ANP, characterizing them in

terms of size, particle number and mass concentration both at laboratory and pilot-plant-scale. Regardless the laser wavelength used and type of ceramic tile, a high particle number concentration of ANP, from $3.5 \times 10^4/cm^3$ to $2.5 \times 10^6/cm^3$ was released. Particles of SiO_2 and Al_2O_3 with sizes superior to 10 nm were formed and released during the LA process of the ceramic tiles. ANP emissions were associated with different mechanisms including nucleation and melting, which highly contributed to the particle number concentration observed. In addition, the ceramic surface and chemical properties exerted a great effect on the particle number and mass emissions of ANP (Salmatonidis et al., 2018).

Viana et al. (2017) evaluated airborne UFP (<100 nm) and NP (<50 nm) emissions during atmospheric plasma spraying (APS) of ceramic coatings at industrial-scale pilot level. Plasma spraying was performed inside a closed chamber located inside the worker's room, where the breathing zone was 1.5 m away. Particle size ranged between 10 and 700 nm and ultrafine emissions were higher than initial background concentrations, reaching up to 3.7×10^6 particles/cm^3 and $2.0 \times 10^6/cm^3$ inside the spraying chamber and at workers' area, respectively. These results demonstrate the hazardous potential of these airborne particles in ceramic industrial environments. In this study, it has also been applied a risk prevention protocol consisting of (1) improved air circulation in the plasma chamber and delayed door-opening system, (2) improvement of the sealing of the extraction system ducts and (3) air exchange rates (forced ventilation in the worker area). These measures proved to be effective in reducing UFP concentrations in the workers area (Viana et al., 2017).

Recently, Salmatonidis and colleagues have evaluated particle emission and its impact on worker's exposure during thermal spraying of ceramic coatings onto metallic surfaces (Salmatonidis et al., 2019a). Several parameters were analysed including particle number and mass concentrations, LDSA, mean diameter, and size distributions of NP, fine and coarse particles. Inside the thermal spraying booths, high particle number ($>10^6/cm^3$) and mass concentrations (60-600 µg PM_1/m^3) have been detected. Those particles were transported towards the worker area, increasing the concentrations in this region by one order of magnitude in terms of number (10^4-10^5 particles/cm^3), and up to a factor of 4 in terms of mass (44-100 µg PM < 1µm/m^3) contributing for the potential worker's exposure to these particles (Salmatonidis et al., 2019a). Characterization of the emitted ANP found at the workers area revealed that they were irregularly-shaped, mostly between 26–90 nm and constituted by metals such as nickel (Ni), Cr and tungsten (W). ANP generation and emission were mainly associated with mechanical attrition, but also melting-evaporation-condensation of the feedstock materials. Inhaled dose rates ranged from 353×10^6 - 1024×10^6 particles/min, where 70% of particle deposition was estimated to occur in the alveolar region (Salmatonidis et al., 2019a).

2.2.3. Handling and packaging of ceramic materials

Ribalta et al. evaluated the workers personal exposure to airborne particles during handling of five highly used ceramic materials with different characteristics (silica sand, three types of quartz and kaolin), as well as material dustiness, at pilot-plant-scale (Ribalta et al., 2019a). Dustiness measures the predisposition of a material to generate airborne dust during the handling and constitutes a relevant parameter to be taken into account in the context of ANP exposure evaluation in occupational settings. In this study, several parameters were evaluated including particle mass, number concentration, LDSA and particle size distribution. All ceramic materials under study presented a great impact on workers exposure regarding inhalable and respirable mass and images of Transmission Electron Microscopy (TEM) supported the presence of ANP in the form of aggregates (300 nm - 1 µm). In terms of mean inhalable mass concentrations, higher levels were consistently found during materials handling under high-energy settings compared to background levels. Nonetheless, in terms of particle number concentrations, no major differences were found before (background levels) and during materials handling. Moreover, a correlation between exposure concentration and dustiness has been demonstrated under the conditions and materials used, strengthening the idea that dustiness is a relevant parameter for the prediction of worker exposure (Ribalta et al., 2019a).

Ribalta et al. have also investigated the effectiveness of source enclosure in particle release during packaging of ceramic raw materials (Ribalta et al., 2019b). Worker's exposure was monitored during the packaging process of seven ceramic materials in three packaging lines equipped with different levels of source containment: low (L), medium (M) and high (H). As expected, real-time measurements showed that packaging lines L and M significantly increased exposure concentrations, while non-significant increases were detected in line H. These findings demonstrated the effectiveness of source enclosure as a mitigation strategy in the case of packaging of ceramic materials. The ICRP human respiratory tract model revealed that particle deposition occurred mainly in the alveoli (51–64%) followed by head airways (27–41%) and trachea bronchi (7–10%). In this study, different risk assessment tools (Stoffenmanager, ART, NanoSafer) were also employed to test the effectiveness of source containment. The comparison between the results from different risk assessment tools and the measured exposure concentrations evidenced that all of the tools overestimated exposure concentrations, by factors of 1.5–8. These findings underline the limitations of the available risk assessment tools to predict real scenario exposure levels and the urgent need to improve them.

2.2.4. General remarks

All of the aforementioned case studies evidence the relevance of studying fine, ultrafine and ANP process-generated emissions in ceramic workplaces and their impact on worker air exposure. Even though the number of workers in each of the case studies is not especially high (ranging approximately between 2 and 10 workers/activity) (Salmatonidis et al., 2019b; Viana et al., 2017;

Voliotis et al., 2014), there are two main factors supporting the relevance of these exposures: (1) the fact that particles are rapidly transported across the industrial facilities (Ribalta et al., 2019b), impacting workers active in other tasks different from the ones assessed in the case studies, and therefore not wearing any personal protective equipment (PPE), and (2) the increasing number and type of activities during which process-generated NP are being identified (see the recent case studies above), which indicates that this type of particles may be more frequent in industrial scenarios than previously thought. Overall, the reported observations and findings emphasize the importance of the risk assessment and the implementation of prevention procedures to improve occupational air quality in ceramic industrial settings.

3. Human health effects of exposure to intentional and unintentional nanoparticles in the ceramic industry: what do we know so far?

In spite of the great number of studies addressing the issue of NP toxicity, many challenges remain to identify the health impact of exposure to these materials. In fact, inconsistent and often conflicting data regarding the safety of NP are found in the literature. Consequently, relatively little is known about their effects on human health. Despite their distinct origins, NM and UFP share many similarities in terms of their physicochemical properties and *in vitro* mode of action (MoA) (Stone et al., 2017). Accumulating evidence shows that exposure to ambient air PM is associated with negative health outcomes and nano-sized (ultrafine) particles are likely to play an important role. The lung is a main target for inhaled NP though they may also translocate into the bloodstream triggering nonspecific interactions with secondary organs and systemic tissues (Oberdörster et al., 2005). Indeed, exposure to nano-sized particles has been widely associated with impaired lung function and inflammation, vascular dysfunction and adverse acute respiratory and cardiovascular effects (Stone et al., 2017). In turn, these adverse effects are strongly linked with different diseases such as lung cancer (Knaapen et al., 2004), bronchitis, acute asthma (Kreyling et al., 2006), cardiac infection, hypertension, atherosclerosis, ischemia and cardiac arrhythmia (Brook et al., 2004; Kelly and Fussell, 2015; Schulz et al., 2005; Shannahan et al., 2012), among others. In the context of the ceramic industry, many reports show that occupational exposure to ceramic dusts and fibres is associated with chronic bronchitis, chronic obstructive pulmonary disease, reduced lung function, wheezing, breathlessness and dry cough (Jaakkola et al., 2011; Kargar et al., 2013; Trethowan et al., 1995).

From the *in vitro* and *in vivo* studies conducted so far, NP mechanisms of action start to be unravelled. Major mechanisms involved in NP-induced pulmonary toxicity events already described in the literature include: (1) ineffective clearance of NP; (2) intracellular uptake/internalization of NP; (3) impairment of lung macrophage phagocytosis; 4) loss of plasma membrane integrity; (5) mitochondrial dysfunction; (6) oxidative stress (ROS generation, glutathione depletion, lipid peroxidation); (7) cytokine production and activation of inflammatory

signalling cascades; (8) genotoxicity (DNA and chromosomal damage, altered DNA methylation and repair); (9) altered cell cycle regulation, among others (Bakand et al., 2012; Li et al., 2010; Paur et al., 2011; Pietroiusti et al., 2018 ; Stone et al., 2017).

Singh et al. reviewed several aspects related to cellular uptake and possible toxicity mechanisms of ceramic NP for drug delivery applications. In this paper, aspects related to the mechanisms of NP internalization, possibly through passive uptake or simple adhesive interactions, accumulation in phagosomes, pattern of subcellular distribution (e.g. cytoplasm, mitochondria, lipid vesicles or nucleus) and its relation to observed adverse biological outcomes (e.g. organelle and genetic material damage, cell death) are discussed (Singh et al., 2016).

Over the years, more and more NM have been introduced in the ceramic industry. At the same time, as previously described, NP emissions can arise from multiple processes employed in the ceramic industry that neither produce nor use NM, which are referred as process-generated nanoparticles (PGNP). Below, a major overview of the existing *in vitro* and *in vivo* pulmonary toxicology studies of representative ENP and PGNP found in ceramic occupational settings (described in section 2.2) will be presented.

Clays are one of the most common materials applied in the ceramic sector. Lately, there has been a wide implementation of nano-sized clays in the industry, which raises concerns for the potential risks of these NM for the exposed workers health. *In vitro* studies have shown that nanoclays exposure (e.g. montmorillonite) decreases cell viability and induces changes in morphology and cell-cell interactions in human lung epithelial cells (Wagner et al., 2017a; Wagner et al., 2017b; Wagner et al., 2018). Stueckle et al. also evaluated the effects of pre- and post-incinerated forms of uncoated and organomodified nanoclays in mice and observed that pulmonary inflammation and toxicity relies on coating presence and incineration status. The obtained data revealed that coated and incinerated nanoclays induced less inflammation and granuloma formation in mice than pristine montmorillonite (Stueckle et al., 2018).

Metals and metal oxides NP are also commonly utilized in the ceramic industry. Brunner et al. (2006) evaluated the toxicity of CeO_2, TiO_2, ZrO_2 and ZnO NP in human lung mesothelioma (MSTO) exposed to 0-30 ppm for 3- and 6-days. Among the tested NP, ZnO NP were the most cytotoxic, while CeO_2, ZrO_2 and TiO_2 NP induced analogous responses in MSTO cells. Similar findings were observed by Xia et al. that have compared the effects of ZnO and CeO_2 NP in human bronchial epithelial cells (BEAS-2B). These authors found that ZnO NP induced greater cytotoxicity and cell death through generation of ROS and induction of inflammation than CeO_2 NP, whose exposure suppressed ROS production and induced resistance to an exogenous source of oxidative stress in BEAS-2B cells (Xia et al., 2008). Lanone et al. have also comparatively assessed the toxicity of Al_2O_3, CeO_2, TiO_2, ZrO_2, CuO and ZnO NP up to 5000 µg/mL at 24 h after exposure in human alveolar epithelial (A549) and macrophage (THP-1) cell lines. While exposure to Al_2O_3, CeO_2, TiO_2 and ZrO_2 NP caused a moderate toxicity in both cell lines,

incubation with CuO and ZnO NP markedly decreased cell viability of A549 and THP-1 cells (Lanone et al., 2009). Moreover, Kim et al. also evaluated Al_2O_3, CeO_2, TiO_2 and ZnO NP cytotoxicity to human lung cells and found out that ZnO NP were the most cytotoxic with regard to cell proliferation, viability, membrane integrity and colony formation endpoints. On the other hand, Al_2O_3, CeO_2 and TiO_2 NP did not significantly affect cell proliferation and viability, being Al_2O_3 NP the least toxic NP tested (Kim et al., 2010).

Regarding the CeO_2 NP, there is some controversy around its toxicological potential in pulmonary cell models. While some studies have demonstrated that exposure to CeO_2 NP decrease cell viability, induce oxidative stress (Eom and Choi, 2009a; Lin et al., 2006b; Park et al., 2008b) and affect DNA integrity (De Marzi et al., 2013) of human lung epithelial cells, others reported no signs of cytotoxicity following exposure to these NP (Park et al., 2008a; Rothen-Rutishauser B, 2009).

Monocultures are a convenient but a rather simplified model that can be less sensitive to predict toxicity than more advanced cell culture models. Three-dimensional (3D) cultures with a fully differentiated epithelium, more than one cell type, and with a morphology and genome wide expression similar to that observed *in vivo* have been shown to closely mimic human exposure to aerosolized NP (Clippinger et al., 2016), offering a good alternative to *in vivo* testing. In addition, lung cell models grown and exposed to aerosols at the air-liquid interface (ALI) are increasingly being recognized as a more realistic system to address the toxicity of inhaled agents compared to the classical submerged exposures (Lacroix et al., 2018). In this regard, Kupper et al. investigated the toxicity of CeO_2 NP in human lung epithelial A549 and BEAS-2B cell lines under submerged conditions but also in 3D cultures of human bronchial epithelium (MucilAir™ cultures) at ALI conditions. The obtained results showed that CeO_2 NP did not induce cytotoxicity, as assessed by the LDH release assay, but caused a concentration-dependent increase in DNA damage levels in BEAS-2B exposed cells, while exposure of A549 cells to CeO_2 NP induced a minimal increase in LDH and a distinct increase in DNA damage. On the other hand, none of these responses were observed in MucilAir™-exposed cells, where minimal translocation of CeO_2 NP across the 3D barrier was detected (Kuper et al., 2015). The mucociliary clearance appeared to prevent aerosolized CeO_2 NP to reach the respiratory epithelial cells in the 3D airway cultures. Nevertheless, toxic responses such as cytotoxicity (e.g. loss of viability and plasma membrane integrity), inflammation responses, recruitment of alveolar macrophages and neutrophils were observed *in vivo*, in the lung tissue of rats exposed to CeO_2 NP by intratracheal instillation (Ma et al., 2011), nose-only (Srinivas et al., 2011) and whole-body inhalation (Keller et al., 2014) to CeO_2 NP.

TiO_2 NP are widely used in the industry and consumer products worldwide due to their high stability, anticorrosive and photocatalytic properties (Shi et al., 2013). Still, the International Agency for Research on Cancer (IARC) has classified bulk TiO_2 as possibly carcinogenic to

humans (group 2B) (Baan, 2007), which raised concerns about the genotoxic potential of TiO_2 in the nanoform. At present, the toxicological potential of TiO_2 NP is controversial. According to the previously mentioned *in vitro* cytotoxicity studies, TiO_2 NP seem to moderately affect lung cell lines. However, several *in vitro* studies have shown that TiO_2 NP can cause DNA damage and impair DNA repair mechanisms in lung cells. In this regard, Biola-Clier et al. compared the response of bronchial (BEAS-2B) and alveolar (A549) epithelial cells upon exposure to 1–100 µg/mL of TiO_2 NP in terms of DNA integrity. Both cell lines exhibited similar responses, i.e., moderate cell death, oxidative DNA damage and impaired DNA repair. So far, no consistent *in vivo* genotoxic profile has been established for TiO_2 NP, with the route of exposure and dose influencing the genotoxic outcome (Chuang et al., 2014). Several *in vivo* inhalation and instillation studies showed negative genotoxicity outcomes for TiO_2 NP (Lindberg et al., 2012; Naya et al., 2012). At the same time, Relier et al. found that only under overload conditions (3 instillations of 10 mg/kg) TiO_2_NM105 (rutile-anatase) induced delayed genotoxicity in lung, associated with persistent inflammation (Relier et al., 2017). In fact, the lung inflammation is the most common adverse outcome derived from TiO_2 NP exposure (Noël and Truchon, 2015).

Silica (SiO_2) is one of the most common and well-studied occupational hazards (Poinen-Rughooputh et al., 2016). Occupational exposure to crystalline SiO_2 is intimately related with the development of silicosis, a fibrotic lung disease (Leung et al., 2012). An increased risk of lung cancer has been found in groups exposed to high levels of respirable SiO_2 such as miners and brick, diatomaceous earth, pottery, sand and stone workers. However, carcinogenicity of inhaled crystalline SiO_2 has also been observed in a population with a wide variety of exposure circumstances, suggesting that the burden of cancer induced by SiO_2 may be much greater than previously expected (Vida et al., 2010). Micro-sized SiO_2 NP is widely used in the ceramic industry, but the use of nanosized SiO_2 has potential to grow in the coming years. SiO_2 toxicological potential was believed to be related with its crystallinity. Amorphous SiO_2 has been considered less harmful than crystalline SiO_2 (Murugadoss et al., 2017). Notwithstanding, most recent findings (Pavan et al., 2019; Pavan and Fubini, 2017; Turci et al., 2016) suggested that crystallinity per se cannot explain toxic effects of SiO_2, which are more linked to surface chemistry, specifically to silanol disorganization. The comparison studies show that amorphous SiO_2 NP can induce similar acute toxicological activity compared to crystalline silica, but much less chronic effects (at 3-months), which can be attributed to its lower biopersistence (Arts et al., 2007). *In vitro* studies in lung cell lines have shown decreased cell viability, increased levels of oxidative stress (e.g. ROS production, lipid peroxidation) (Akhtar et al., 2010; Eom and Choi, 2009b; Lin et al., 2006a; McCarthy et al., 2012), induction of DNA damage (Decan et al., 2016; Maser et al., 2015) and inflammatory responses (Panas et al., 2014; Panas et al., 2013) following exposure to SiO_2 NP. Most of the *in vivo* instillation and inhalation studies for amorphous SiO_2 NP available in the literature reported induction of inflammatory responses (Cho et al., 2007;

Guichard et al., 2015) but no genotoxic responses (Guichard et al., 2015; Maser et al., 2015; Sayes et al., 2010) though *in vitro* these NP seemed to present a high toxic potential.

Copper (CuO) and nickel (NiO) oxide NP can also be used in the ceramic industry incorporated in inks for surface coating treatments. There are several studies showing a marked toxicity effect of CuO NP in lung cells lines, most of them showing a decrease in cell viability, increased DNA damage and oxidative stress (Ahamed et al., 2010; Cronholm et al., 2013; Fahmy and Cormier, 2009; Ivask et al., 2015; Karlsson et al., 2008; Midander et al., 2009; Wang et al., 2012). *In vivo*, CuO NP has been investigated in Wistar rats after short-term inhalation (STIS) exposure for 5 days/6h per day to doses up to 13.2 mg/m^3 (Gosens et al., 2016). Twenty-four hours after the last exposure, a dose-dependent lung inflammation and cytotoxicity were observed. However, after a recovery period of 22 days, limited lung inflammation was only observed at the highest dose (Gosens et al., 2016). Cho et al. (2012) evaluated CuO, NiO and ZnO NP toxicity following intratracheal instillation in the rat. In this study, a severe pulmonary immune response with recruitment of eosinophils and neutrophils has been observed in rats exposed to the CuO and ZnO NP, while in NiO NP-exposed animals only neutrophils were recruited into the lung (Cho et al., 2012). Special attention should been given to NiO NP considering that Ni compounds are classified as carcinogenic to humans (International Agency for Research on Cancer, 2012; Mulware, 2013). Horie and his colleagues evaluated the cytotoxicity of ultrafine and fine NiO particles and observed that the UFP induced higher toxicity than the fine particles (Horie et al., 2009) and caused an acute oxidative stress response (Horie et al., 2011). Marked toxic responses including cell damage, induction of oxidative stress and activation of antioxidant systems in the lungs of rats intratracheally instilled with ultrafine NiO particles have also been reported by Horie et al. (2011), which are consistent with the marked toxic effects observed *in vitro*. Interestingly, a case report on occupational handling of a NiO NP powder by a 26-year-old female described the occurrence of Ni sensitization caused by manipulation of the nanopowder without any respiratory protection or control measures (Journeay and Goldman, 2014). This case highlights the importance of the nanotoxicological studies, and the evaluation of adverse health effects associated with these materials, particularly at industrial settings, in order to develop precautionary measures to protect workers from NP exposure and help preventing these work-related incidents.

As previously mentioned, graphene and CNT are used in the ceramic industry for their reinforcing ability. Previous toxicity studies on materials from the graphene family (e.g. graphene oxide, graphene nanosheets, among others) have shown that inhalation of these materials may potentially cause adverse biological responses. For instance, a decrease in cell viability and apoptosis in lung cells was already observed *in vitro*, while in animal studies, lung granuloma formation, inflammatory responses, pulmonary edema, severe and persistent lung injury were some of the effects caused from exposure to graphene family materials to rodents (Su et al., 2016). Regarding

CNT, these are valuable industrial products. However, studies commonly suggest that human pulmonary exposure during production and manipulation might present pathogenic effects similar to asbestos fibers, due to their alike fibrous morphology (Donaldson et al., 2013; Shvedova et al., 2009). However, it is worth mentioning that depending on the diameter and rigidity of the CNT, they may present different toxicological mechanisms from asbestos. For instance, while asbestos are endocytosed by mesothelial cells regardless of their diameter, CNT are internalized in a diameter- and rigidity- dependent manner, preferentially smaller diameters and higher rigidity nanotubes, which may influence their toxicity on those cells (Nagai et al., 2011; Nagai and Toyokuni, 2012). Both *in vitro* and *in vivo* studies have shown that CNT induce oxidative stress, apoptosis in different cell lines and induce cytotoxic effects in the lung (Kayat et al., 2011). Also, in animal studies, CNT have shown to be highly biopersistent, being capable to induce pulmonary inflammation, fibrosis, lung cancer after long-term inhalation and gene damage in the lung (Kobayashi et al., 2017). However, Manke et al. (2014) suggests that additional research is needed to understand if the airborne CNT generated in workplace settings are comparable in terms of size and structure to the ones generated for the *in vitro* and *in vivo* studies.

Despite the great importance of *in vitro* and *in vivo* testing, care should be taken regarding the interpretation and extrapolation to humans, particularly in case of animal inhalation toxicology area, where the anatomical and physiological differences between laboratory animals and humans could result in distinct responses to the airborne and inhalable particles (Irvin and Bates, 2003; Ware, 2008). Though, these studies might give a major clue of the possible mechanisms of toxicity that may occur in humans after exposure to such particles and the associated harmful health effects.

Due to the increasing number of workers exposed to fine and nano-sized particles of different origins and sources, further studies must be carried out for toxicity and dose-response assessment of ANP deemed relevant in occupational settings, in particular for the ceramic industry. Therefore, identification of potential sources and characterization of airborne particles emissions in terms of emitted levels, chemical composition, size distribution, etc., is of utmost importance not only for the risk assessment of exposure to these particles but also to develop plans to prevent or reduce workers exposure, namely the establishment of OEL for ANP.

4. Conclusions and future directions

Several industries are benefiting from advances provided by nanotechnology-derived materials and innovative processes. Indeed, owing their unique physicochemical properties, the utilization of NM as input materials is widespread in the industrial field. At the same time, high-energy processes aimed to enable the rapid manufacture of high-quality, innovative and cost-competitive products may also generate incidental ANP, the so-called PGNP, meaning that these workers are a susceptible population to NP exposure. At present, there is some uncertainty around the true

risk of NM to the environment and human health, which raises serious public health concerns. These concerns are further aggravated by the existing epidemiological evidence linking exposure to high ambient concentrations of PM to morbidity and mortality, for which the ultrafine particle fraction seems to be an important contributor.

The ceramic industry is a paradigmatic case of potential occupational exposure to airborne nano-sized particles, mainly when high energy processes are implemented, as evidenced by the existing exposure monitoring data. Advances in the instrumentation used for ANP workplace measurements shed light on the possible exposure scenarios arising from ENP handling or from different ceramic industry activities (e.g. machining, firing, surface coating, packaging), many of them transversal to other industrial branches. This knowledge is crucial for an effective NM risk assessment and management, in particular for the implementation of risk prevention and mitigation measures for protecting workers from intentional or unintentional exposure to ANP but also for helping in the establishment of meaningful OEL for ANP. Therefore, more exposure assessment studies are needed, in particular in the ceramic industry, for a more extensive identification of workplace exposure scenarios and a more detailed characterization of the ANP found in terms of number, size, shape, aggregation/agglomeration, chemical composition and toxicological properties. In this context, CERASAFE (http://www.cerasafe.eu/) has been a pioneering European project that contributed to innovating in the field of characterization methods relevant to environmental health and safety (EHS) issues, namely to discriminate ENP from background aerosols in the ceramic industry and good practices to guarantee that exposure to hazardous NP may be acceptable.

In parallel with exposure assessment, is urgent to fill the gaps on the knowledge of the adverse health effects derived from ANP exposure and their relation to dose to move forward our understanding of the occupational hazard of ENP and ANP. Currently, no OEL specific to NM have been officially established and adopted by the authoritative agencies, on one hand due to the vast heterogeneity and number of available NM, on the other to the limited and controversial knowledge of NM toxicity and harmful health effects. Furthermore, increasing evidence supports that the commonly used mass metrics for OEL may need to be carefully analysed and considered to be replaced by a particle number-based approach, a fact that has also been hampering the OEL developing process. Meanwhile, NRV may be considered as a provisional precautionary tool to protect the workers from NP exposure. Concerted efforts within the EU Nanosafety Cluster are being done in order to develop grouping and read-across approaches, similar to what is already well-established for conventional chemicals, that can be used to fill data gaps without further testing, with the ultimate goal of accelerating NM safety assessment and assisting in the establishment of OEL for specific NM groups. In this regard, several research projects (e.g. Gracious, NanoToxClass, PATROLS, SmartNanoTox) are contributing to NM categorization based on the joint consideration of NM physicochemical properties and modes of action.

Inflammation, oxidative stress, genotoxicity are the most frequently reported responses to NM exposure as revealed by the *in vitro* and *in vivo* studies conducted so far.

In light of the current knowledge linking exposure to PM, where UFP play a major role, to the etiology of malignant and cardiovascular diseases, implementation of effective risk mitigation measures for protecting workers from (un)intentional exposure to ENP and ANP is of paramount importance in ceramic industrial settings. Health authorities, researchers, occupational health professionals and workers should cooperate to establish the most appropriate strategies to prevent and mitigate NP exposure. WHO preconizes the adoption of a precautionary approach that seek to minimize exposure to NM. Some of the recommendations to do so include assessing workers' exposure in workplaces and evaluating whether it exceeds a proposed OEL value for the specific NM, reduction of exposures to a range of NM that have been consistently detected in workplaces, control measures based on the principle of hierarchy of controls (i.e elimination of the source of exposure before implementing control measures that are more worker-dependent, with protective PPE being used only as a last resort). Finally, the importance of providing data on exposure and efficiency of protective measures in industrial scenarios should be highlighted, in order to help policy-makers to establish a realistic OEL, that is, with a good balance between adequate worker's health protection and achievable OEL using the current available technologies.

Conflicts of interest

The authors declare that they have no competing interests.

Figure and Tables captions

Figure 1. Main stages of the manufacturing process of ceramic products (Adapted from European Commission (2007)).

Figure 2. Overview of potential scenarios of intentional and/or unintentional workplace exposure to nanoparticles in the ceramic industry.

Table 1. List of raw materials commonly used in the ceramic industry.

Table 2. Existing methods and instruments used for airborne nanoparticle quantification.

Table 3. Provisional Nano Reference Values (NRV) for four classes of engineered nanoparticles (ENP) (Adapted from Social and Economic Council (2012)).

Table 4. Summary of the available case studies on ultrafine and airborne nanoparticle release and exposure in the ceramic industry.

Tables

Table 1.

Raw materials		
Oxide-based	*Non-oxide based*	*Nanoscale*
Clays e.g. kaolinite, pyrophyllite, montmorillonite, muscovite, illite, halloysite, hydrotalcite	**Borides** magnesium (MgB_2)	**Nanoclays**
Metal oxides alumina (Al_2O_3), antimony-tin oxide (Sb_2O_3/SnO_2), barium titanate ($BaTiO_3$), beryllia (BeO), boria (B_2O), ceria (CeO_2), chromia (Cr_2O_3), magnesia (MgO, $MgOH_2$), nickel oxide (NiO), silica (SiO_2), tin oxide (SnO_2), titania (TiO_2), urania (UO_2); zinc oxide (ZnO), zirconia (ZrO_2)	**Carbides** silicon (SiC), tungsten (WC), titanium (TiC) **Carbon-based** diamond, graphite	**Carbon-based** carbon nanotubes (CNT), carbon black (CB), fullerenes graphene **Carbides and nitrides** boron (BN), silicon (SiC, Si_3N_4), tungsten (WC); titanium (TiC)
Mixed oxides bismuth strontium calcium copper oxide (BSCCO), lead zirconate titanate ($Pb[Zr_xTi_{1-x}]O_3$), partially stabilized zirconia (PSZ), silicon aluminum oxynitride (Sialon), yttrium barium copper oxide (YBCO)	**Fluorides** silicon (SiF) **Metals** antimony (Sb), barium (Ba), cadmium (Cd), copper (Cu), lead (Pb), silver (Ag), zinc (Zn)	**Metal and metal-oxide nanoparticles** alumina (Al_2O_3), ceria (CeO_2), copper oxide (CuO), silica (SiO_2), titania (TiO_2), tin oxide (SnO_2), zinc oxide (ZnO), zirconia (ZrO_2), magnesia (MgO), yttria (Y_2O_3)
Minerals calcite ($CaCO_3$), feldspar, quartz, magnesite ($MgCO_3$), wollastonite ($CaSiO_3$); lithium carbonate (Li_2CO_3)	**Nitrides** boron (BN), silicon (Si_3N_4) **Sulfides** calcium (CaS), calcium ytterbium (CaYb2S4), ytterbium (Yb_2S_3)	**Nanocomposites** e.g. silicon carbide/silicon nitride (SiC/Si_3N_4) composites

Table 2.

	Parameters	Stationary equipment	Portable equipment	Personal equipment
Time-Resolving Instruments	Particle number concentration	CPC	Hand-held CPC	DisCmini Nano Tracer (e.g. Aerasense Nanoparticle monitor)
	Particle LDSA concentration	NSAM	Downsize NSAM	
	Particle size distribution	Electrical mobility analysis (SMPS, DMPS, DMA) and Inertial separation	PAMS, DMA	
	Mean particle size			
Time-Integrating Instruments	Physicochemical analysis	Filter sampling Electrostatic sampling	Hand-held ESPnano	Thermophoretic sampling (thermal precipitator sampler) Sampling on different filtration media (PENS, NanoBadge, Personal NRD)

Condensation Particle Counter (CPC); Nanoparticle Surface Area Monitor (NSAM); Scanning Mobility Particle Sizer (SMPS); Differential Mobility Particle Sizer (DMPS); Differential Mobility Analyser (DMA); Portable Aerosol Mobility Spectrometer (PAMS); Personal Nanoparticle Sampler (PENS); Nanoparticle Respiratory Deposition (NRD).

Table 3.

Type of Nanomaterial (NM)	**Nano Reference Value (NRV) (for long-term exposure)**	**Examples**
Rigid, biopersistent nanofibres	0.01 fibres.cm^{-3}	Carbon nanotubes, metal oxide fibres
Biopersistent granular NM (density > 6000 Kg.cm^{-3})	20 000 particles.cm^{-3}	Silver, gold, cerium oxide, cobalt oxide, iron/iron oxide, lead, antimony pentoxide, tin oxide
Biopersistent granular and fibre from NM (density < 6000 Kg.cm^{-3})	40 000 particles.cm^{-3}	Aluminium oxide, silicon oxide, tin, titanium oxide, zinc oxide, nanoclay
Non-biopersistent granular NM	Applicable OEL	e.g. Sodium chloride

Table 4.

References	Ceramic manufacturing process	Experimental settings	Sampling type	Evaluated parameters	Main findings	Identified elements/particles
Voliotis et al., (2014)	Firing	Industrial scale (traditional small-sized pottery studio)	Stationary; location: emissions source (kiln)	Particle size distribution and concentration; elemental composition	First firing stage: mean size ranged 30-70 nm; peak number concentration 6.5×10^5 cm^{-3}; Second firing stage: mean size ranged from 15-40 nm; peak number concentration 1.2×10^6 cm^{-3}.	Silicon (Si), lead (Pb) and copper (Cu)
Fonseca et al., (2015b)	Laser sintering and ablation	Laboratory pilot-plant scale furnace	Stationary; locations: emissions source (furnace), indoor (breathing zone) and outdoor air	Particle size distribution; particle formation and emission mechanisms; LDSA; chemical characterization	Nanoparticle emissions: 9.7×10^5 particles.cm^{-3}; mean diameter of 18 nm; spherical shaped morphology (TEM images); Ablation emissions: mean diameter 80 nm; Breathing zone: 2.6×10^6 particles.cm^{-3}, LDSA=$2.3 \times 10^3 \mu m^2$.cm^{-3}, mean size range 13-27 nm, mean diameter of 8-18 nm in the furnace, mean diameter size of 38 nm in the background air.	Zinc (Zn), lead (Pb), copper (Cu), chromium (Cr), arsenium (As) and thallium (Tl) found in the ultrafine fraction
Fonseca et al., (2016)	Laser ablation	Industrial pilot-plant scale furnace	Stationary; locations: emissions source (furnace), indoors (breathing zone), exhaust tube (connecting the	Particle size distribution; particle number and diameter; LDSA; chemical characterization	Emission source: ultrafine and nanoparticle emissions reaching up to 1.0×10^7 cm^{-3}, diameter range 14, 12 and 58 nm for red clay, porcelain tiles, and background air particles, respectively, with spherical and	Quartz (SiO$_2$) was the main inorganic component released from both tiles; metal oxide NP of zinc (Zn), chromium (Cr), aluminium (Al) and iron (Fe); other components found in both

			emission source to outdoor air)		irregularly shaped morphologies (TEM images);	tiles: calcium carbonate ($CaCO_3$), zinc oxide (ZnO)
					Exposure concentrations to ultrafine and nanoparticles generated in this workplace would exceed the NRV.	
Viana et al., (2017)	Atmospheric plasma spraying	Industrial pilot-plant scale furnace	Stationary; locations: inside (worker's room) and outside spraying chamber, outdoor air	Particle size distributions; particle number, mass and concentrations; LDSA	Inside the spraying chamber: ultrafine emissions concentration up to $3.7 \times 10^{6\cdot}cm^{-3}$, diameter range 28-45 nm, spherical and irregularly shaped morphologies (TEM images); Worker area (potential breathing zone): $2.0 \times 10^6\ cm^{-3}$, diameter range 33-48 nm; Ultrafine emissions were mainly process-related.	ZrO_2-Y_2O_3 nanoparticles, gadolinium (Gd) based engineered nanoparticles, mineral (Ca) particles
Salmatonidis et al., (2018)	Laser ablation (two different laser setups: near-IR and mid-IR)	Laboratory and pilot-plant scale	Stationary; locations: emission source, near-field, far-field, outdoor air	Particle size, number and mass concentration; chemical characterization	High particle number concentrations were detected ($3.5 \times 10^4\ cm^{-3}$ to $2.5 \times 10^6\ cm^{-3}$) for all types of tiles and under both laser setups; Spherical shape; Particle number and mass emissions were dependent on the tile surface characteristics and chemical properties.	Silica (SiO_2) nanoparticles
Salmatonidis et al., (2019a)	Thermal spraying coating	Industrial scale	Stationary; locations: near-field (inside	Particle size distribution;	Inside spraying booths: high particle number ($>10^6\ cm^{-3}$; 30–40 nm) and mass (60–600 µgPM1 m^{-3}) concentration	Metal-containing particles: nickel (Ni), chromium (Cr), tungsten (W)

					Results	
			spraying booths), far-field	Particle number concentration, size-segregated mass concentrations; LDSA	Worker area: 10^4–10^5.cm^{-3} particle number, 40–65 nm and 44–87 µg PM1.m^{-3} mass concentration; Irregularly-shaped nanoparticles with small diameters were detected inside (31–41 nm) and outside (40–64 nm) the spraying booths; Inhaled dose rates: $353x10^6$–$1024x10^6$.min^{-1}, with 70% of deposition occurring in the alveolar region.	
Ribalta et al., (2019a)	Handling of powder materials	Pilot-plant	Stationary and personal; locations: worker area (breathing zone), indoor, outdoor	Particle mass and number concentration; LDSA; chemical characterization	Particle number concentration during handling: 15 033–40 498. cm^{-3}, different particle shape (prismatic and platy) (TEM images); LDSA during background: 27-101 $µm^2$.cm^{-3}; LDSA during materials handling: 22-42 $µm^2$. cm^{-3}; High degree of correlation between dustiness and exposure concentrations was found during handling.	Silicon (Si), aluminium (Al), iron (Fe), oxygen (O), calcium (Ca) Silica (SiO_2) nanoparticles
Ribalta et al., (2019b)	Packaging of raw materials	Industrial scale	Stationary and personal; locations: three packing lines	Particle mass and number concentrations; LDSA	LDSA during packaging: 5.4-$11.8x10^5$ $µm^2$.min^{-1} Particles depositing mainly in the alveoli (51–64%) followed by	Silica (SiO_2), aluminia (Al_2O_3), iron oxide (Fe_2O_3), titania (TiO_2), potassium oxide (K_2O), magnesium oxide (MgO), sodium oxide

| | head airways (27–41%) and trachea bronchi (7–10%). | (Na$_2$O), calcium oxide (CaO), lithium oxide (Li$_2$O) |

Lung Deposited Surface Area (LDSA); Nano Reference Value (NRV); Infrared (IR), Transmission Electron Microscopy (TEM).
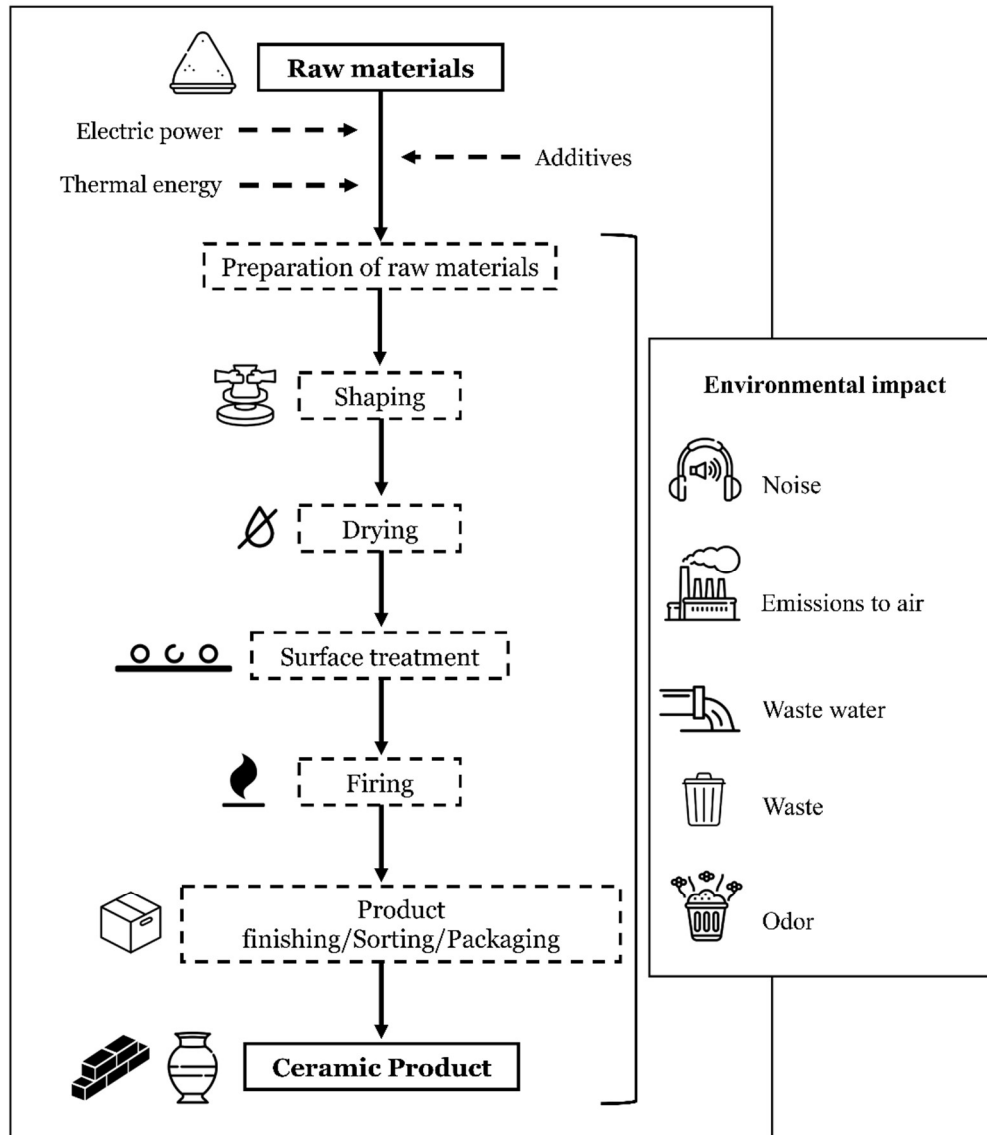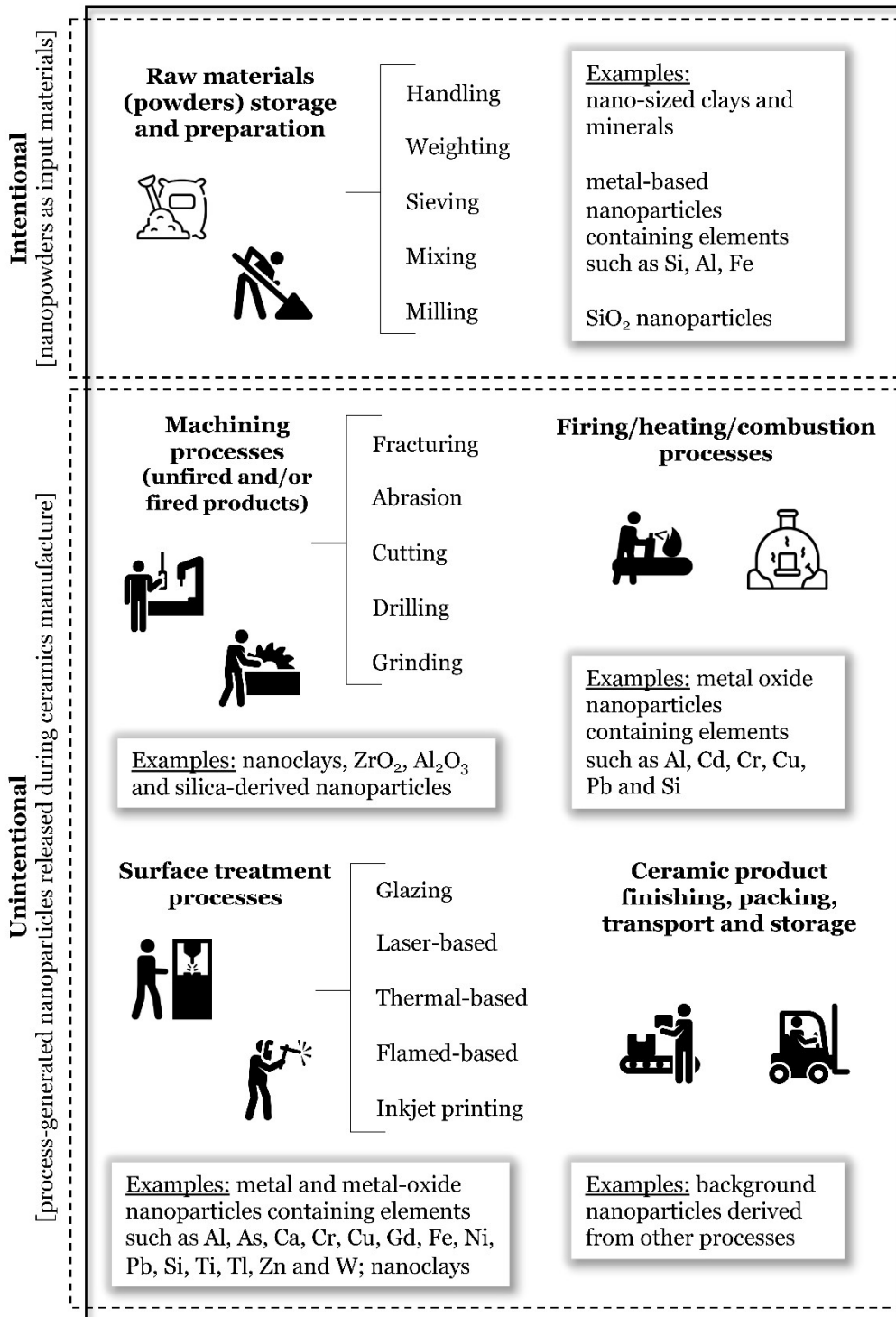
Figures

Figure 1

Figure 2

Workplace exposure to (nano)particles in the ceramic industry

Intentional [nanopowders as input materials]

Raw materials (powders) storage and preparation

- Handling
- Weighting
- Sieving
- Mixing
- Milling

Examples:
nano-sized clays and minerals

metal-based nanoparticles containing elements such as Si, Al, Fe

SiO_2 nanoparticles

Unintentional [process-generated nanoparticles released during ceramics manufacture]

Machining processes (unfired and/or fired products)

- Fracturing
- Abrasion
- Cutting
- Drilling
- Grinding

Examples: nanoclays, ZrO_2, Al_2O_3 and silica-derived nanoparticles

Firing/heating/combustion processes

Examples: metal oxide nanoparticles containing elements such as Al, Cd, Cr, Cu, Pb and Si

Surface treatment processes

- Glazing
- Laser-based
- Thermal-based
- Flamed-based
- Inkjet printing

Examples: metal and metal-oxide nanoparticles containing elements such as Al, As, Ca, Cr, Cu, Gd, Fe, Ni, Pb, Si, Ti, Tl, Zn and W; nanoclays

Ceramic product finishing, packing, transport and storage

Examples: background nanoparticles derived from other processes

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