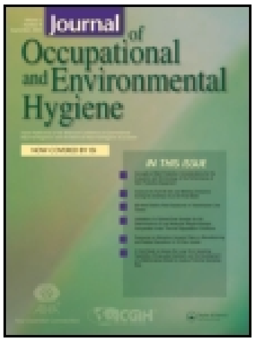

Journal of Occupational and Environmental Hygiene

ISSN: 1545-9624 (Print) 1545-9632 (Online) Journal homepage: https://www.tandfonline.com/loi/uoeh20

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Journal of Occupational and Environmental Hygiene, 8: 580–587
ISSN: 1545-9624 print / 1545-9632 online
DOI: 10.1080/15459624.2011.613348

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This study presents exposure data for various metal oxides in facilities that produce or use nanoscale metal oxides. Exposure assessment surveys were conducted at seven facilities encompassing small, medium, and large manufacturers and end users of nanoscale (particles <0.1 μm diameter) metal oxides, including the oxides of titanium, magnesium, yttrium, aluminum, calcium, and iron. Half- and full-shift sampling consisting of various direct-reading and mass-based area and personal aerosol sampling was employed to measure exposure for various tasks. Workers in large facilities performing handling tasks had the highest mass concentrations for all analytes. However, higher mass concentrations occurred in medium facilities and during production for all analytes in area samples. Medium-sized facilities had higher particle number concentrations in the air, followed by small facilities for all particle sizes measured. Production processes generally had the highest particle number concentrations, particularly for the smaller particles. Similar to particle number, the medium-sized facilities and production process had the highest particle surface area concentration. TEM analysis confirmed the presence of the specific metal oxides particles of interest, and the majority of the particles were agglomerated, with the predominant particle size being between 0.1 and 1 μm. The greatest potential for exposure to workers occurred during the handling process. However, the exposure is occurring at levels that are well below established and proposed limits.

Keywords exposure, metal oxide, nanoparticles, ultrafine particles, workplace

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INTRODUCTION

Engineered nanomaterials, including nanoparticles, have the potential for creating new opportunities and substantial benefit to society; however, they also pose a new potential risk. The European Agency for Safety and Health at Work considers nanomaterials one of the top ten emerging risks in the workplace.[1] Various properties of nanomaterials have led to their growing production and use, resulting in increasing numbers of workers and consumers exposed to them. In the United States, the estimated nanomaterials market in 2008 was $1.2 billion.[2] It has been estimated that funding for nanotechnology in the United States was $4.34 billion in 2006, from three major sources: government, corporate, and venture capital.[3]

Inhalation is considered the predominant route of exposure and most important for uptake for nanomaterials. As particles get smaller to a certain point, they travel deeper into the lungs. Particles with an aerodynamic diameter of less than 2.5 μm will reach the alveoli, and nanoparticles with an aerodynamic diameter of between 20 nm and 100 nm are largely deposited in the alveolar region.[4,5] As particles become less than 20 nm, however, they deposit less in the alveolar region. At 1 nm, particles deposit predominantly in the nasopharyngeal area, with essentially no particles depositing in the alveolar region.[5]

Poorly soluble, low toxicity (PSLT) particles such as certain metal oxides (e.g., titanium dioxide, aluminum oxide, magnesium oxide) are generally considered relatively benign if lung clearance mechanisms are not overloaded and sufficient lung burden is not achieved. For example, titanium dioxide (TiO_2) has been used as a negative control in experimental studies investigating particle toxicity.[6] However, it has been hypothesized that nano-sized or ultrafine particles (<100 nm), due to their small size and greater surface area to mass ratio, can penetrate the epithelial lining and lung interstitial spaces to a greater extent, can more readily enter cells, and can cause greater lung inflammation and oxidative stress compared with larger particles.[7,8] In one study, ultrafine TiO_2 (∼20 nm) particles had longer clearance times and greater translocation to interstitial sites and regional lymph nodes than fine TiO_2 (∼200 nm).[9]

Further, it is hypothesized that the dose of particles, expressed as particle surface area, has been associated with lung responses and this relationship is similar for different PSLT particles.[8,10–12] Persistent inflammation, tissue damage, fibrosis, and lung cancer have been observed in rats at lung doses of PSLT particles that impair lung clearance,[13] and particle surface area dose has been shown to be a better predictor of lung clearance inhibition than other particle exposure metrics.[12]

Ultrafine metal particles have shown increased toxicity per mass dose compared with their larger counterparts.[14,15] In a review of the health risk of nanoparticles, Hoet et al.[4] compared the health effects from two studies of chronic TiO_2 inhalation and noted that exposure with ultrafine TiO_2 particles (~20 nm) resulted in greater lung tumor incidence than exposure to fine TiO_2 particles (~300 nm) even though the exposure levels in ultrafine study were 25-fold lower (10 mg/m^3 vs. 250 mg/m^3).

Currently, there are very limited workplace exposure data for engineered nanoparticles. A few studies have measured particle number and mass concentrations but have not measured specific compounds, or have measured carbon nanofibers.[16–19] A few have also measured metal oxide exposure in a limited capacity.[19–22] This study presents exposure data for various metal oxides in facilities that produce or use nanoscale metal oxides.

METHODS

Exposure assessment surveys were conducted at seven facilities encompassing small, medium, and large manufacturers and end users of nanoscale metal oxides, including the oxides of titanium, magnesium, yttrium, aluminum, calcium, and iron. Nanoscale particles, for the purpose of this article, are defined as those with a diameter of less than 0.1 μm. This definition is not based on any inherent toxicological or physical basis but, instead, for convenience, as this tends to be the conventional definition. Half- and full-shift sampling consisting of various direct-reading and mass-based area and personal aerosol sampling was employed to measure exposure while performing various tasks.

Aerosol sampling relies heavily on area sampling, which may hamper interpretation and increase the inaccuracy of the exposure estimate. However, this approach is currently the best one available for estimating exposure to nanoparticles. By combining several different exposure metrics that can only be measured statically (i.e., area sampling), with an exposure metric that can be measured both statically and personally (respirable dust and metal analysis), it is hoped that this limitation can be overcome, and that the static only measures can be related to the personal measures. Sampling, whether half- or full-shift, occurred for the duration of a specific process and might encompass several production or handling tasks. Sample analysis included gravimetric, elemental metal, and transmission electron microscope with energy dispersive X-ray spectrometry (TEM-EDX). The aerosol sample metrics included respirable dust mass, elemental metal mass, particle number concentration, and particle surface area.

Sample Collection and Analysis

Respirable dust mass concentration was measured with SKC pumps (SKC, Eighty Four, Pa.), using NIOSH Method 0600, "Particles not Otherwise Regulated, Respirable."[23] Samples were collected on 37-mm cassette polyvinyl chloride (PVC) filters, with a pore size of 0.8 μm, attached to a 10-mm nylon cyclone with a 4-μm median cut point at a flow rate of 1.7 L/min. The filters underwent gravimetric analysis to determine respirable dust concentration and then were analyzed for elemental metals using NIOSH Method 7300, "Elements by ICP."[24] Due to limitations with the analytical methodology, the specific metal oxides could not be analyzed. Instead, the metal oxide concentrations were determined based on a molecular weight calculation and assuming that all the elemental metal found came from its oxide.

Additional respirable samples, using 37-mm cassette mixed cellulose ester (MCE) filters with a 0.8 μm pore size, were collected and analyzed using transmission electron microscopy (TEM). A random section (approximately one-quarter) of each filter was cut with a clean scalpel and prepared for TEM analysis. The samples were then placed in a Phillips CM-12 TEM for analysis. The sample was reviewed and particulates were analyzed at magnifications from 135× to 31000×. The length and widths for 100 particles on the samples were recorded at an appropriate magnification. The particle chemistry was verified with a light element detector IXRF digital processing system. For the particle sizing, 100 particles were counted and sized when sufficient particles were present.

Elemental mass size distribution was measured using a micro-orifice, uniform-deposit impactor (MOUDI; MSP, Shoreview, Minn.). The MOUDI collects size-fractionated particles ranging in size from 56 nm to 18 μm on 12 stages. The main stages housed 47-mm MCE filters with 0.8 μm pore size, greased with oleic acid to prevent particle bounce. The end stage housed a 37-mm MCE filter with 5.0 μm pore size and was not greased. The MOUDI filters were analyzed for elemental metals using NIOSH Method 7300.[24]

Direct-reading particle surface area measurements were made with the DC2000 CE portable diffusion charger (DC; EcoChem, League City, Texas). Direct-reading particle number concentrations were determined using the TSI 3007 condensation particle counter (CPC; TSI, Minneapolis, Minn.) and an HHPC-6 optical particle counter (OPC; Hach Ultra Analytics, Grants Pass, Ore.). The TSI 3007 CPC recorded number concentration for particles between 0.01 and 1 μm, and the HHPC-6 OPC recorded number concentration for particles between 0.3 and 5 μm. The CPC and OPC number concentrations overlap in the size range from 0.3 μm to 1 μm. Therefore, the summed values in the OPC channels in the 0.3 μm to 1 μm range were subtracted from the CPC results to give a value in the 0.01μm to 0.3 μm range. This has been done previously by Peters et al.[22]

The above six samples—PVC filter (respirable dust and metal analysis), MCE filter (TEM analysis), MOUDI (size distribution), DC (surface area), CPC (condensation particle counter), and OPC (optical particle counter)—were located together in areas close to potential sources of metal particle emission (Figures 1a, 1b). A control sample to determine background levels was also collected for each of these six samples from a location in the facility where exposure to nanoparticles would not be expected to occur, such as an office. Locations were selected based on professional judgment in

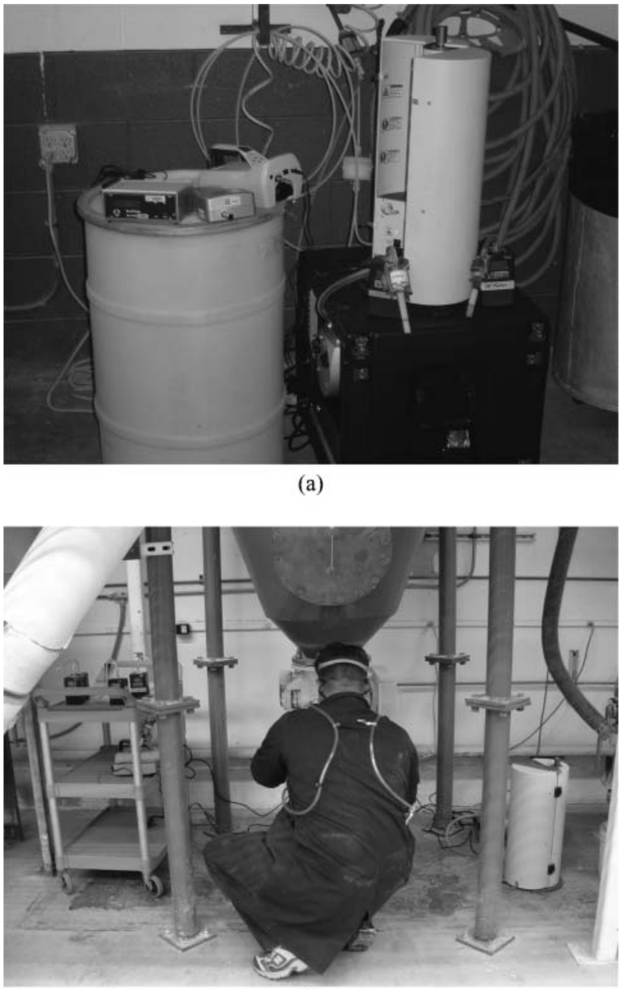

FIGURE 1. (a) Area sample equipment, (b) Personal and area sample equipment.

consultation with facility personnel. In addition to the above samples, PVC filters were worn by workers conducting tasks where exposure to metal particles might occur, such as mixing and pouring. Personal PVC filters were analyzed in the same manner as the area PVC filters described above. All area and personal samples were collected for selected half- and full-shifts, depending on the nature of the tasks involved.

Data Analysis

All statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, N.C.). The dependent variables (particle number concentration and metal analysis) were right skewed so a natural log transformation was applied to normalize the data. Linear regression modeling was used to test for differences in the means of the log transformed dependent variables at different levels of facility size and process. For the particle number concentration and size data, Tukey's multiple comparison test in the GLM procedure was used to simultaneously test for differences among the different levels of process and facility size.

Since the metal analysis data had values below the limit of detection (LOD), the LIFEREG procedure in SAS was used to obtain maximum likelihood estimates of the parameters as described by Slymen.[25] Levels with 100% censoring were excluded from the analyses. For example, there were four samples of area dust data collected from large facility sizes, all below the LOD. Therefore, only medium and small facility sizes were compared for the area dust data. For comparison purposes, maximum likelihood estimates for the GMs and GSDs were estimated in the LIFEREG procedure at each level separately.

RESULTS

Seven companies participated in the study. Two were considered large companies, three were considered medium, and two were considered small. Large companies were defined as having more than 100 employees, medium companies were defined as having 20–100 employees, and small companies were defined as having fewer than 20 employees. Of the seven companies, two were end users only (large), three were manufactures only (two small, one medium), and two were both (medium).

The processes observed can be broken into two broad categories—production and handling. The production process broadly included spray drying, combustion reaction, and chemical reaction that were observed in manufacturing facilities. Handling included weighing, mixing, pouring, and collecting that were observed at both manufacturing and end use facilities. The number of employees specifically involved in producing and handling the nanosized metal oxides in each facility was small, with usually only one or two employees involved. The production processes were all closed systems, with the only personal exposure potential occurring at the end of the process during the collection of the particles. Handling tasks were of short duration ranging from a few minutes up to 2 hr. Longer-duration tasks (i.e., $\sim$2 hr) occurred when using the metal oxides (specifically, titanium dioxide) in the manufacture of other products. This involved loading many 50-lb bags of titanium dioxide into mixing tanks.

The mass of dust, titanium (Ti), other elemental metals expressed as a titanium equivalent (Ti Eq), and titanium dioxide (TiO_2) by facility size and process is shown in Table I. Since the predominant metal sampled and analyzed was titanium, the other elemental metals were expressed as titanium equivalent for comparison purposes. The Ti results are limited to those samples that were analyzed for Ti. The other metals were converted to Ti Eq through the following equation:

$$MW_{Ti}/(MW_{metal} * C_{metal}) \qquad \textbf{(1)}$$

where

MW_{Ti} is the molecular weight of titanium.

TABLE I. Dust and Metal Mass Concentration (μg/m^3)

		By Facility Size						By Process					
	Type	Facility Size	n	% Cens.	GM[A]	GSD[A]	Diff.[B]	Process	n	% Cens.	GM[A]	GSD[A]	Diff.[B]
Dust	Area	Large	4	100				Handling	11	73	59.69	4.34	A
		Med	15	67	38.68	6.83	A	Production	7	57	45.80	6.70	A
		Small	4	75	41.86	4.50	A	Control	5	100			
	Peronal	Large	4	25	162.76	2.75	A	Handling	8	38	182.02	2.50	A
		Med	9	44	107.55	3.79	A	Production	6	50	62.71	4.54	A
		Small	1	100									
Ti Eq	Area	Large	4	25	0.73	17.58	A	Handling	9	67	0.11	23.73	A
		Med	12	42	1.23	13.66	A	Production	6	33	3.34	16.44	A
		Small	4	100				Control	5	40	0.66	5.17	A
	Peronal	Large	4	0	47.67	5.59	A	Handling	6	17	12.19	15.15	A
		Med	6	33	3.32	3.02	B	Production	5	40	2.69	3.53	A
		Small	1	100									
Ti	Area	Large	4	25	0.87	13.70	A	Handling	5	40	0.42	19.28	A
		Med	5	0	1.47	4.06	A	Production	3	0	3.43	1.92	A
		Small	2	100				Control	3	33	0.24	3.30	A
	Peronal	Large	4	0	47.65	5.59	A	Handling	5	0	32.11	5.64	A
		Med	4	0	6.35	1.88	B	Production	3	0	6.26	2.07	A
		Small	0										
TiO_2	Area	Large	4	0	2.07	8.44	A	Handling	5	20	1.10	11.44	A
		Med	5	0	2.47	4.04	A	Production	3	0	5.67	1.94	A
		Small	2	100				Control	3	33	0.36	3.51	A
	Peronal	Large	4	0	78.30	5.60	A	Handling	5	0	53.14	5.61	A
		Med	4	0	10.56	1.88	B	Production	3	0	10.33	2.07	A
		Small	0										

[A]Maximum likelihood estimates for the GM and GSD were obtained using the LIFEREG procedure due to values below the LOD.
[B]Levels with the same letter are not significantly different with a level of significance of .05.

MW_{metal} is the molecular weight of the metal being converted.
C_{metal} is the mass concentration (ug/m^3) of the metal being converted.

There was a substantial amount of censored data (i.e., non-detect data) for all analytes of interests, with the greatest amount occurring in the small facilities. In fact, practically all the samples collected from small facilities were non-detect. The personal samples tended to have less censoring than the area samples and had higher concentrations. Workers in large facilities and performing handling tasks had the highest exposures for all analytes. However, higher exposures occurred in medium facilities and during production for all analytes in area samples. For the most part, though, with some exceptions, there were no statistically significant differences between facilities and processes.

The particle number concentrations by facility size and process are shown in Table II. In general, for all particle sizes measured, medium-sized facilities had more particles in the air, followed by small facilities. At particle diameters of 0.5, 0.7, and 1 μm, the large facilities had significantly lower particle concentrations than medium and small facilities. Production processes generally had the highest particle number concentrations, particularly for the smaller particles. Particle surface area is shown in Table III. Similar to particle number, the medium-sized facilities and production process had the highest particle surface area concentration.

TABLE II. Particle Number Concentration (particles/cm^3)

	By Facility Size						By Process					
Particle Size (μm)	Facility Size	n	GM	GSD	Differences[A]		Process	n	GM	GSD	Differences[A]	
< 0.3[B]	Large	4	7255	1.36	A		Handling	12	13496	2.92	A	
	Med	13	28991	2.69		B	Production	6	37882	2.18	A	
	Small	5	7214	1.27	A		Control	4	8461	1.30	A	
0.3	Large	5	87	1.47	A		Handling	12	102	1.55	A	
	Med	13	100	2.01	A		Production	6	128	1.77	A	
	Small	5	88	1.37	A		Control	5	54	1.61	A	
0.5	Large	5	5	1.32	A		Handling	12	11	2.00	A	B
	Med	13	16	2.51		B	Production	6	22	1.68	A	
	Small	5	7	1.17	A	B	Control	5	4	1.66		B
0.7	Large	5	1	1.43	A		Handling	12	3	2.41		B
	Med	11	4	2.82		B	Production	5	4	1.63		B
	Small	5	2	1.06	A	B	Control	4	1	1.79	A	
1	Large	5	1	1.80	A		Handling	12	2	2.46	A	B
	Med	13	2	2.65		B	Production	6	2	1.64	A	
	Small	5	1	1.10	A	B	Control	5	0	1.92		B
2	Large	5	0	2.59	A		Handling	12	1	2.78	A	
	Med	11	1	2.21	A		Production	5	1	1.41	A	
	Small	5	0	1.29	A		Control	4	0	1.46		
5	Large	5	0	3.24	A		Handling	12	0	3.61	A	
	Med	13	0	3.61	A		Production	6	0	2.96	A	
	Small	5	0	2.11	A		Control	5	0	1.65	A	

[A]Levels with the same letter are not significantly different in a Tukey multiple comparison procedure with a level of significance of 0.05.
[B]Calculated by subtracting the summed OPC values in 0.3 μm to 1.0 μm range from the CPC values that record particle number concentration in the 0.01μm to 1 μm range.

TEM analysis confirmed the presence of the specific metal oxide particles of interest, and the majority of the particles were agglomerated, with the predominant particle size being between 0.1 and 1 μm. Fifty-five percent of the particles were between 0.1–1 μm, 14% were less than 0.1 μm, 30% were between 1–2.5 μm, and only 1% were greater than 2.5 μm. Figures 2a and 2b show photos of TiO_2 particles from the TEM analysis.

TABLE III. Particle Surface Area (μm^2/cm^3)

Facility Size	n	GM	GSD	Differences[A]
Large	5	73	1.73	A
Med	13	145	7.08	A
Small	5	32	2.44	A
Process	**n**	**GM**	**GSD**	**Differences[A]**
Handling	12	78	4.59	A
Production	6	233	6.29	A
Control	5	25	2.41	A

[A]Levels with the same letter are not significantly different in a Tukey multiple comparison procedure with a level of significance of 0.05.

A MOUDI cascade impactor was used to determine the mass concentration size distribution for the elemental metals. As with the total mass concentrations, the metals were expressed as titanium equivalent to allow for better comparison. The mass concentrations for each MOUDI stage, by process and facility size, are shown in Figures 3 and 4. The cumulative distribution is calculated by normalizing the MOUDI results by the bin width, since not all bins widths are equal. Cumulative mass concentration size distribution, by process and facility size, is shown in Figures 5 and 6. Generally, the greater mass of particles is found in the larger particle sizes. However, for production processes, the predominant mass of particles is found in the 0.1 to 1.0 μm particle diameter range.

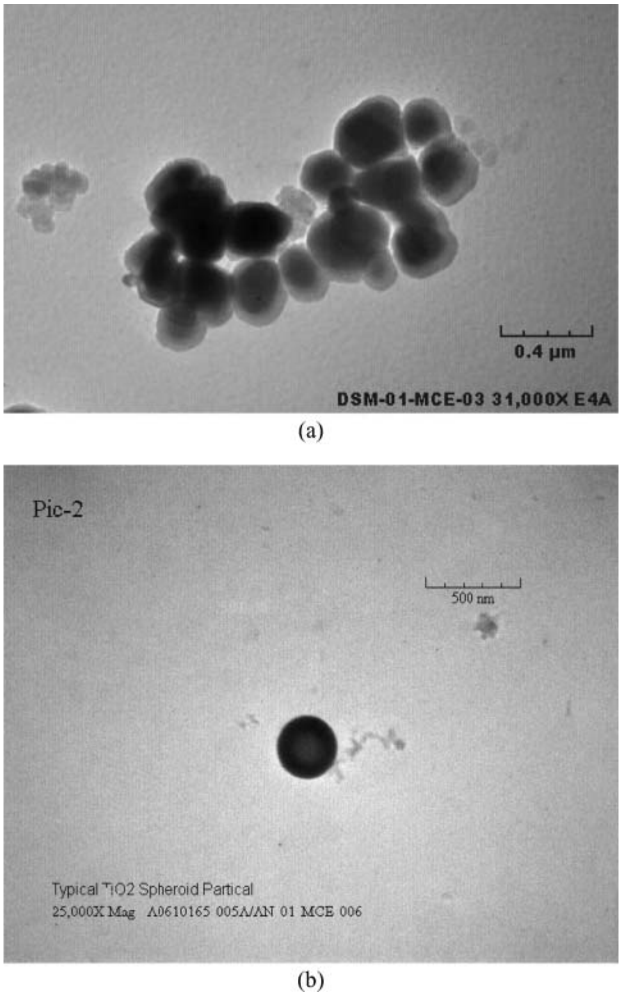

FIGURE 2. (a) TiO_2 particle agglomerate, (b) TiO_2 individual particle.

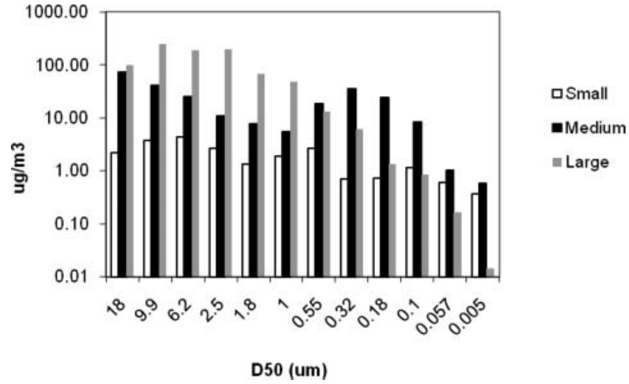

FIGURE 4. Ti equivalent mass concentration for each MOUDI stage by facility size.

DISCUSSION

Production and use of nanomaterials are increasing. While society has the potential to benefit from nanotechnology, there are still uncertainties about the potential health effects that might occur as a result. Workers producing and handling nanomaterials are potentially the individuals most likely to suffer any ill effects from this new technology. Therefore, it is important to characterize workplace exposure to nanomaterials while concomitant health effects research is being conducted.

Characterizing exposure for nanomaterials is challenging as there is no standard method for assessing exposure to them, or even a standard metric. Despite this, an attempt to characterize exposure to metal oxides, using several exposure measuring methods, was undertaken. Brouwer et al.[26] recommended that all relevant characteristics of nanoparticle exposure be sampled. Following that recommendation, samples were collected for mass, number, and surface area. Of the three metrics, only mass can be analyzed for specific compounds. Both particle number and surface area are not compound-specific.

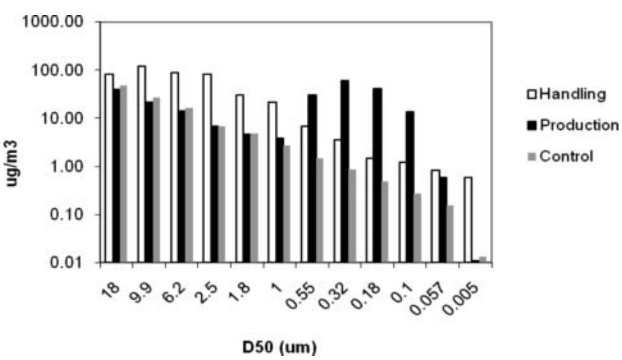

FIGURE 3. Ti equivalent mass concentration for each MOUDI stage by process.

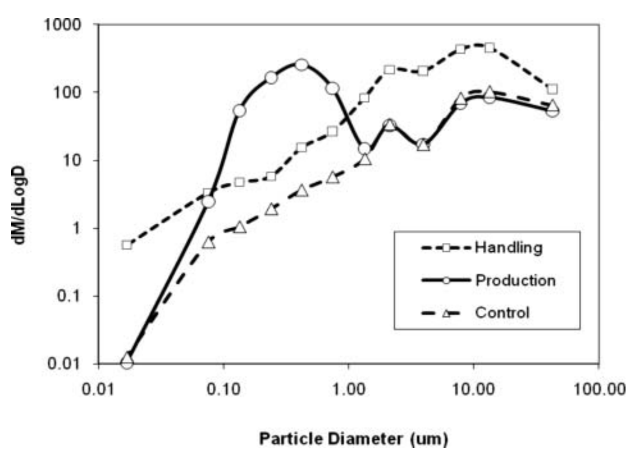

FIGURE 5. Ti equivalent mass concentration size distribution by process.

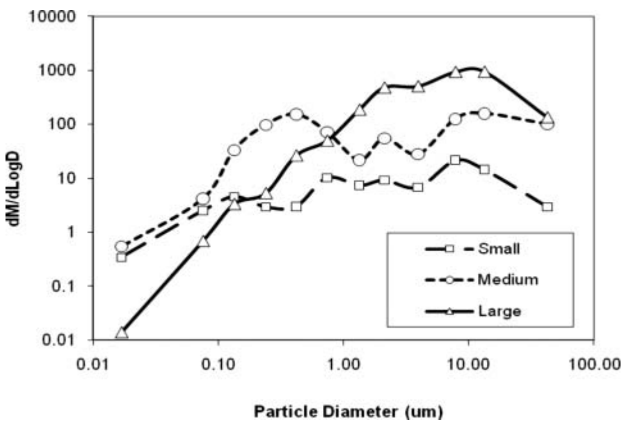

FIGURE 6. Ti equivalent mass concentration size distribution by facility size.

However, when analyzing all three metrics in concert, a picture can be formed about the overall exposure pattern, and how the non-specific metrics might relate to the compound of interest. For example, in the data presented, both total particle number concentration and surface area concentration were higher for production than handling or control (background). Total mass concentration for titanium equivalent was also highest for production. Therefore, it can be assumed that the number and surface area concentration are largely resulting from the metal oxides present in the air. The presence of the metal oxide compounds in the TEM analysis supports this assumption.

In addition to respirable mass concentration, number concentration, or surface area concentration for all particles in a wide size range (e.g., 0.01–10 μm), information is needed on the size distribution of these metrics. Currently, there is no portable measuring device to determine surface area size distribution. Particle number and mass size distribution can be measured using a combination of an optical (OPC) and condensation (CPC) particle counter for particle number and a MOUDI cascade impactor for mass. In general, particle number concentration increases as particles get smaller, while the mass concentration increases as particles get larger. The data presented here follow that pattern. However, when looking at specific particles under TEM, the particles are largely agglomerated in the size range of 0.1 to 1.0 μm. Further, for the production processes at least, the predominant size range for Ti equivalent mass concentration is 0.1–1.0 μm. This is not unexpected, even when nanoscale particles are involved. Small particles tend to agglomerate and mechanical process, such as some production and handling tasks, would not overcome the binding forces for agglomeration.

The greatest potential for exposure to workers appears to be during the handling process. The highest mass concentrations for the personal samples were from handling. This makes sense: while workers may be present during production processes, workers only come into close contact with the metal oxide powders when collecting, weighing, and transferring the powders. It is interesting to note that for the area samples, the production processes had higher dust and metal oxide mass concentrations. It is unclear why this is the case. Results for the personal samples were higher than the area samples, but the two were not correlated (data not shown). Therefore, the area samples may not be giving a clear picture of the exposure encountered by the workers. NIOSH proposes a recommended exposure limit (REL) of 2.4 mg/m^3 for fine TiO_2 (defined as <2.5 μm diameter) and 0.3 mg/m^3 for ultrafine particles (defined as <0.1 μm diameter).[27] So while the workers in this study may be exposed to TiO_2 particles, the exposure is much less than the proposed REL and also much less than the OSHA PEL of 5 mg/m^3 for the respirable fraction of particulates not otherwise regulated (PNOR).

It is difficult to compare the results from this study with those in other metal oxide exposure studies due to differences in exposure measurement, metals analyzed, and data analysis. However, some comparisons can be made. The particle number concentrations found in this study are generally in the range of those from other studies. The average number concentration for particles less than 300 nm ranged from 8000 particles/cm^3 for background to 38,000 particles/cm^3 during production processes in this study, which compares with the range found in other studies. For example, in a lithium titanate production facility, particles less than 300 nm ranged from approximately 10,000 to 30,000 particles/cm^3.[22] In a titanium dioxide production facility, particles less than 1000 nm ranged from 12,000–17,000 particles/cm^3, while the range in this study was 8000–38000 particles/cm^3.[19] When comparing mass concentration, however, the results presented here are considerably lower than those found in a titanium dioxide pigment production factory. Huang et al.[20] measured respirable dust levels ranging from 80–350 μg/m^3 and respirable titanium levels from 3.5 to 85 μg/m^3.

In contrast, the results presented here showed levels of $<$LOD – 60 μg/m^3 and 0.2 to 3.4 μg/m^3 for respirable dust and titanium, respectively. The results presented here are an average of several facility types of different sizes, including manufacturing and end use, while the other papers describe results from individual facilities. Methner et al.[21] visited five metal oxide facilities, but again, a comparison is difficult to make due to different exposure methods, data analysis and presentation, and metal analysis. The number concentration for particles less than 1000 nm in Methner et al. ranged from 0–145,000 particles/cm^3; however, if you exclude the upper and lower extremes, the range was 100–81,000 particles/cm^3.[21]

This work has several limitations. The sample size is small, and censored data are an issue. Further, there is no clear method for determining personal exposure to nanomaterials at this time, and therefore, most of the samples collected were area samples. This makes it difficult to interpret personal exposure. Last, the sampling was not task-specific, so it is impossible to determine which specific tasks are influencing the results the most. Sampling durations encompassed an entire process (either handling or production), which might include several specific tasks. However, the data do provide some characterization of exposure among producers and users of nanometal oxides, and when looking at the data as whole, a pattern of exposure does emerge, suggesting, at least, that exposure to nano metal oxides is occurring. This exposure, though, is occurring at levels that are well below established and proposed limits.

ACKNOWLEDGMENTS

The authors would like to thank the many people involved in providing technical and administrative support for this study. Special thanks go to Kevin L. Dunn and Donnie Booher (NIOSH) for their help with equipment preparation, logistics, and sample collection, and to Shawna Watts (NIOSH) for travel preparation and logistics. The authors are indebted to Donna Olsen (IHI Environmental) for her tireless efforts in company recruitment.

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