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A Quantitative Validation of the Control Banding Nanotool

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Abstract

Eleven years (by publication) years after the development and application of the control banding (CB) Nanotool for the qualitative assessment and control of engineered nanoparticles (ENP), there remains no quantitative gold standard to serve as an alternative to the qualitative assessment. Many CB models have been developed during the years subsequent to the initial development of the CB Nanotool and the literature continues to blossom with comparisons and applications of these various tools; however, these developments have hitherto been made in the absence of validating and verifying their effectiveness using existing, albeit limited, quantitative methods. This paper reviews the existing literature on the CB Nanotool to evaluate its effectiveness in a variety of settings and presents a summary of qualitative and quantitative information from its application in a broad range of ENP handling activities performed in two different research institutions. A total of 28 ENP activities were assessed using the CB Nanotool (Version 2.0). Due to the lack of guidance on a single exposure assessment methodology, a combination of real-time monitoring, filter analysis, and microscopic analysis was used to assess various quantitative metrics, including mass concentration, particle number concentration, and particle speciation. All the results indicated that the control outcomes from the CB Nanotool qualitative assessment were sufficient to prevent workers from being exposed to ENP at levels beyond established exposure limits or background levels. These data represent an independent quantitative validation of CB Nanotool risk level outcomes and give further credence to the use of the CB Nanotool to effectively control worker exposures in the absence of quantitative air monitoring results.

Keywords: CB Nanotool; control banding; engineered nanoparticles; quantitative validation

Introduction

Control banding (CB) strategies offer simplified solutions for controlling worker exposures to constituents often found in the workplace. While the original CB model was developed within the pharmaceutical industry, the modern movement of CB involves models developed for non-experts in small and medium enterprises to input hazard and exposure potential information for bulk chemical processes, with control advice as the outcome (Nelson and Zalk, 2010). The simplicity afforded by CB can be particularly useful when dealing with engineered nanoparticles (ENP). ENP present a number of real challenges to industrial hygiene (IH) practitioners. This is in one part due to the lack of a clear toxicological basis for setting ENP-specific occupational exposure limits (OELs), as nanoparticles can affect a broad range of toxicological endpoints with their high degree of reactivity, their ability to deposit in various regions of the respiratory tract, and their ability to cross normally impenetrable barriers (e.g. blood–brain barrier, skin). The challenge is in another part due to their growing presence in the workplace, as applications for ENP appear endless and both government and private industries are investing substantially into the research and development of nanotechnologies. As products utilizing nanotechnologies are becoming more and more commonplace, given the general lack of understanding of their toxicological parameters, there has been an urging for caution as groups of ENP that appear promising in, say, nanomedical applications have themselves been found to be potentially toxic to the patient or consumer (Card *et al.*, 2008; Liu *et al.*, 2009).

The potential for worker exposures during the handling of ENP is also very real, as evidenced by worker exposures to polyacrylate nanoparticles (Song *et al.*, 2009), silicon dioxide ENP playing a major role in the development of cardiovascular diseases (Petrick *et al.*, 2016), and nickel ENP causing sensitization (Journeay and Goldman, 2014). A systematic review of ENP exposure studies from 2000 to 2015 found high-quality evidence of workplace exposures to multi-walled carbon nanotubes (CNTs), single-walled CNTs, carbon nanofibers (CNFs), aluminium oxide, titanium dioxide, and silver ENPs; moderate-quality evidence for non-classified CNTs, nanoclays, iron and silicon dioxide ENPs; and low-quality evidence for fullerene C60, double-walled CNTs, and zinc oxide ENP (Debia *et al.*, 2016). Through these studies, it is becoming increasingly clear that the very properties that make ENP technologically beneficial may also make them hazardous to humans and the environment. Recognizing the power of people to decide which technologies succeed and which do not, whether based on real or perceived risks (Renn, 2005), the role of the IH practitioner becomes increasingly critical for establishing appropriate means for assessing and controlling the risks presented by ENP, as workers represent the first line of people to face possible risks. Only a proper understanding and acceptance of the risks presented by ENP, by both workers and the public at large, will enable nanotechnologies to develop and thrive. To work toward this goal, the IH practitioner needs a quantitatively validated method to assess ENP occupational risks and implement controls in line with traditional IH professional expectations.

Challenges to the traditional industrial hygiene approach

As described in the original publication of the CB Nanotool (Paik *et al.*, 2008), an appropriate health-relevant index of exposure that is typical of the IH traditional approach has not yet been satisfied for nanoparticles, with no international scientific community consensus on what the relevant index of exposure is (NIOSH, 2006; ISO, 2007, 2012). This lack of consensus leads directly to the lack of sampling and analytical methods to define what needs to be measured. Some commercially available instruments can measure surface area concentration, number concentration, or mass concentration, but these generally measure larger particles in addition to nanoparticles, introducing potentially large biases (summarized in ISO, 2007 and NIOSH, 2006). This leads to IH practitioners having no traditional methods to assess exposure from working with ENP, as very little toxicological data for determining exposure limits for ENP, and virtually no human studies, are available (Maynard and Kuempel, 2005; Gordon *et al.*, 2014).

To overcome some of these challenges, CB was proposed, at least conceptually at first, as an alternative to the traditional IH approach (Thomas *et al.*, 2006; Maynard, 2007; Warheit *et al.*, 2007; Schulte *et al.*, 2008). Analogous to the pharmaceutical industry, this strategy would facilitate decisions on appropriate levels of control based upon product and process information, without complete information on ENP hazards and exposure scenarios. CB uses categories, or 'bands', of health hazards, which are combined with exposure potentials, or exposure scenarios, to determine desired levels of control (Zalk, 2010). The bands of health hazards for some CB approaches are based upon the Safety Data Sheet (SDS) hazard statements (H-statements), formerly risk phrases, while exposure potentials may include the volume of the chemical used and the likelihood of the chemical becoming airborne, estimated by the dustiness or volatility of the source compound (Maidment, 1998). CB strategies have been further refined through International CB Workshops which explored possibilities to apply the CB approach to other domains, like ergonomics, occupational safety, and environmental hazards, as well as in multidisciplinary formats for the construction industry and as an occupational health and safety management system (Zalk, 2001; Swuste, 2007; NIOSH, 2009a,b; Zalk et al., 2010, 2011; Coleman and Zalk, 2014). Although CB has received criticism (see for instance Kromhout, 2002; Swuste *et al.*, 2003; Jones and

Nicas, 2006; ACGIH, 2008), the focus on controls is a strong point of the approach and makes it applicable for operations with many uncertainties in hazard, exposure, and consequence data (ACGIH, 2008; NIOSH, 2009a,b). CB's simplicity is viewed both as a strength and as a weakness, as much of its criticism has focused on issues relating to the simplicity of the CB approach and how this has forsaken the experts and their traditional, quantitative methods. With nanoparticle exposure and its many toxicological and quantitative measurement uncertainties, however, one can argue that the CB qualitative risk assessment approach, at this time, may in fact be superior to the traditional quantitative methods (Zalk *et al.*, 2010). CB for work with ENP is now recommended by many countries, including Australia, Canada, The Netherlands, France, Switzerland, Germany, and South Korea (Marquart, 2008; IRSST, 2009; Safe Work Australia, 2009, 2010; ISO, 2014).

Risk prioritization tools for nanomaterials

Over the years, the number of CB strategies has grown in support of this pragmatic approach to preliminary risk management (Brouwer, 2012). CB strategies for ENP include: CB Nanotool, Stoffenmanager Nano 1.0, Precautionary Matrix, NanoSafer, Guidance, and ANSES, as well as others that have not been formally published (Hock *et al.*, 2008; Paik *et al.*, 2008; Zalk *et al.*, 2009; Cornelissen *et al.*, 2011; Riediker *et al.*, 2012; Van Duuren-Stuurman *et al.*, 2012; Liguori *et al.*, 2016). Brouwer (2012) reviewed many of these CB tools for ENP relating to their applicability and scope, hazard and exposure banding parameters, and risk classification or control bands. Each strategy appeared to target different users and work area applications, with some focusing on research laboratories and others on medium- and small-size enterprises. In addition, the extent and detail of preliminary information required contrast between these CB tools, which leads to a variety in levels of potential user knowledge necessary for implementing each of the strategies. For those that utilize hazard and exposure bands, there were differences in the parameters that were addressed and the methods necessary to assign the appropriate bands. Brouwer identified a consistent need for calibration of these tools and some aspect of a performance check on both inputs and outputs of these CB strategies.

Many of these CB tools tend toward bringing in experts, both to fill knowledge gaps and also as a default outcome based on some input parameters. In addition, ENP presents a unique situation in that there is limited 'expert opinion' and this is the primary reason the CB tools were developed in the first place. Defaulting to experts for nanofibers, as an example, does not necessarily yield more information on how to control a given work application. The CB Nanotool does not have individual input factors that default in this manner to experts, but rather captures potential uncertainty for each of the input parameters with an 'unknown' option. An independent evaluation of the CB Nanotool found this option particularly useful in overcoming this precautionary approach challenge (Casuccio *et al.*, 2010). In January, 2014, the International Organization for Standardization (ISO) issued a new technical specification standard on the use of CB for managing inhalation risk from engineered nanomaterials (ISO, 2014). The standard provides a description of CB for both proactive and retroactive risk assessment, which is distinguished by whether or not existing controls are used as input variables in determining the control band. The CB Nanotool is described as an example of the proactive approach and Stoffenmanager Nano is described as an example of the retroactive approach.

The CB nanotool

Since the publication of the original CB Nanotool, which was the first CB tool developed specifically for the qualitative risk assessment of ENP (Paik *et al.*, 2008), the tool has been the subject of several studies and has become an integral part of the prevention of ENP exposures at various institutions around the world. Safe Work Australia has evaluated the applicability of both CB for ENP in general and the CB Nanotool itself, where it was determined that CB is likely to be the most suitable risk control method for managing ENP exposures in the Australian ENP industry (Safe Work Australia, 2010) and the CB Nanotool, in particular, is currently being used as their method of choice for addressing the control of ENP in the workplace (Workplace Health and Safety Queensland, 2017). Scientific review articles of the latest ENP sciences have found that the CB Nanotool's approach, which determines an overall risk level (RL) outcome based on properties intrinsic to the ENP (severity band) and how the ENP is handled (probability band), has the potential to offer the greatest utility to ENP producers as well as users, on both the local and the national scale (Savolainen *et al.*, 2010; Schulte *et al.*, 2010). In a study that assessed the quality of evidence of studies pertaining to CB in the context of ENP using Grading of Recommendations Assessment, Development and Evaluation (GRADE), only two studies out of 235 records were identified to meet the inclusion criteria (Eastlake *et al*., 2016). Both of them used the CB Nanotool as their risk assessment method in workplaces where ENP were being handled.

Validation of the CB nanotool

For the qualitative validation of the CB Nanotool, Paik *et al*. (2008) and Zalk *et al*. (2009) focused on a sample of representative research and development (R&D) activities within the Lawrence Livermore National Laboratory (LLNL) institutional safety document database. Prior to the development of the CB Nanotool, expert IH advice using best practice references such as the NIOSH 'Approaches to Safe Nanotechnology' publication (NIOSH, 2009a,b), had been used to select the most appropriate controls for a given ENP activity. CB Nanotool outcomes from these activities were directly compared with IH-prescribed controls, which, at the time, was as close as one could come to validating the CB Nanotool method in the absence of quantitative methods. A total of 32 risk assessments with the CB Nanotool were performed on activities in this database. The CB Nanotool recommendation was equivalent to the existing controls for 20 of them, it prescribed a higher level of control for 8 of them, and it prescribed a lower level of control for 4 of them. These results indicated that the CB Nanotool produced control recommendations that were generally equal to or in some cases more conservative than the existing controls that were implemented by experts. The results were consistent with what the authors hoped to achieve through the tool, which was to develop a consistent approach that would generally err on the safe side, in light of the uncertainty associated with ENP health effects.

While considerable success has been attained for qualitative risk management methods in general, quantitative methods should continue to be evaluated for their role in validating the qualitative outcomes (NIOSH, 2012; Dunn *et al*., 2018). Though still limited, a number of quantitative methods are currently available that can measure some aspect of ENP exposure. When used strategically, these methods, together, can paint a picture that provides valuable insight into exposure. Toward this end, a variety of quantitative methods were used as part of this study for the quantitative validation of CB Nanotool RL outcomes, which is considered the next logical step after the qualitative validation.

Materials and Methods

Activities at Lawrence Livermore National Laboratory

For the quantitative validation of the CB Nanotool for activities performed at LLNL, three different sampling methods were adopted, including the use of two real-time instruments (TSI P-Trak Ultrafine Particle Counter and the TSI Nanoscan Scanning Mobility Particle Sizer) and traditional filter-based air sampling. The sampling approach is based primarily on the procedure outlined in the Department of Energy's Nanoscale Science Research Centers *Approach to Nanomaterial ES&H* Attachment 1 (Example Industrial Hygiene Sampling) (DOE, 2008), which recommends the use of direct-reading instruments and filter-based sampling. For these measurements, this study used the Department of Energy's (DOE) definition of nanoparticle (i.e. dispersible particles having in two or three dimensions greater than 1 nanometer and smaller than about 100 nm), which is based on ASTM International's definition of nanoparticles as defined in E 2456-06 'Terminology for Nanotechnology' (ASTM, 2007). This definition varies slightly from the US National Institute for Occupational Safety and Health's (NIOSH, 2006) and International Organization for Standardization's (ISO, 2014) definition of nanoparticle, which define nanoparticles as having at least one dimension between 1 and 100 nm and all three dimensions between 1 and 100 nm, respectively. The European Union, in contrast, uses a broader definition of nanomaterial, which defines a nanomaterial as 'having particles, in an unbound or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more dimensions is in the size range 1 nm–100 nm'. While the real-time Nanoscan SMPS method (see below) used in this study was based on the US's and ISO's definitions of nanoparticles, which have an upper cutoff of 100 nm, it should be noted that the filter-based method for CNTs collected all respirable particles, which have a 50% cutoff at 4 μm. Similarly, the filter-based method for metals collected all 'total' particles, up to the inhalability limit of 100 μm. Moreover, the real-time P-trak (see below) collected particles up to 1000 nm. As such, most, if not all, of the aggregates or agglomerates with size dimensions larger than 100 nm, if present, would have been collected by these samplers and thus accounted for, which is important given the potential for aggregates or agglomerates to separate into individual nanoparticles after entering the lungs.

The activities assessed as part of this study were based on activities that were performed from May 2017 to August 2018. Since most activities at LLNL are not performed routinely, several industrial hygienists at LLNL were engaged to help coordinate sampling sessions for these activities when such opportunities arose. The activities included any task that could result in dispersible nanoparticles in the air, which included both dry and wet processes. Nanoparticle exposure during the handling of nanomaterials embedded, or bound, on solid structures were not assessed due to the unlikelihood of dispersible particles being generated from this process. Based on a review of all the activities at LLNL involving unbound nanoparticles, these activities were considered representative of activities that would typically occur in a research and development environment.

Below are descriptions of each sampling method, how each sampling technique was used in the field and how the data was interpreted.

TSI P-Trak ultrafine particle counter

The P-Trak device (Model 8525) is a portable instrument that measures nanoparticles. This device is used to provide a general quantity of the particle concentrations, in units of particles/cm^3. The particle sizes detected by the P-Trak range from 20 to 1000 nm, which encompass most of the size range for nanoparticles (1 to 100 nm). The P-Trak does not measure the actual size of the ENP. Consequently, this instrument is used as a semi-quantitative screening tool and further real-time analysis can be conducted using the Nanoscan SMPS.

TSI Nanoscan scanning mobility particle sizer (SMPS)

The Nanoscan device (Model 3910) is a portable instrument that uses a condensation particle counter and a SMPS spectrometer that measures both the number and size of nanoparticles. The measurement range is 10–420 nm and the readings provide 13 different channel sizes. By scanning the complete measurement range during each minute of run time, this instrument delivers a particle size distribution every minute, providing a more thorough evaluation than that provided by the P-Trak. Channel sizes larger than 115.5 nm were not included in the results analyses based on the definition of ENP adopted for this study. As such, aggregated or agglomerated particles larger than 115.5 nm were not specifically considered for the real-time quantitative analyses; however, the air samples collected using filter-based sampling would measure larger (aggregated or agglomerated) particles up to 10 µm (for BGI cyclone) and up to 100 µm (for 37-mm closed-face-cassette). For each activity that was assessed using the Nanoscan SMPS, measurements were collected for 10 min before, during, and after the activity.

Filter-based sampling

The filter-based sampling approach applies traditional NIOSH methods, depending on the ENP being used. This type of sampling is used to provide supplemental and specific information on the ENP material. The following filter-based sampling methods were used for the different ENP encountered in this study:

- Metal nanoparticles: NIOSH Method 7300 (elements by ICP) was used in cases where the metals were the base material of the ENP. The primary purpose of this method was to determine the presence/absence of airborne ENP. Secondarily, this method was used for comparing the nanoparticle exposures with applicable OELs for the metal(s) of concern, based on OSHA standards and ACGIH TLVs. Cobalt, which has a TLV of 0.02 mg/m^3, was analyzed for 2 of the 20 activities assessed at LLNL. Metal-specific methods are more appropriate than gravimetric methods for metals analysis since they provide better analytical sensitivity. Air samples were collected using a 37-mm filter cassette with 0.8 µm pore size mixed cellulose ester (MCE) filter and sampled during the reasonable worst-case activity duration. The maximum flow rate for these samples was set at 4 l/min.
- Carbon nanotubes or nanofibers (CNT/CNF): These were measured using NIOSH Method 5040 (diesel particulate matter as elemental carbon) for comparison against the NIOSH-recommended exposure limit (REL) of 1 µg/m^3. Air samples were collected using 25-mm filter cassettes with a quartz fiber filter and a respirable GK 2.69 BGI cyclone. The flow rate was set at 4.2 l/min to collect the respirable fraction and the sampling pump was run for a minimum of 3 h.

Once the specific type of ENP being used had been determined, the following sampling approach was implemented. For real-time monitoring, measurements were collected before, during, and after the activity was performed. The averages of measurements collected before and after the activity were considered 'background' measurements. If a filter cassette was used, simultaneous sampling was performed inside the fume hood or ventilated enclosure (if used), from the worker's personal breathing zone, and in some cases, inside the general work area but away from the activity (background). For ENP activities conducted on a benchtop or outdoors, not involving engineering controls, samples were collected from the personal breathing zone and from the background away from the activity. Where a fume hood or enclosure was used, results collected from the generation source and from the worker's breathing zone and/or background were compared to determine if the engineering controls helped to reduce airborne levels in the worker's breathing zone and/or background. The specific details of the sampling methods employed for each activity are described in Tables 1 and 2.

Table 1. CB Nanotool and air monitoring results at LLNL.

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
1	Stress testing of carbon nanotubes inside a ventilated enclosure. Tests are carried out to the specimen's failure.	Carbon nanotubes	High	Less likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before, during, and after stress testing. The number concentration measured during testing was 3.5 times higher than background levels. See Table 3.	Yes. Results suggest that RL2 controls are appropriate.
2	Sample preparation of carbon nanotubes, including dry weighing and mixing into liquid media.	Carbon nanotubes	High	Likely	3	25-mm filter cassettes with BGI cyclone were used to collect air samples from inside the fume hood, inside the lab away from the activity, and from the worker's personal breathing zone (PBZ). Results were non-detect for elemental carbon for all samples. Duration: 183 min; Flow rate: 4.2 l/min; Quantity of CNT weighed and transferred: 400 mg; 8-h TWA results: <0.35 μg/m^3 (hood), <0.35 μg/m^3 (PBZ), <0.35 μg/m^3 (background).	Yes. Results suggest that RL1 controls are appropriate.
3	Machining, handling and processing of aerogels and foams.	Carbonized Resorcinol Formaldehyde	High	Less likely	2	A TSI P-trak was used to compare background measurements (number concentration) to PBZ measurements during machining. There was no significant difference in number concentrations during machining compared to background levels.	Yes. Results suggest that RL1 controls are appropriate.
4	Ethanol was poured into a glass vial containing samarium cobalt oxide nanoparticles.	Samarium cobalt oxide	High	Less likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before, during, and after pouring ethanol into an open glass vial containing ENP. There was no significant difference in ENP number concentrations during the activity compared to background levels. Filter sampling results from inside the hood and PBZ during this activity did not indicate any detectable cobalt. Duration: 30 min; Flow rate: 4 l/min; 8-h TWA results: <6.9 μg/m^3 (hood), <6.9 μg/m^3 (PBZ). See Fig. 1 and Table 3.	Yes. Results suggest that RL1 controls are appropriate.

Table 1. Continued

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
5	Scooping a few grams of samarium cobalt oxide nanoparticles into a glass vial.	Samarium cobalt oxide	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before, during, and after scooping powder from primary container into glass vial using a spatula. This was done three times over a 10-min period. There was no significant difference in ENP number concentrations during the activity compared to background levels. Filter sampling results from inside the hood and PBZ during this activity did not indicate any detectable cobalt. Duration: 30 min; Flow rate: 4 l/min; 8-h TWA result: <6.9 µg/m^3 (hood), <6.9 µg/m^3 (PBZ). See Fig. 1 and Table 3.	Yes. Results suggest that RL1 controls are appropriate.
6	Cleaning up spilled fused silica nanoparticles	Fused silica	Medium	Less likely	1	NanoScan SMPS Model 3910 was used to measure particle size distribution before, during, and after cleaning spilled ENP with water-wetted wipes. There was no significant difference in ENP number concentrations during the activity inside the fume hood compared to background levels. See Table 3.	Yes. Results suggest that RL1 controls are appropriate.
7	Cleaning extruder filters contaminated with CNTs that are mixed with lipid bilayers	Carbon nanotubes	High	Extremely unlikely	2	25-mm filter cassettes with BGI cyclone were used to collect air samples from right next to activity, from inside the lab away from the activity, and from the PBZ. Results were non-detect for elemental carbon for all samples. Duration: 43 min; Flow rate: 4.2 l/min; 8-h TWA results: <0.35 µg/m^3 (PBZ), <0.35 µg/m^3 (next to activity), <0.35 µg/m^3 (background).	Yes. Results suggest that RL1 controls are appropriate.
8	Transfer and weighing of fused silica inside fume hood. Fused silica nanoparticles are transferred from large container to small container.	Fused silica	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before, during, and after transferring and weighing ENP. The number concentration measured during testing was 3.9 times higher than background. during transfer and weighing of ENP. See Fig. 2 and Table 3.	Yes. Results suggest that RL2 controls are appropriate.

Table 1. Continued

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
9	Baking of vial containing CNTs on hot plate to remove catalysts/off-gases. Vial is covered with aluminum foil.	Carbon nanotubes	High	Less likely	2	25-mm filter cassettes with BGI cyclone were used to collect air samples from right next to activity, from inside the lab away from the activity, and from the PBZ. Results were non-detect for elemental carbon for all samples. Duration: 68 min; Flow rate: 4.15 l/min; 8-h TWA results: $<0.35\ \mu g/m^3$ (PBZ), $<0.35\ \mu g/m^3$ (next to activity), $<0.35\ \mu g/m^3$ (background).	Yes. Results suggest that RL1 controls are appropriate.
10	Sonication of CNTs in solution within an enclosure	Carbon nanotubes	High	Extremely unlikely	2	25-mm filter cassettes with BGI cyclone were used to collect air samples from right next to activity and from the PBZ. Results were non-detect for elemental carbon for all samples. Duration: 43 min; Flow rate: 4.2 l/min; 8-h TWA results: $<0.35\ \mu g/m^3$ (PBZ), $<0.35\ \mu g/m^3$ (next to activity).	Yes. Results suggest that RL1 controls are appropriate.
11	Cleaning of sonicator tips contaminated with visible carbon using ethanol.	Carbon nanotubes	High	Extremely unlikely	2	25-mm filter cassettes with BGI cyclone were used to collect air samples from right next to activity and from the PBZ. Results were non-detect for elemental carbon for all samples. Duration: 43 min; Flow rate: 4.2 l/min; 8-h TWA results: $<0.35\ \mu g/m^3$ (PBZ), $<0.35\ \mu g/m^3$ (next to activity).	Yes. Results suggest that RL1 controls are appropriate.
12	Transfer and weighing of CNTs on benchtop. CNTs are transferred from original vendor container to glass vial.	Carbon nanotubes	High	Less likely	2	25-mm filter cassette with BGI cyclone were used to collect air samples from right next to activity and from the PBZ. Results were non-detect for elemental carbon for all samples. Duration: 68 min; Flow rate: 4.15 l/min; 8-h TWA results: $<0.35\ \mu g/m^3$ (PBZ), $<0.35\ \mu g/m^3$ (next to activity).	Yes. Results suggest that RL1 is appropriate.
13	Sample preparation of sodium yttrium fluoride, ytterbium, SiO^2 and erbium in liquid suspension.	NaYF4, Yb and Er	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during sample preparations in a fume hood. There was no significant difference in ENP number concentrations during the activity inside the hood compared to background levels. See Table 3.	Yes. Results suggest that RL1 controls are appropriate.

Table 1. Continued

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
14	pH waste sampling of CNT in acetone solution.	Carbon nanotubes	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during the pH waste sampling task. There were no significant differences in number concentrations inside the worker's breathing zone compared to background levels. See Table 3.	Yes. Results suggest that RL1 controls are appropriate.
15	Waste container opening/closing of CNT in acetone solution (Indoor activity).	Carbon nanotubes	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during the waste container opening/closing task. There were no significant differences in number concentrations inside the PBZ compared to background levels. See Table 3.	Yes. Results suggest that RL1 controls are appropriate.
16	Waste container opening/closing of Cu ENP powder w/ acetone (Outdoor activity).	Copper	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during the waste container opening/closing task. The task of closing the ENP waste container was slightly lower in total concentration when compared to the outdoor air/background total concentrations but slightly higher in the 11.5 nm and 15.4 nm particle size range. The differences, however, were not statistically significant. See Table 3.	Yes. Results suggest that RL1 controls are appropriate.
17	Handling dry mixed ENP waste (Indoor activity).	Mix	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during the waste handling task. There were no significant differences in number concentrations inside the PBZ compared to background levels in the lab.	Yes. Results suggest that RL1 controls are appropriate.
18	Handling dry mixed ENP waste from liquid suspension (Indoor activity).	Mix	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during the waste handling task. There were no significant differences in number concentrations inside the PBZ compared to background levels in the lab.	Yes. Results suggest that RL1 controls are appropriate.
19	Waste container opening/closing of Dry Mixed ENP w/solvents (Outdoor activity).	Mix	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during the waste container opening/closing task. There was no significant difference in ENP number concentrations during the activity compared to background levels. See Table 3.	Yes. Results suggest that RL1 controls are appropriate.

Table 1. Continued

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
20	Waste container opening/closing of Cu ENP powder w/ solvent (Outdoor activity).	Copper	Medium	Likely	2	NanoScan SMPS Model 3910 was used to measure particle size distribution before and during the waste container opening/closing task. The task of closing the ENP waste containers was slightly higher in the 11.5nm to 15.4 nm range around 30% higher in the 36.5nm – 48.7 nm particle size range. The differences, however, were not statistically significant. See Fig. 3 and Table 3.	Yes. Results suggest that RL1 controls are appropriate.

Activities at Lawrence Berkeley National Laboratory

For the quantitative validation of the CB Nanotool for activities performed at Lawrence Berkeley National Laboratory (LBNL), the NIOSH Nanoparticle Emission Assessment Technique (NEAT) program was used. The NEAT approach includes the use of a condensation particle counter (TSI Condensation Particle Counter 3007) and an optical particle counter/sizer (Grimm SubMicron Aerosol Spectrometer 1.108) direct-reading instruments along with filtration-based air sampling with laboratory analytical analysis. A detailed description of LBNL's methodology is provided in their Phase 3 study (Casuccio *et al.*, 2010).

Validation criteria

RL outcomes from the CB Nanotool are derived from a standard four by four risk matrix with severity and probability. The severity and probability bands are ranked on a scale from 0 to 100. The severity band is ranked from low (0–25 points) to very high (76–100 points) while the probability band is ranked from extremely unlikely (0–25 points) to probable (76–100 points). The controls for the different RL outcomes are as follows: RL 1 requires general ventilation, RL 2 requires fume hoods or local exhaust ventilation, RL 3 requires containment, and an RL 4 outcome would be to seek advice from a specialist. The qualitative validations of the CB Nanotool found that the outcomes tended toward the conservative; therefore, it was anticipated that the quantitative results, most of which were non-specific to ENP, and therefore would not take the severity of the ENP into account, may predict lower RLs than the CB Nanotool.

When interpreting the results from the direct-reading instruments or from microscopic analysis of ENP, the level of control that was considered appropriate for worker protection was based on a comparison of particle number concentrations measured from right next to the activity (generation source) to those concentrations measured from the worker breathing zone and/or background. For source particle concentrations that were not significantly different from worker breathing zone/background levels (based on statistical analyses of particle size distributions), general ventilation (RL 1) was considered the appropriate level of control. For source particle concentrations up to 10 times the worker breathing zone/background (one order of magnitude), a fume hood or other LEV system (RL 2) was considered the appropriate level of control. In the absence of LEV, a half-face air-purifying respirator (assigned protection factor of 10) or higher-level respirator

Table 2. CB Nanotool and air monitoring results at LBNL.

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
1	Transfer acetylene black from original container to glass jar using spatula. Weighing of ENP using balance.	Acetylene black	Medium	Likely	2	Air samples using 25-mm open-faced cassette showed '<500 nm' levels approximately 2 times the background and PBZ levels when measured inside the fume hood next to the activity. This suggests that fume hood is the appropriate control.	Yes. Results suggest that RL2 controls are appropriate.
2	Transfer of fumed silica from original container to glass jar using spatula. Weighing of ENP using balance.	Fumed silica	Medium	Likely	2	Air samples using 25-mm open-faced cassette showed '<500 nm' levels approximately three times the background and PBZ levels when measured inside the fume hood next to the activity. This suggests that fume hood is the appropriate control.	Yes. Results suggest that RL2 controls are appropriate.
3	Weighing of nanosilicon powder with a metal spatula on copper substrate.	Nanosilicon	Medium	Likely	2	Air samples using 25-mm open-faced cassette showed '<500 nm' levels less than the background for both PBZ samples and when measured inside the fume hood next to the activity. This suggests that ENP beyond background levels are not being generated by this activity.	Yes. Results suggest that RL1 controls are appropriate.

Table 2. Continued

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
4	Funneling nanosilicon powder into a volumetric flask	Nanosilicon	Medium	Less likely	1	No significant differences were observed between background readings and during handling inside the fume hood based on CPC monitor and Optical Particle Counter measurements. The average particle concentration inside the fume hood and at background was 2024 (standard deviation of 181) and 2229 (standard deviation of 237) particles/cm^3, respectively.	Yes. Results suggest that RL1 controls are appropriate.
5	Funneling carbon black powder into a volumetric flask	Carbon black	Medium	Less likely	1	No significant differences were observed between background readings and during handling inside fume hood based on CPC monitor and Optical Particle Counter measurements. The average particle concentration inside the fume hood and at background was 2703 (standard deviation of 253) and 2766 (standard deviation of 286) particles/cm^3, respectively.	Yes. Results suggest that RL1 controls are appropriate.
6	Milligram quantities of gold rods and spheres in an aqueous solution are manipulated in a fume hood. Sonication of the solution is performed on a countertop.	Nanogold	High	Less likely	2	Air samples using 25-mm open-faced cassette showed '<500 nm' levels that were non-detect for background samples, PBZ samples, and when measured inside the fume hood next to the activity. Gold ENP were not detected on any air samples.	Yes. Results suggest that RL1 controls are appropriate.

Table 2. Continued

Activity number	Scenario description	Name or description of nanomaterial	Severity band	Probability band	CB Nanotool risk level	Air monitoring results	Do quantitative results support CB Nanotool risk level?
7	Involves the thinning of graphene, using adhesive tape to delaminate layers of graphene to a single layer flat sheet of carbon until ~0.3 nm thickness is obtained. Task is performed on countertop.	Graphene	Medium	Less likely	1	Air samples using 25-mm open-faced cassette showed '<500 nm' levels that were non-detect for background samples, PBZ samples, and when measured inside the fume hood next to the activity. Gold ENP were not detected on any air samples.	Yes. Results suggest that RL1 controls are appropriate.
8	Involves manipulation of dry nanomaterials (silica, metals, and carbon black) in mg to g quantities. Process conducted in a glovebox.	Fumed silica and carbon black	Medium	Likely	2	No difference between background readings and during handling of carbon black or fumed silica inside glovebox based on CPC monitor and Optical Particle Counter measurements. Particle concentrations spiked up when opening the pass-through door, likely due to incidental ultrafine particles coming into the glovebox.	Yes. Results suggest that RL1 controls are appropriate.

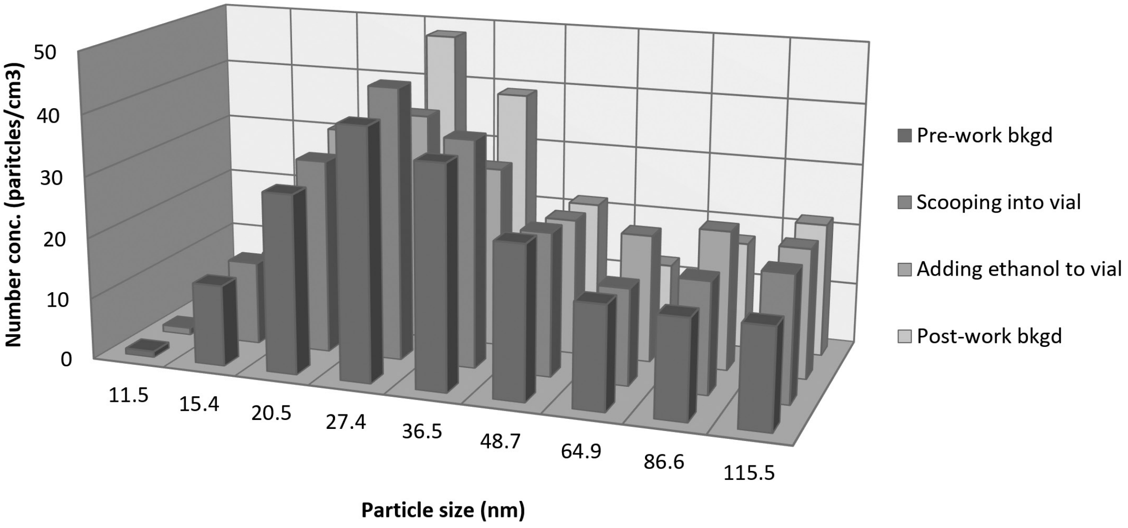

Figure 1. Particle size distribution during scooping and weighing of samarium cobalt oxide ENP.

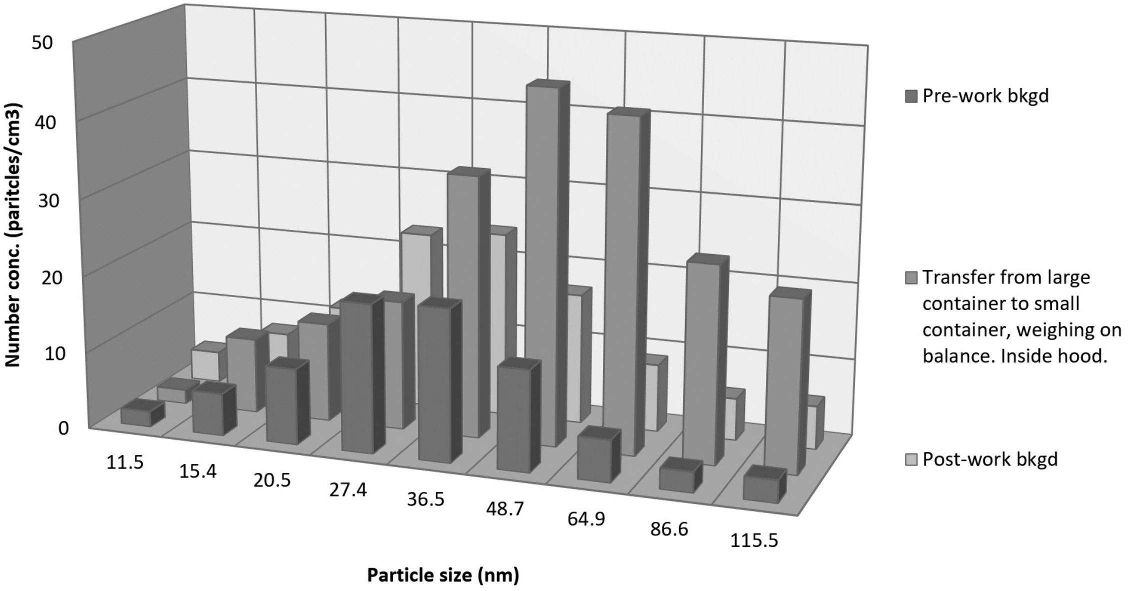

Figure 2. Particle size distribution during transfer of fused silica ENP.

was considered to provide a comparable level of protection as the LEV system. For source particle concentrations more than 10 times the background, a glove box or similar containment (RL 3) was considered appropriate.

When interpreting mass concentration results from filter analyses for ENP with existing OELs, the level of control that was considered appropriate was based on a comparison of the measured 8-h TWA for the analyte of interest and the 8-h TWA OEL. For results that were below the 8-h TWA OEL, general ventilation (RL 1) was considered appropriate. For results that were up to 10 times the OEL, a fume hood or other LEV system (RL 2) was considered appropriate. In the absence of LEV, a half-face air-purifying respirator (assigned protection factor of 10) or higher-level respirator was considered to provide a comparable level of protection as the LEV system. For results greater than 10 times the OEL, a glove box or similar containment (RL 3), or minimum full-face air-purifying respirator, was considered appropriate.

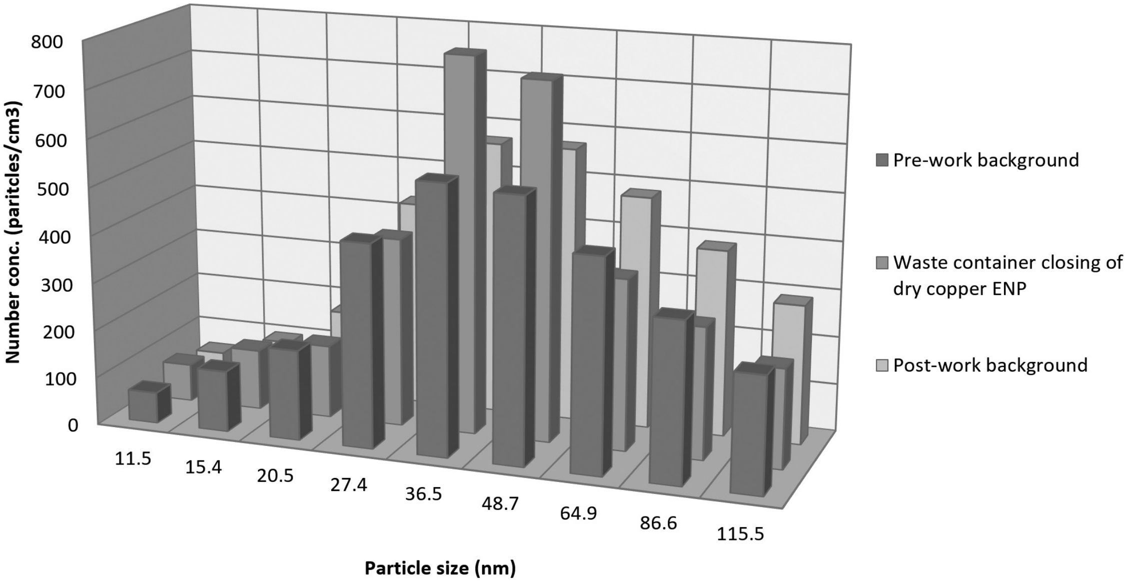

Figure 3. Particle size distribution during closing of containers containing copper ENP (outdoors).

When RL outcomes from the quantitative analyses were equal to or lower than the RL outcomes from the CB Nanotool, the CB Nanotool RL was considered to be quantitatively validated. The decision to define this validation criterion as such was based on the recognition that quantitative methods for ENP are still subject to various limitations, as described in the Introduction section, and therefore do not provide a definitive assessment of risk. The purpose of the quantitative analyses was to determine if, through a multi-pronged approach, the quantitative data would either support the CB Nanotool outcome or provide contrary information. Thus, for scenarios where the CB Nanotool outcome was *at least as* protective as the quantitative determination, we considered this to be an acceptable validation of the tool.

RESULTS

To perform the quantitative validation of the CB Nanotool, 20 activities performed at LLNL were first assessed using the CB Nanotool (Version 2.0) and then air monitoring was performed for each of these activities using one or more of the following quantitative methods: real-time monitoring using the TSI P-trak (Shoreview, MN), TSI Nanoscan SMPS Nanoparticle Sizer Model 3910 (Shoreview, MN), filter sampling using a 25-mm filter with BGI cyclone, and/or filter sampling using a 37-mm closed-face cassette (CFC) sampler. The results are shown in Table 1 and Figs 1–3, which pertain to specific activities described in Table 1 and are referenced within the table, present examples of SMPS data obtained for select ENP activities. For all the activities that were assessed using filter-based sampling, the activities were assessed for the entire duration of the task involving ENP, and for comparison against the applicable OELs, 8-h Time-weighted Averages (TWA) were calculated (zero exposure was assumed for the remainder of the shift when total task duration of the ENP task was shorter than a full shift; this was verified at the time of monitoring). This allowed the analyses to achieve analytical reporting limits, expressed as mass concentration, at around one-third of the OEL for both CNTs and cobalt.

Similarly, for the purposes of this study, eight activities described during the Phase 3 LBNL study (Casuccio *et al.*, 2010) were first re-assessed using the full version of the CB Nanotool (Version 2.0), since the original study used a simplified version of the tool, and air monitoring results obtained from each of these activities were summarized. The quantitative methods used in this study included real-time monitoring using the TSI Condensation Particle Counter (CPC) Model 3007 (Shoreview, MN) and Grimm SubMicron Aerosol Spectrometer 1.108 (Ainring, Germany), and filter sampling using the 25-mm PC filters used in open-face configuration for microscopic analysis. The results are shown in Table 2.

Table 3. NanoScan SMPS Model 3910 (LLNL) and NEAT (LBNL) results and statistics.

Activity number	Scenario description	Average total background concentration (particles/cm^3)	Average total activity concentration (particles/cm^3)	Average concentration ratio (activity: background)	*T*-test *P*-value (2 sample, unequal variance)	Statistically significant difference (*P*-value < 0.05)?
1 (LLNL)	Stress testing of carbon nanotubes inside a ventilated enclosure. Test are carried out to the specimen's failure.	151	440	3.5	0.017	Yes
4 (LLNL)	Ethanol was poured into a glass vial containing samarium cobalt oxide nanoparticles.	195	199	0.95	0.93	No
5 (LLNL)	Scooping a few grams of samarium cobalt oxide nanoparticles into a glass vial.	195	206	1.1	0.84	No
6 (LLNL)	Cleaning up spilled fused silica nanoparticles	80.8	95.7	1.3	0.62	No
8 (LLNL)	Transfer and weighing of fused silica inside fume hood. Fused silica nanoparticles are transferred from large container to small container.	80.8	212	3.9	0.022	Yes
13 (LLNL)	Sample preparation of sodium yttrium fluoride, ytterbium, SiO2 and erbium in liquid suspension.	265	282	1.2	0.62	No
14 (LLNL)	pH waste sampling of CNT in acetone solution	359	412.	1.1	0.7	No
15 (LLNL)	Waste container opening/closing of CNT in acetone solution	359	331	0.89	0.82	No
16 (LLNL)	Scooping a few grams of samarium cobalt oxide nanoparticles into a glass vial.	2936	3115	1.0	0.85	No
17 (LLNL)	Handling of dry mixed UNP waste	1644	1143	1.4	0.45	No
18 (LLNL)	Handling of dry mixed UNP waste from liquid suspension	2964	2727	0.88	0.85	No
19 (LLNL)	Waste container opening/closing of dry mixed UNP w/ various solvents	3003	3015	0.99	0.98	No
20 (LLNL)	Waste container opening/closing of Cu UNP powder w/ solvent	2790	2856	1.1	0.93	No
4 (LBNL)	Funneling nanosilicon powder into a volumetric flask	2229	2024	0.91	Did not determine	Not likely
5 (LBNL)	Funneling carbon black powder into a volumetric flask	2766	2703	0.98	Did not determine	Not likely

Statistical analyses using two-sample, unequal variance *T*-tests were conducted using Microsoft Excel® for all the Nanoscan SMPS measurements, which only applied to activities assessed at LLNL. The test was to determine if there were statistically significant differences between ENP number concentrations (measured at each particle size) close to the activity and background concentrations. The average of the total particle concentrations summed across the 11.5 nm to 115.5 nm particle size range for a 10-min measurement duration was used to compare the activity and background concentrations. The p-values were determined at the 95% significance level. For the LBNL real-time particle measurements, the average total particle concentrations were used to compare the activity and background concentrations. The results are shown in Table 3. Statistically significant differences were found in only 2 out of the 13 activities assessed using the Nanoscan SMPS. One activity involved stress testing of CNTs and the other activity involved weighing/transfer of fused silica ENP. In both cases, ENP particle concentrations were three to four times higher inside the fume hood or ventilated enclosure compared to outside the fume hood or enclosure, based on the average of the activity-to-background ratios calculated at each particle size. These results demonstrated the efficacy of the existing engineering controls in reducing worker exposures to ENP. While a *T*-test was not performed for the LBNL measurements, the activity to background ratios were close to 1, suggesting there were no significant differences between activity and background concentrations.

Discussion

As described earlier, CB may be the best option for consistently and systematically controlling exposures to ENP in the absence of a gold standard for quantitative exposure assessment. In the absence of traditional IH methods for ENP, it is especially important that methods developed and implemented reflect a consistently conservative bent toward risk assessment and control outcomes. Toward this end, recognizing that quantitative methods for measuring some aspect of ENP exposure are available, many of which were developed since the original publication of the CB Nanotool, these quantitative tools can play an important role in providing additional confidence in qualitative risk assessments. A multi-pronged approach using real-time instruments and offline filter analysis was used for that purpose in this study. For all 28 activities that were assessed as part of this study, the quantitative data satisfied the validation criteria defined in this study. No statistically significant differences were found between background measurements and worker breathing zone measurements and statistically significant differences were found for 2 of the 28 activities when comparing background or worker breathing zone measurements with measurements right next to the activity (inside a fume hood or ventilated enclosure).

For 8 of the 28 activities, the RL outcomes from the quantitative data were the same as those from the CB Nanotool. For the remaining 20 activities, a downgrade of controls from the CB Nanotool outcome would be considered if looking strictly at the quantitative data. However, given the current limitations in quantitative methods for ENP, the uncertainty associated with ENP hazards (and concomitant lack of ENP OELs), the proliferation of ENP products and their uses in research and production industries, and the desire by IH practitioners to generally err on the conservative side, the CB Nanotool outcomes were preferred over the outcomes determined solely from the quantitative analyses. While the ENP activities were limited to 2 institutions and 28 activities, these activities represent ENP work, in terms of variety and scale that would typically be conducted in a R&D laboratory environment. These cumulative results, therefore, provided an effective quantitative validation of the CB Nanotool.

The CB Nanotool offers a practical approach and can be used by a variety of personnel in a research environment; however, opportunities for improvement do exist such as expanding the scope of scenarios evaluated, increasing the types of ENP materials used, and further evaluation and standardization of the validation sampling approach presented, especially if new quantitative methods become available. In addition, there is a need address the assessment of risk and application of appropriate controls that address the broader scope applications of ENP in manufacturing sectors. The CB Nanotool was initially designed for use at a US research laboratory with a large working population focused on R&D but was never intended to be a static tool for R&D activities. The inclusion of the CB Nanotool by ISO (2014) as an example approach for proactive risk assessment is seen as a formalized understanding of the potential expansion of its utility as an initial step in the risk management process for ENP in general industry as well as in R&D settings. As discussed in Zalk *et al.* (2009), for larger-scale activities in a manufacturing environment, some adjustment to the choices within each input factor (e.g. applicable masses of ENP would be greater in magnitude) and the control options would likely be required as well as a quantitative determination of control effectiveness. As proposed in earlier research, there should be task-based 'airborne' factors derived by industry for standardization (Schneider 2008). The utility of such 'dustiness' factors within a set range is already a uniform application in many CB strategies and exposure models (Tielemans *et al.*, 2008; Zalk and Nelson, 2008). Quantitative evaluations of control effectiveness should be considered an essential part of the validation effort. However, perhaps in a manufacturing process, there should also be the expectation of SDSs becoming an integrated part of ENP risk assessment by communicating ENP and Parent Material parameters that could be directly transferred into an industrial-scale CB tool. Research that focuses on providing the key data inputs for these CB tools and including standard information on SDSs would facilitate the utility of these tools (Dunn *et al.*, 2018), as ENP experts agree that research parameters affording comparisons and sharing of findings is a primary requirement for controlling exposures (Liao *et al.*, 2008; Warheit *et al.*, 2008, Yang *et al.*, 2008). The nanotechnology industries also need to assist in the development of a standardized database of toxicological research findings harnessed and presented in a consistent format. This process could help in presenting a uniform format for further evaluation of the severity input factors of the CB Nanotool and, more importantly, play an essential role in the protection of workers in the nanotechnology industries.

At the scientific level, the CB Nanotool approach has been found by numerous researchers to have the potential to offer increased utility to ENP producers at both the micro and macro levels. However, it should be recognized that and the CB Nanotool and CB toolkits in general, must always be used with some degree of caution. The different factors considered, weighted, and influencing the overall RLs and control bands are determined as educated 'guesses' as to factor importance and range delineation. Any qualitative risk assessment requires frequent use, validation, and evaluation of recommended control effectiveness. The authors, therefore, strongly encourage the further utilization of this or other similar tools for a wide range of applications as these efforts will undoubtedly improve and refine the tool.

CB strategies have been known over decades to offer a simplified control of worker exposures when there is an absence of firm toxicological and exposure information and the nanotechnology industry fits this classification perfectly. The overwhelming uncertainties of work-related health risks posed by ENP have appropriately led many experts to suggest CB as a solution for these issues. The CB Nanotool was created to fulfill this request and its applications internationally continue to grow. As presented, the CB Nanotool has been proven, through comparisons with both expert advice and quantitative air monitoring data, to accurately provide a qualitative risk assessment toward the control of nanoparticle exposures. In addition, this quantitative evaluation has further confirmed the CB Nanotool's conservative outcome trend that remains useful for IH field practitioners given the ongoing uncertainty of ENP hazards and absence of OELs. Further research that affords expansion of its use, evaluation, and validation will assist in ensuring that risk assessments by ENP users are accurate, accessible and affordable, which would ultimately facilitate the protection of workers as the science of ENP grows.

Conclusions

Many ENP CB models and related journal publications have been produced during the eleven years since the initial development of the CB Nanotool. This quantitative validation effort presents a positive verification of the CB Nanotool and its effectiveness in a variety of settings for a broad range of ENP handling activities. This effort addressed the lack of guidance on a single exposure assessment methodology by combining real-time monitoring, filter analysis, and microscopic analysis to assess various quantitative metrics, including mass concentration, particle number concentration, and particle speciation. The results indicate that the control outcomes from the CB Nanotool qualitative assessment are appropriately conservative toward preventing worker exposure to ENP at levels beyond established exposure limits or background levels. These data represent an independent validation of CB Nanotool RL outcomes and give further credence to the use of the CB Nanotool to effectively control worker exposures in the absence of quantitative air monitoring results.

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