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Control Banding Tools for Engineered Nanoparticles: What the Practitioner Needs to Know

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Abstract

Control banding (CB) has been widely recommended for the selection of exposure controls for engineered nanomaterials (ENMs) in the absence of ENM-specific occupational exposure limits (OELs). Several ENM-specific CB strategies have been developed, but have not been systematically evaluated. In this paper, we identify the data inputs and compare the guidance provided by eight CB tools, evaluated on six ENMs, and assuming a constant handling/use scenario. The ENMs evaluated include nanoscale silica, titanium dioxide, silver, carbon nanotubes, graphene, and cellulose. Several of the tools recommended the highest level of exposure control for each of the ENMs in the evaluation, which was driven largely by the hazard banding. Dustiness was a factor in determining the exposure band in many tools, although most tools did not provide explicit guidance on how to classify the dustiness (high, medium, low) and there is a dearth of published data on this topic. The CB tools that recommended more diverse control options based on ENM hazard and dustiness data appear to be better equipped to utilize the available information, although further validation is needed by comparison to exposure measurements. Local exhaust ventilation was recommended at a minimum to control exposures to ENMs in the workplace. Generally, the same or more stringent control levels were recommended compared to the ENM proposed OELs, suggesting that these CB tools would generally provide prudent exposure control guidance, including when data are limited.

Keywords

control banding; engineered nanomaterials; hazard banding; occupational exposure banding; occupational exposure limits; dustiness

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INTRODUCTION

The introduction of ENMs into the workplace has created a challenge in assuring that their development, manufacture, production, and use can be performed safely. Given the limited information about the health risks associated with occupational exposure to these ENMs, individual companies, trade associations, and government agencies have instituted various risk management strategies to protect the health of workers (Schulte et al. 2013). In the absence of specific information, precautionary approaches to exposure control are recommended to ensure worker health protection (BSI 2007; NIOSH 2009a, 2012, 2013b; Schulte and Salamanca-Buentello 2007).

The traditional approach to protecting worker health is to measure worker exposures to potentially hazardous agents, compare them to occupational exposure limits (OELs), then determine if existing control measures provide adequate protection (NIOSH 2009b). Reliance on this approach has become increasingly difficult due to the growing number of potentially hazardous materials in the workplace that do not have OELs (Garrod and Rajan-Sithamparanadarajah 2003). Control banding (CB) strategies have been proposed to make engineering control decisions for general chemical substances without OELs (NIOSH 2009b). Many engineered nanomaterials (ENMs) and ENM-enabled compounds also lack specific OELs and may have little or no toxicity information, and thus CB strategies have been proposed for evaluating and controlling exposures to ENMs in the workplace. These strategies are evaluated in this paper. Although regulatory OELs for ENMs are not available to date, various groups have derived OELs for a number of ENMs based on nanotoxicology data and using various derivation methods (Mihalache et al. 2017). These OELs provide a basis for comparison of the hazard and control banding results based on the ENM CB tools for a set of ENMs.

Early efforts to address the control of exposures to potentially toxic or biologically active materials with little or no toxicity information available were simultaneously developed in the pharmaceutical (Sargent and Kirk 1988; Naumann et al. 1996a) and chemical (Brooke 1998; Henry and Schaper 1990) industries. Gardner and Oldershaw (1991) proposed the use of pragmatic exposure-control concentrations (PECC) for volatile organic compounds without OELs in response to classification, packaging, and labelling directives in Europe; the proposed PECC were set at the mean OELs for similar substances with both OELs and risk-phrases. CB strategies have also been used for many years to support hazard communications and labeling and to provide practical approaches to hazard evaluation and exposure control for use in small businesses, including the Control of Substances Hazardous to Health (COSHH) Essentials (HSE 2009); Global Harmonization System (GHS) (UNECE 2011); and Occupational Safety and Health Administration (OSHA) guidance (OSHA 2012).

Typically, CB strategies consist of two main components: (1) hazard bands, and (2) exposure (or emission potential) bands. These qualitative bands provide rankings of substances based on their hazardous properties and their production/use, which range from low to high levels of hazard and/or exposure potential. The combination of the hazard and exposure bands is used to derive the control band and associated engineering control options for a given occupational scenario.

Hazard bands are typically derived from toxicological data of adverse responses associated with acute or chronic exposures to hazardous substances in experimental animal studies, as well as data in humans when available. The five hazard categories, ranging from minimal to severe, are related to the health hazard rating system proposed by Henry and Schaper (1990). In addition to qualitative descriptors of the toxic effects, some hazard bands include quantitative exposure concentration ranges. Some of the earliest “target airborne concentration ranges” were proposed by Brooke (1998) and are included in the COSHH Essentials CB tool. A general term for these exposure concentration ranges is occupational exposure bands (OEBs), which are typically order-of-magnitude, 8-hour time-weighted average (TWA) concentrations (McKernan and Seaton 2014). OEBs are related to the severity of the hazard such that the more severe the hazard, the lower the OEB (Figure 1).

Exposure bands or emission potential bands are qualitative descriptors of potential exposure levels given the factors that influence exposure such as dustiness (propensity of the material to become airborne), type of process or task being performed, and amount of material being handled (ISO 2014). The CB recommendations on exposure control options often include the following four main areas: (1) good occupational hygiene practices, including general ventilation and intermittent use of personal protective equipment (PPE); (2) engineering controls, including local exhaust ventilation; (3) containment systems; and (4) the need to seek guidance from a specialist. Other CB schemes include five control bands and associated performance-based exposure control limits, as shown in Figure 1.

CB strategies has also been suggested as a pragmatic approach to manage the potential health risk resulting from exposure to nanomaterials (Maynard 2007; Schulte et al. 2008; Kuempel et al. 2012). Selection of appropriate control bands is uncertain in the absence of specific toxicology and exposure data for many nanomaterials . Several of the proposed ENM-specific CB tools attempt to address this concern by: (1) taking a precautionary approach in assigning higher hazard bands, and consequently assigning higher risk or control bands, when information is limited or lacking; (2) identifying high-concern substances based on particle properties (e.g., fibrous structure); and (3) identifying the most severe health endpoints (e.g., carcinogenicity) to drive the selection of the control band. Some ENM-specific CB tools (e.g., French Agency for Food, Environmental, and Occupational Safety (ANSES) and International Organization for Standardization (ISO)) recommend adding one or more bands when using bulk material information to assign a hazard band for the nanomaterial (ANSES 2010; ISO 2014).

Currently available CB tools that are specific to ENMs include the following eight tools: the CB Nanotool © (Paik, Zalk, and Swuste 2008; Zalk, Paik, and Swuste 2009); ANSES (ANSES 2010); Stoffenmanager® Nano (Duuren-Stuurman et al. 2011); Precautionary Matrix (Höck et al. 2013); ISO (ISO 2014), EC Guidance (European Commission 2014), NanoSafer (v. 1.1 beta) (Nanosafer 2016 and Jensen 2013) and the GoodNanoGuide (GoodNanoGuide 2016). These strategies have both similarities and differences in their features, including: their scope and applicability, parameters used in the hazard/severity banding and exposure/probability/emission potential banding, and in the classification of risk or control bands (Brouwer 2012; Sánchez Jiménez et al. 2016). Each strategy targets different users and applicability domains (e.g., laboratory versus small business). The amount and detail of information and professional knowledge required for implementing each strategy also varies. A recent article by Ligouri et al. (2016) provides a detailed review of six of these CB tools and updates the overview by Brouwer (Brouwer 2012). Draft guidance on developing OEBs for chemical hazards was issued by the National Institute for Occupational Safety and Health (NIOSH) which includes ENMs when sufficient toxicity data are available for either the ENM or its parent material (NIOSH 2017). The NIOSH (2017) process does not provide control banding recommendations, and it is not considered further here. All of the CB strategies currently available for ENMs are evaluated in this paper using a set of six ENMs and defined working conditions, and cross-tool comparisons of the inputs and outcomes are provided.

The objectives of this paper are to utilize the available CB tools for ENMs on a pilot set of ENMs to: (1) identify the types and sources of information required, as illustrated by assessing a diverse set of ENMs, (2) compare and evaluate the specific guidance provided by each tool, including its utility and limitations, and (3) identify important data gaps that hinder the effective use of these tools, and suggest areas of research to improve the evidence basis needed for hazard and control banding of ENMs.

METHODS

Description of Selected Engineered Nanomaterials

Six ENMs were evaluated in this paper, including nanoscale silicon dioxide (SiO_2), titanium dioxide (TiO_2), silver (Ag), single-walled carbon nanotubes (SWCNT), graphene, and cellulose. These materials were selected because they are commonly used nanomaterials worldwide (Future Markets Inc.© 2013) and because they represent a range of information available for nanomaterials in terms of hazard and dustiness (Table 1). SiO_2 nanoparticles are used in a wide variety of markets, including medical, transportation, building materials, electronics, energy, and food industries. TiO_2 nanoparticles have been used extensively in cosmetics, pigments, paints, and coatings (Piccinno et al. 2012). Silver nanoparticles have been used in various applications such as jewelry, photography, and antibacterial products, and are increasingly being used in medical and consumer products including electronics and textile coating due to their physicochemical properties at the nanoscale (Nowack, Krug, and Height 2011; Wijnhoven et al. 2009). Carbon nanotubes consist of nanoscale cylinders of carbon that can be produced with very large aspect ratios and are used in many industrial applications including electronics, polymer composites, and coatings, and in biomedical applications including enhanced electron-scanning microscopy imaging and biosensors (NIOSH 2013a). Graphene is made of pure carbon with atoms arranged in a regular hexagonal pattern and in a flat one-atom thick sheet; its commercial applications utilize its properties such as mechanical stiffness, strength and elasticity, and very high electrical and thermal conductivity (Novoselov et al. 2012). Nanocellulose is one of the newest commercially available ENMs which has high strength and thermal stability and is gaining attention within “green chemistry” as a renewable and biodegradable material (Isogai 2013).

Overview of Control Banding Tools Examined

The various CB tools have been reviewed in recent publications (Eastlake, Zumwalde, and Geraci 2016; Liguori et al. 2016; Sánchez Jiménez et al. 2016). Several of the tools (ANSES, ISO, EC Guidance) follow a decision tree approach where the user answers questions about the nanomaterial, such as material form (solid/liquid/powder form), process (e.g. high/low energy process), and quantity to derive an exposure potential and then uses material characteristics (such as solubility, shape, biopersistence, and availability of toxicological data) to derive hazard bands. The second primary type of CB tool follows a score-based approach which assesses overall hazard and exposure potentials using explicit numerical criteria.

The score-based approach gives a range of scores based on characteristics (similar to those in the decision tree approach) of the nanomaterial or parent material. CB Nanotool is the only tool to utilize a score-based approach for both hazard and exposure potential (Paik, Zalk, and Swuste 2008; Zalk, Paik, and Swuste 2009). Exposure potential and hazard severity are scored on a potential total of 100 points (higher values indicate higher hazard/ exposure potential). Any unknown properties or information should be assigned as "unknown" and scored as 75% of the maximum value for each category. This score-based approach in CB Nanotool results in a default recommendation of containment control when key information is missing.

Stoffenmanager Nano is a tiered approach in which the risk prioritization score allows for the implementation of controls followed by further evaluation of hazard and exposure potential. The exposure banding process in Stoffenmanager Nano is a score-based approach that utilizes a range of user inputs including type of task, room ventilation and whether engineering controls or protective equipment is used. In contrast, the hazard banding process in Stoffenmanager Nano opts for a decision tree approach, which relies on classification and labeling of products in accordance with the European classification of chemicals scheme (Duuren-Stuurman et al. 2011; Duuren-Stuurman et al. 2012).

NanoSafer focuses on nanomaterials in powder form. This tool uses physical data (particle size, density and surface area) and toxicological data from the safety data sheet (SDS) along with process data to determine a Hazard Band score (Jensen et al. 2013). NanoSafer places materials in one of four hazard bands: HB1 (0-0.25); HB2 (0.26-0.50); HB3 (0.51-0.75); HB4 (0.76-1.00). The exposure potential is calculated for both short (15 minute) and longer (8-hour) exposures and for workers near the process (near field) and further from the work area (far field). This scoring takes into account dustiness, handling energy, amount handled, work duration and process cycles, volume of the room and air exchange rate. The exposure potential is placed into 5 bands: EP1 (<0.11); EP2 (0.11-0.25); EP3 (0.26-0.50); EP4 (0.51-1.00), and EP5 (>1.00). The final risk level (RL1- RL5) is based on a combination of the hazard band and exposure potential scores.

The output for most of the CB tools discussed in this paper are a control band which recommends an appropriate exposure control approach in four or five levels (e.g. general ventilation, local exhaust ventilation, containment or seek specialist advice). The two exceptions are Stoffenmanager Nano and the Precautionary Matrix. Stoffenmanager Nano combines the hazard and control bands into a risk matrix which results in a three-level prioritization scheme (high, medium and low priority). This approach allows the user to implement appropriate controls and then assess exposure or utilize the tool to reevaluate the process and material based on risk. The Precautionary Matrix is unique in that it is designed to help businesses address the need for nanospecific action based on factors that consider both human and environmental risks. The final output of this tool provides a score indicating precautionary need with respect to employees handling materials and/or environmental issues. Any score above 20 indicates a need for caution.

Description of Control Banding Tool Inputs

The primary parameters for the hazard and exposure banding process for each tool are summarized in Tables 2 and 3, respectively, along with the main input values for each of the tools in this evaluation. For comparison of the various CB strategies, the handling/use scenario was kept constant (e.g., hours worked, quantity of material used). The assumptions in this scenario include: (1) ENMs were used in a small-scale production setting (i.e. research and development) that would include a small number of employees (1-5 workers); (2) employees performed tasks associated with handling a dry powder form of the ENM of interest approximately less than or equal to 4 hours per day and 5 days per week; and (3) the quantity used was approximately 50 grams (g) per day which is based on reported levels in several carbonaceous production and downstream plants showing typical use quantities between 5 and 100 g in a standard weighing task (Dahm et al. 2012).

It should be noted that the rates of production from TiO_2 and silver may be much higher—in the range of 1-5 kilogram (kg) per day based on published data (Lee et al. 2011). However, the upper range of material quantity for scoring of exposure potential of any of the CB tools evaluated herein is 1 kg, with most tools giving quantities of greater than 1 g the highest score in this category. The physical properties of the ENMs utilized in this evaluation were obtained from the manufacturer’s technical data sheets and/or Safety Data Sheets (SDSs). The dustiness of the materials was classified in this paper (based on judgment) as low, medium, or high according to the following respirable fraction: 0.1-1% low, 1-10% medium, >10% high. This information was used in the tools requiring dustiness category inputs (Tables 2 and 3). The data on the ENM dustiness were taken from the results of dustiness characterization reported in Evans et al. (2012), since no other large scale dustiness test dataset for fine and nanomaterials was available. These data were collected using a Venturi test procedure which may not be applicable to all models. Specifically, NanoSafer and ANSES recommend the use of methods from the EN 15051 standard for dustiness testing which employ less aggressive methods of dispersion (European Committee for Standardization (CEN) 2013). Thus the values used in this evaluation may overestimate the relative dustiness of the materials and result in higher exposure potential scores.

For the hazard banding of these six ENMs, data were collected from a variety of sources including, governmental sources, professional organizations, online databases, and published guidance/literature (Table 4). SDSs were consulted to obtain information specific to the properties of each ENM: the physical, health, and environmental health hazards; protective measures; and safety precautions for handling, storing, and transporting the material. If a

SDS specific to that ENM was available, then that information was obtained and used. OELs for the bulk (non-nanometer sized) material most similar to each ENM in this study were used in the banding. The lowest authoritative OELs were used, which were not necessarily regulatory OELs. Information from NIOSH and other authoritative guidance documents was used to address questions regarding toxicity and health hazards associated with each substance. As most ENMs do not have guidance documents with extensive literature and data reviews, these data may be obtained from online databases. For this study, we used a German substance database (GESTIS), United States National Library of Medicine Toxicology Data Network (TOXNET), and the European Chemicals Agency (ECHA) Classification and Labeling Inventory. In general, surface reactivity for a given mass-based exposure to each ENM was assumed to be high due to both the unknown potential for functionalization and the higher surface area of most ENMs versus the parent (or bulk) material. Solubility was determined based on information provided in the SDS or database literature search. If more than one type of solubility (soluble and insoluble) was listed, then the ENM was considered insoluble. If the parent material was indicated to be carcinogenic, a dermal hazard, or an asthmagen, then the ENM was also assumed to have similar health effects. Otherwise, when information was not available, all ENM data were indicated or interpreted as unknown.

Hazard data on the adverse effects from repeated exposure to these nanomaterials in animals were also evaluated given the relevance to potential worker exposures for up to a working lifetime. Rat is the rodent species used in the criteria for specific target organ toxicity – repeated exposure (STOT-RE) in many of the hazard banding schemes. Therefore, subchronic inhalation studies in rats were identified from literature searches in Pubmed, using the search terms “nanomaterial name” and “rat” and “inhalation.” The adverse effect levels from the identified rat studies are compared to the effect levels in the ANSES and GHS hazard banding schemes for STOT-RE. OELs that have been proposed for nanomaterials (Supplementary material, Table S-1) are used in comparisons with the control banding results in this evaluation. OELs are typically based on a more in-depth analysis of the data, although different data, methods, and assumptions may have been used in deriving those OELs.

The steps involved in selecting and using the evaluated CB tools are shown in Figure 2. This figure references the process and data sources which are used in conducting the analyses described in this article.

RESULTS

A summary of results of the recommended risk/control bands for each CB strategy and for all six ENMs evaluated are shown in Table 5. The results of both the exposure and hazard bands are presented, when applicable. This table shows that the output for each tool is unique. For example, the Precautionary Matrix is different than the other tools discussed in that the process does not result in the determination of a control band. Rather the Precautionary Matrix specifies whether precautionary, nano-specific safety measures are needed or not based on a calculated score. The ANSES and ISO tools are very similar in nature and include five control banding levels: 1-General Ventilation; 2- Local Exhaust

Ventilation (exterior hood, table hood); 3-Enclosed ventilation (fume hood, ventilated booth); 4-Full containment, or 5-Full containment and review by specialist. Nanosafer also has five risk levels which correspond to control recommendations including: RL1-LEV/Fume Hood, RL2-LEV/Fume Hood potentially with Respirator, RL3- LEV/Fume Hood with Respirator, RL4-Fume Hood/Enclosure/Glovebox with Respirator, RL5- Fume Hood/Enclosure/Glovebox with Supplied Air Respirator. CB Nanotool, GoodNanoGuide, and the EC Guidance have four control bands: 1-General Ventilation, 2- Local Exhaust Ventilation/Engineering Controls, 3-Containment, or 4-Seek specialist advice. In contrast, Stoffenmanager Nano assigns one of three risk priority bands (1-high priority, 2-medium priority, or 3-low priority).

Reviewing the results of the evaluation shown in Table 5 illustrates the differences between both the ENMs and the CB strategies evaluated by keeping the handling/use scenarios constant, as discussed in Methods. For the **CB Nanotool**, the risk levels (RL) ranged from RL4—Seek Specialist Advice for CNTs to RL3 for titanium dioxide, nanoscale silver, graphene, and nanocellulose to RL2 for silicon dioxide. For these ENMs, the lowest hazard (severity) score was for SiO_2 while the highest was for CNTs. The primary difference which resulted in the differing risk level bands was the severity (Hazard Band) score which placed all ENMs except for SiO_2 in the High severity category. **Stoffenmanager nano**, indicated that SiO_2, CNTs, graphene and nanocellulose are overall a high risk priority. TiO_2 and nanosilver were both considered a high risk priority when task-weighted, but considered to be a medium risk priority when the time and frequency of handling were taken into account indicating a lower overall risk. For the **Precautionary Matrix**, evaluation indicated that a risk is present for both workers and the environment based on a final calculated score of over 20 for all ENMs evaluated. For both the **ANSES** tool and **ISO guidance**, all EMNs fell into the same hazard and exposure bands resulting in similar control band—CB5—full containment and requiring expert advice. For the **EC Guidance**, nanosilver, CNTs, silica, and graphene fell into the highest risk level resulting in the recommendation to adopt process-based control measures. TiO_2 and nanocellulose were in the next lowest level which recommended the use of closed systems or containment of the process. For the **GoodNanoGuide**, SiO_2, graphene, nanocellulose and nanoscale silver were put into the highest hazard grouping due to lack of information on the health effects associated with these ENMs. TiO_2 and CNTs were placed into a lower hazard group because of the availability of hazard data (NIOSH 2011). Finally, for **NanoSafer**, CNTs and graphene fell into the highest risk level resulting in the recommendation for a fume hood/enclosure/glovebox with supplied air respirator. Nanocellulose, silica (amorphous), nanosilver, and TiO_2 were in the next lowest level which recommended the use of highly efficient local exhaust ventilation, fume hood or glovebox along with a respirator.

The evaluation of the repeated exposure data in rodents for those ENMs with these data showed that the lowest observed adverse effect levels (LOAELs) were all <20 mg/m^3, which is the level of concern for chronic adverse effects (STOT-RE). Based on these results, the hazard band would be either "Category D - Serious hazard" according to the ANSES and ISO, or "Category 1 - Health hazard - Danger" based on the GHS and US OSHA hazard banding strategies for nanoscale amorphous silica, TiO_2, silver, and multi-walled carbon nanotubes. These hazard bands are similar to or lower than the equivalent concentrations at the OELs (Supplementary material, Table S-1).

Discussion

Relatively limited evaluation and validation have been performed on the available CB tools for ENMs. This study adds to the current scientific literature by providing a systematic evaluation and application of all eight of the currently available CB tools for ENMs, using six different types of ENMs of varying dustiness level, for a fixed exposure and use scenario in the workplace. Outcomes are examined across the CB tools and compared with the proposed OELs for these ENMs. Data gaps in the key inputs to these CB tools are identified. Finally, the drivers for these outcomes are identified, and research needs are suggested to improve the information available and the utility of these CB tools for making workplace exposure control decisions.

Recent papers by Eastlake et al., Ligouri et al., and Sanchez Jiménez et al. are complementary with the current paper but also differ in both approach and scope (Eastlake, Zumwalde, and Geraci 2016; Liguori et al. 2016; Sánchez Jiménez et al. 2016). Eastlake et al. (2016) provide a systematic review of the ENM-specific CB tools and conclude that few of these tools have been validated with regard to their effectiveness in controlling exposure. Ligouri et al. provide an update of the earlier review by Brouwer (Brouwer 2012), including a more in-depth description of those tools. Ligouri et al. review six of the eight CB tools examined in this current paper (which also includes GoodNanoGuide and ISO/TS 12901-2). Ligouri et al. also describes the different inputs and possible outputs of the CB tools, but they did not conduct any actual evaluations on ENMs as performed in this current paper on a set of six EMNs. These evaluations show that differences in the particle properties can influence the outcomes of the different CB tools, depending on how a particular property is treated in the various hazard and exposure banding approaches. The Sanchez Jiménez et al. article provides a broad evaluation of four of these CB tools, including a sensitivity analyses of the tool inputs and limited exposure validation testing using airborne number concentration data on one ENM (cloisite) and three processes. The Sanchez Jiménez et al. article focused on assessment of the tools geared more to researchers, while the current article provides step-by-step information and examples that may be useful to the practitioner in selecting CB tools, gathering the input information, and assessing the usefulness of the results.

Evaluation of CB Tool Outcomes

The findings of this current evaluation show that the ANSES and ISO tools recommended the highest level of exposure control for the majority of ENMs in this use scenario (Table 6). CB Nanotool, EC Guidance, NanoSafer, and GoodNanoGuide recommended lower levels of control by ENM. The control banding resulted in either the same or higher levels of exposure control to those suggested by the proposed OELs for nanoscale TiO_2 and CNTs (Table 6). CNTs were generally in the most protective band “Seek Expert Advice” with a controls performance level of <1 $\mu g/m^3$. In contrast, the recommended control bands for silica and graphene differ widely between CB Nanotool and EC Guidance, i.e., either level 2 or level 4, respectively, in this evaluation. The proposed OELs for carbon nanotubes also vary over two or more orders of magnitude and control bands. However, these OELs for ENMs are all lower on a mass basis than their bulk counterparts (Supplementary material, Table S-1). The EC Guidance and NanoSafer recommended a similar or higher level of exposure control to that based on the OELs proposed for CNTs, TiO_2, and silver, while CB Nanotool recommendations were either higher (TiO_2 and CNTs) or lower (silver) in this scenario compared to the proposed OELs (Table 6). The ISO and ANSES tools required the most complete hazard data and yielded the highest level of exposure control. It is useful to the practitioner to understand how the input data can influence the control banding findings, which factors are most influential on these results, and how these findings compare to existing OELs.

The primary drivers for the control bands were the hazard scores in this small-scale production scenario. The hazards scoring approach used by the CB Nanotool resulted in the ranking of several of these ENMs to lower overall control bands than other decision tree tools (ISO, ANSES, Stoffenmanager Nano). The CB Nanotool approach combines scores for all hazards for the ENM and parent material into a total composite score, so positive research findings in any hazard category (carcinogenicity, mutagenicity, reproductive toxicity) do not automatically drive the ENM to the highest control band like the decision tree tools. For instance, for inhaled TiO_2, the International Agency for Research on Cancer (IARC) has classified this chemical agent as a 2B (Possibly carcinogenic to humans), which automatically places it in the highest hazard class for ISO, ANSES, NanoSafer, and Stoffenmanager Nano. However, when considered with all of the other hazard categories, TiO_2 was scored as high severity (band 3 of 4) in CB Nanotool resulting in the containment control band. It is difficult to determine whether a more precautionary approach (as provided by ANSES, ISO, NanoSafer and Stoffenmanager Nano) is a better choice given the lack of full hazard data on these ENMs. The best assessment that can be made at this point is to compare these tools to published risk assessments which derive OELs based on a more thorough hazard analysis. However, variability in the proposed OELs for these ENMs also results in uncertainty in the appropriate level of exposure control (as shown in Table 6 and Supplementary material Table S-1).

The primary driver for the different control bands by the EC Guidance tool was also the differences in hazard assessment. All of the ENMs evaluated were insoluble in water (based on the SDS or technical data sheets), but for CNTs and nanocellulose, these differences were due to the fibrous geometry/shape of these materials. And finally, the lower control bands for CNTs and TiO_2 by the GoodNanoGuide was driven by availability of information on these ENMs. The GoodNanoGuide tool categorizes hazard groups by “known to be inert” (Hazard group A), “understand reactivity/function” (Hazard Group B), or “unknown hazard” (Hazard group C). So an ENM such as TiO_2 would be a group B since information is available, including that it has been classified as possibly carcinogenic by IARC and NIOSH, while other ENMs would be at a higher level since there is little or no information available on their hazard. That feature of GoodNanoGuide is mainly driven by exposure potential (based on material form and task duration) and does not consider hazard potential in depth. The minimal assessment of hazard may limit the utility of the tool.

Despite some differences in approach, most tools gave similar exposure bands (typically medium-high exposure potential) primarily since the use scenario was consistent among these six ENMs evaluated. In general, exposure bands are driven by three primary factors: 1) material form; 2) amount of material used; and 3) process/task. In addition, all models except the Precautionary Matrix utilize dustiness as a factor in determining exposure potential. Stoffenmanager Nano and NanoSafer, however, use much more detailed exposure models utilizing parameters such as process energy, volume and ventilation rate of the work room, as well as frequency and duration of the evaluated task. With the CB Nanotool, the exposure probability score differed primarily on the dustiness determination of the ENM used and ranged from “Probable exposure” (CNT-high dustiness) to “Likely exposure” (TiO_2, SiO_2-medium dustiness; Graphene, Nanocellulose—unknown dustiness; and, silver-low dustiness). Although dustiness can be a differentiating factor in these tools, another important factor is the amount of ENM used (by mass), and in this area, the tools differ considerably. For ISO, the highest exposure factor related to amount handled is applied when using >1 kg of powdered nanomaterials. However, with CB Nanotool, EC Guidance, and Precautionary Matrix, the highest material quantity category is bounded at a much lower level, i.e., less than 1 g of the nanomaterial. An evaluation of a few of these CB tools on a different set of nanoscale and microscale particles also showed a range of hazard and exposure outputs across tools, and concluded that some of the recommendations may be excessive in some situations (Sánchez Jiménez et al. 2016).

In general, the more specific and complete the input information, the more accurate and useful the CB tool outcomes would be expected, although the structure and flexibility of the tools to utilize specific parameter data (e.g., dustiness) also differs across tools. Such evaluations provide useful insights into the performance of these tools for the practitioner to gain an understanding of the utility and limitations of these various tools.

Existing OELs for ENMs Examined in CB Tools

One way to evaluate the utility and validity of the outcomes of these CB tools is to compare their recommended controls and associated performance levels with the OELs that have been proposed for these same or similar ENMs (as discussed above). OELs proposed by nonregulatory governmental agencies or by nongovernmental organizations (Supplementary material, Table S-1) include nanoscale titanium dioxide, silica, silver, carbon nanotubes, and cellulose, which are all examined in this paper. No published OELs for graphene were found in the literature or reported in a recent systematic review of ENM OELs (Mihalache et al. 2017). The OELs for nanoscale particles are typically lower airborne mass concentrations than the closest applicable regulatory OELs (Supplementary material, Table S-1). For example, 5 milligrams per cubic meter (mg/m^3) is the Occupational Safety and Health Administration (OSHA) PEL (permissible exposure limit) for either graphite (synthetic), particles not otherwise regulated (PNOR), or cellulose (respirable fraction, 8-hr time-weighted average concentration) (OSHA 1983). This exposure concentration has been used in some nanotoxicology studies (e.g., for single-walled carbon nanotubes) (Shvedova et al. 2008). An OEL of 5 mg/m^3 (i.e., 5,000 micrograms per cubic meter (μg/m^3)) is approximately one to three orders-of-magnitude greater than the proposed OELs for carbonaceous, metal or metal oxide nanoparticles (Supplementary material, Table S-1).

Differences in both the toxicity of the substance and the data and methods used to derive the OELs could contribute to these differences.

Some of the existing OELs may have included information on nanoscale particle exposures (although possibly not defined as such). For example, high combustion processes such as silver refining can produce airborne nanoscale particles (Miller et al. 2010). NIOSH recommended separate mass-based OELs for titanium dioxide by particle size (nanoscale/ultrafine and microscale/file) (Supplementary material, Table S-1) (NIOSH 2011). The pulmonary toxicity of titanium dioxide and other poorly soluble particles is correlated with the total particle surface area, which is greater for an equal mass of smaller particles (NIOSH 2011).

Ease of Use of CB Tools for ENMs

During the course of this study, several observations emerged regarding the user-friendly nature of the various tools. In particular, the level of information required and the complexity in completing the assessments differs among these tools. For quick, high level assessments, the GoodNanoGuide, EC Guidance, and Precautionary Matrix provide results with minimal data. These tools were the easiest to complete given the minimal level of information required for the evaluation. EC Guidance tool categorizes nanomaterial hazard solely based on the physicochemical properties of biopersistence and particle/fiber shape, while GoodNanoGuide includes three simple bands for physicochemical properties; known to be inert, reactivity/function known, or unknown properties.

CB Nanotool utilizes an intermediate level of information on both hazard and exposure potential, which is at a level that would generally be available in a well-documented SDS. The hazard scoring approach of CB Nanotoool is relatively easy to use by answering yes, no, or unknown to the hazard questions and assigning a score. CB Nanotool quantitatively addresses a lack of information by including “unknown” as a choice, which defaults to a containment recommendation when no data are available. The transparent scoring approach in CB Nanotool allows the user to easily assess the drivers of the control band results to explore where changes to materials or use parameters (quantity, material form, etc.) could impact the control band.

ISO, ANSES, Stoffenmanager Nano and Nanosafer require more detailed information, and each of the sources shown in Table 4 were used to complete these assessments (to the extent that data were available). The ANSES and ISO tools are similar to each other and use the GHS system to provide a ready basis for standardization of inputs to Hazard Banding, which is useful but also may require more toxicology expertise (e.g., identifying LD_{50} and other endpoints) than does CB Nanotool, which includes yes/no options for the main endpoints. The ANSES and ISO tools address lack of information in the hazard banding by defaulting to the highest hazard band, which results in recommendations for higher levels of exposure control.

The Stoffenmanager Nano and Precautionary Matrix are different in scope compared to the other tools since they address risk prioritization and do not lead to a control band. The Stoffenmanager Nano and NanoSafe**r** tools utilized the most complex exposure banding approach requiring the most information from the user, including amount of material, process duration and frequency, work room volume and ventilation rate among other parameters. The Precautionary Matrix assesses hazard potential through two primary physicochemical parameters: redox/catalytic activity and stability (half-life) in the body/ environment. It provides a table of reactivity information for 12 nanomaterials. Stoffenmanager Nano provides guidance on hazard banding for 19 commonly used nanomaterials (Duuren-Stuurman et al. 2011; Duuren-Stuurman et al. 2012). However, for those nanomaterials not included in the table, the hazard band is derived from an assessment of hazards based on the parent material. If the hazard band of the parent material is not known (or the material is not characterized according to carcinogenicity, mutagenicity, reproductive, and/or developmental effects), the tool defaults to the highest hazard band.

Finally, several of the tools provide online or downloadable spreadsheets to help guide the user through the process. CB Nanotool provides a downloadable score-based spreadsheet with examples to help guide the user through the process. Stoffenmanager Nano, NanoSafer, and Precautionary Matrix have online tools to help facilitate the process. The various parameters and inputs to these tools, including those used in these assessments, are summarized in Tables 2 and 3. These input parameters are valuable information that are needed to use these CB tools to arrive at the recommended control bands. The parameters that were found to be drivers of the control band findings (e.g., availability of dustiness or specific health effects data), as discussed in this paper, could be considered essential to obtaining more useful and reliable results from these CB tools.

Evidence Available for Evaluating CB Tools for ENMs

Only a few types of ENMs have undergone relatively extensive toxicological evaluation, e.g., TiO_2 and CNTs. Even for these ENMs, significant data gaps remain, especially for chronic adverse health effects. The limited hazard and dustiness data make it challenging to provide relevant information for the SDS. In addition, SDSs are not uniform and provide variable inconsistent amounts of information (Eastlake et al. 2012). A useful addition to SDSs would be a standardized format for CB tool input factors, which would provide the practitioner with more readily available information for applying CB methods to specific ENMs. In particular, the inclusion of standard information needed in control banding tools would be useful information in SDSs. Current toxicity data, where available, would be especially useful in the SDSs, including the adverse effect levels in rodent studies to evaluated severity and potency. In the future, the development of default hazard bands or OEBs for ENMs based physicochemical properties and limited toxicology data would help facilitate the determination of appropriate control bands (Kuempel et al. 2012).

In general, regardless of the CB strategy used, the uncertainty of the potential health risks of ENMs tends to result in a higher level of exposure control than would be used based on the ENM-specific OELs. These higher levels of exposure control appear to be due to the limited data on ENMs for many of the inputs in the CB tools, resulting in the default to the more protective categories in the absence of specific information. Indeed, a utility of these CB tools is that they generally recommend a high level of exposure control in the absence of specific information, which is a protective default. This approach is consistent with using greater precaution in the absence of data (Schulte and Salamanca-Buentello 2007). Such strategies also encourage research to provide the more specific data needed to replace default assumptions. On the other hand, CB tools that do not discern among the hazards based on available data may not be sufficient for decision-making. This analysis has shown that certain factors that drive the control banding decisions (e.g., default toxicity assumptions; dustiness levels) would be useful priorities for future research in order to improve the evidence basis for the application of these control banding tools for ENMs. Dustiness data would be also useful in future validation studies as well as research studies correlating exposure with dustiness levels of ENMs by job task.

Possible limitations in this analysis include the limited number of ENMs evaluated (six). OELs have been proposed for five of these ENMs (Supplementary material, Table S-1). Using the proposed OELs for comparison to the hazard bands/OEBs is an uncertain criterion since the proposed OELs can vary widely and none are regulatory limits. Since the workplace use scenario was kept constant in this analysis, the findings may not apply to other use scenarios. Finally, the performance-based exposure concentrations (Table 6) have not been fully validated for the specific engineering control options, and comparison of the recommendations can be challenging due to the overlapping control bands across the CB tools. It should be noted that all of the CB tools evaluated recommended at a minimum the use of local exhaust ventilation for each of these ENMs (Table 6) in this exposure scenario (dry powder handling of small quantities for 4 hours or fewer per day). For those ENMs with proposed OELs (Table 6), the associated performance-based exposure concentrations would also necessitate the use of local exhaust ventilation or a higher level of control.

The most comprehensive validation studies performed to date have been on the CB Nanotool (Paik, Zalk, and Swuste 2008; Zalk, Paik, and Swuste 2009), as discussed in an earlier systematic review (Eastlake, Zumwalde, and Geraci 2016). In a study of 32 job activities and nanomaterial combinations, the exposure control recommendations from CB Nanotool were reported to be at the same or higher level to those recommended independently by an experienced industrial hygienist for 28 (~88%) of the job activities. Roughly similar results were seen in this study, in which the control band recommendations from CB Nanotool were the same or lower than three of the four (75%) of the ENM OELs (Table 6). By comparison, the control banding recommendations of EC Guidance, Nanosafer, and GoodNanoGuide were all the same or lower than the ENM OELs, while the ANSES and ISO tools recommended the lowest exposure level for each of the ENMs (Table 6). Sánchez Jiménez et al. (2016) provided some limited validation testing of the hazard and exposure results for three of these CB tools. They reported various differences in both the hazard and exposure results of the CB tools compared to reported toxicity and exposure measurement data. For example, the measured airborne number concentrations for closite (the only ENM in that evaluation) were lower for a weighing task, but higher for an extrusion task, compared to the results from the three CB tools (Sánchez Jiménez et al. 2016). A limitation in the validation studies to date is either the lack of data or the limited data on airborne exposure concentrations of ENMs associated with job activities and exposure controls; these data are needed to verify that the recommended controls achieved the expected results. Verification of CB tool recommendations with field-based measurements across jobs/tasks and working conditions has been previously recommended for general chemicals in industry (Jones and

Nicas 2006a, 2006b). In addition, the lack of OELs for many ENMs does not permit verification that the recommended exposure control levels would be protective of workers' health. An evaluation of CB tool recommendations with ENM-specific OELs, as illustrated in this paper (Table 6), could be extended to additional ENMs as more toxicology data and OELs become available.

Key Findings

This study demonstrated the use of the eight CB tools for ENMs currently available, showed what input data are needed, suggested several useful sources and websites to search for the information needed, and demonstrated the application and outcomes in a case study of six different ENMs, most of which have proposed OELs. A fixed workplace exposure scenario allowed focus on the role of the properties of the ENMs themselves, both biological and physicochemical. The key biological input parameters include qualitative hazard information and quantitative effect levels of the ENMs or bulk material (OELs or NOAELs). The key physicochemical input parameters include dustiness, surface activity, shape (fibrous or not), and solubility. Understanding the information needed to utilize these tools and comparing the findings across these tools for a set of ENMs and fixed workplace exposure conditions helps the practitioner to better understand how to select and use these tools. The purpose of this paper is not to recommend the use of any specific tool, but to illustrate and compare the inputs and findings of each tool under the same ENM and exposure scenarios. The findings of this study provide further input into the key drivers for the findings of each of these tools. Ultimately the selection of a tool depends on the purpose of the evaluation (e.g., risk prioritization or exposure control selection) as well as the availability of the input information.

In using these tools, the practitioner will find different levels of information needed and complexity in completing the assessments. For quick, high level assessments, the GoodNanoGuide and EC Guidance provide results with minimal data. Precautionary Guidance is the most basic indicating the need for caution. CB Nanotool utilizes a moderate level of hazard and exposure potential information, while being implemented through an easy to understand tool. ISO, ANSES, Stoffenmanager Nano and Nanosafer use the most information and require more effort in collecting data and completing the assessments. Regardless of which tool is selected, the user should record the sources of information and the input parameters selected in the application of any of these tools. This practice is consistent with good recordkeeping of the information used to arrive at control banding findings, and also facilitates further evaluation when new information becomes available. Figure 2 ppresents an overall approach for using and evaluating the tools while Tables 2 and 3 provide a template of the key information needed for each of these tools. Likewise, Table 4 provides a guide to online databases where input information on hazard inputs can be gathered.

The findings of this study provided limited validation testing of CB tool results compared to OELs proposed for four of the ENMs evaluated in this study. These findings confirm those of other studies (Eastlake, Zumwalde, and Geraci 2016; Sánchez Jiménez et al. 2016) that more information is needed to validate these CB tools in order to determine if the use of control banding can adequately reduce nanomaterial worker exposures to safe levels. Moreover, the inclusion of the basic information needed in control banding reported in a standard format on the SDSs would be especially useful in the application of these tools. Research to provide basic toxicity data is required to fill those data gaps.

The following data gaps were identified in this study, which if filled would reduce uncertainty and improve confidence in the reliability of CB tool findings:

- The amount of information required differs across tools; yet most of the tools recommended higher levels of exposure control for each of the ENMs in this evaluation compared to the proposed OELS, primarily due to the limited hazard data.
  - The default for ISO, ANSES, and Stoffenmanager Nano to the highest risk level based on the highest individual hazard category (carcinogenicity, reproductive toxicity, mutagenicity) and for unknown hazards resulted in the highest priority or highest level of exposure control for each of the ENMs in this assessment.
  - The composite hazard scoring approach by CB Nanotool resulted in lower levels of exposure control for some of the ENMs in this assessment. EC Guidance, Nanosafer, and GoodNanoGuide also recommended some diversity in the control banding recommendations across ENMs.
- All tools recommended the use of local exhaust ventilation, at a minimum, for working with any of these ENMs.

Research Needs

The lack of available data for the main inputs into these tools significantly reduces their utility, at this time. Key information that drives the hazard, exposure, and control banding recommendations would be the most useful to reducing uncertainty and increasing confidence in the application of these tools, including:

- Quantities of ENMs currently produced and used in various applications by job/task needs to be updated and made available to researchers and the practitioner for use in emission potential scoring in control banding.
- Correlation of ENM quantity, dustiness, and process with exposure should be assessed and validated with laboratory and workplace data. Airborne exposure measurement data for specific job activities and ENMs could be used in validation testing of the control banding recommendations.
- More specific information is needed to help classify ENMs according to the hazard and exposure parameters. For instance, relatively minimal information on the surface reactivity and dustiness of ENMs would be useful to classify these as low, medium or high, as requested in several of these tools (some do not include dustiness while Stoffenmanager Nano and NanoSafer have quantitative dustiness categories).

- Further evaluation and refinement of the hazard categories for ENMs are needed to reduce uncertainty given the limited toxicity data for ENMs. Several research efforts are underway in the U.S. and other countries to group ENMs by hazard potential, and could ultimately provide default hazard bands or OEBs using physicochemical properties and limited toxicology data.

In the meantime, the practitioner needs to be aware that while these CB tools can be useful in decision-making about exposure control options when working with ENMs, it is also important when selection a tool to consider the tool purpose, the information needed, and level of validation. Ideally, more than one tool should be selected for comparison of findings and to better inform decision-making. In addition, comparison of the control banding results with any ENM-specific OELs would also be useful. Updating the initial evaluations as new data or tools become available will provide continued improvement in the control banding of ENMs.

Conclusions

The several CB tools that have been developed for nanomaterials represent a good first step in developing approaches to control worker exposure given the paucity of data on many ENMs in use. Findings of this study showed that the ISO, ANSES, and Stoffenmanager-Nano tools recommended the highest level of risk or exposure control for each of the ENMs in this assessment, while CB Nanotool, EC Guidance, Nanosafer, and GoodNanoGuide recommended more diverse control banding recommendations across ENMs. Further validation of these tools is needed, including by comparing the performance-based exposure ranges of control approaches to the measurements of airborne exposure concentration of ENMs in a worker's breathing zone during typical job tasks.

Research towards characterizing dustiness of more ENMs will help improve the utility of these tools. Efforts should continue to synthesize data from workplace studies to gain a better understanding of how well factors such as dustiness represent worker exposures. In addition, as more health hazard data become available, for ENMs individually or within similar physicochemical groups, the ability to provide more constructive exposure control guidance on the range of ENMs seen in the workplace will improve.

The findings from this study show that significant data gaps remain, resulting in uncertainty about the optimal selection of controls to protect workers producing and handling ENMs. 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. In most of the evaluated CB tools, uncertainty in the available data is managed by the selection of higher risk levels and more protective exposure control options. An important finding of this evaluation is that local exhaust ventilation was recommended at a minimum to control exposures to ENMs in the workplace. More stringent controls, such as process containment, may come at a higher installation or maintenance cost, and it may not be certain whether these are necessary given the unknown risks. However, these CB tools generally appear to be providing prudent exposure control guidance in the face of uncertainty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer:

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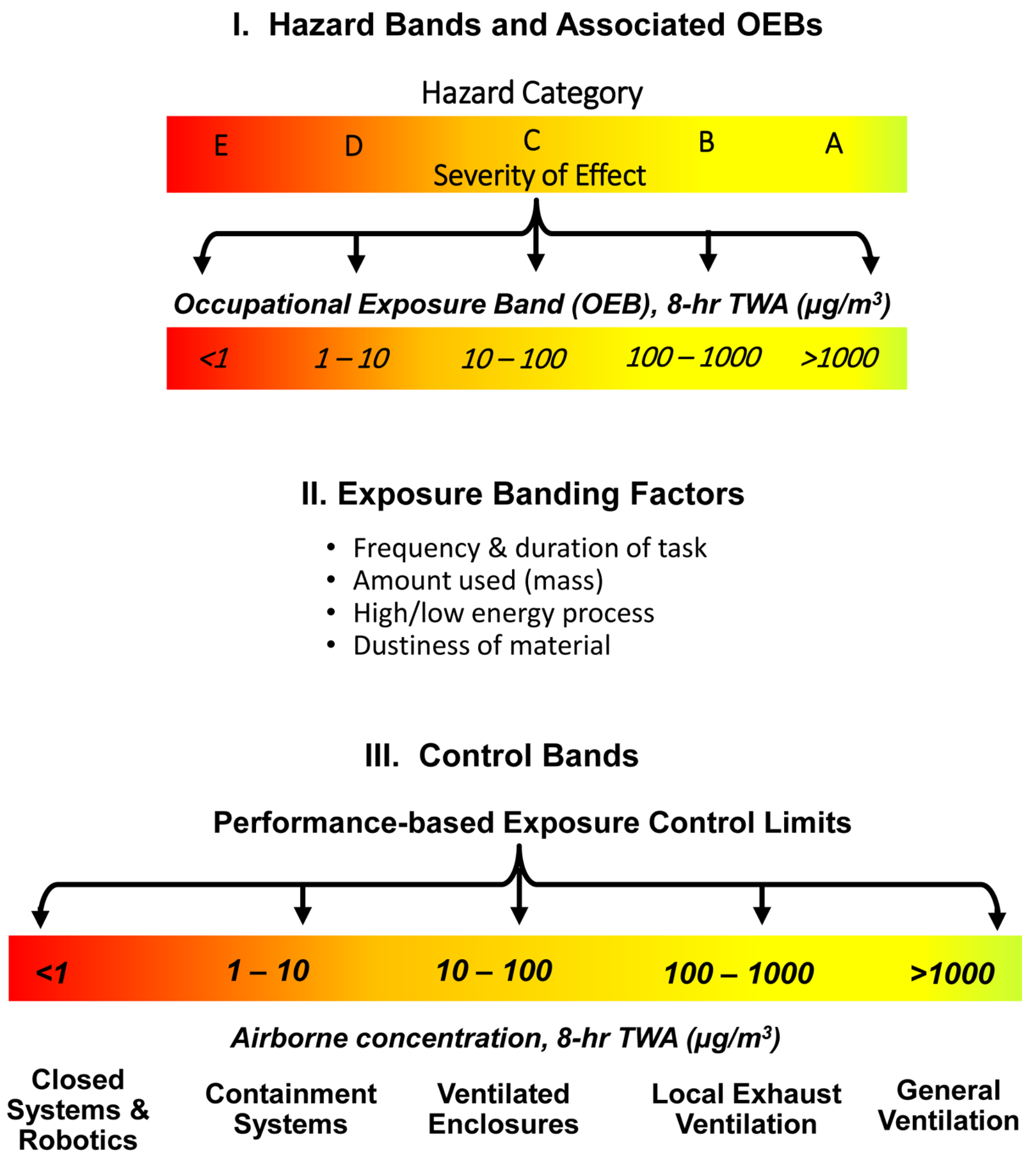

Figure 1. Control Banding for Nanomaterials.

Adapted from: (Ader, Farris, and Ku 2005; ANSES 2010; Brooke 1998; HSE 2009; ISO 2014; Kuempel et al. 2012; Naumann et al. 1996b; OSHA 2012; UNECE 2011; Zalk and Nelson 2008)

TWA: Time-weighted average.

Figure 2. Steps for selecting and using the CB tools.

Table 1.

Characteristics of engineered nanomaterials (EMNs) evaluated in this paper in the various control banding tools.

Chemical composition and form of ENM	Name or description	Manufacturer (Safety Data Sheet revision date)	CAS number	Description	Primary particle dimensions (nm)	Specific surface area (m^2/g) [a]	Dustiness (%) respirable fraction [b]
Silicon dioxide (SiO_2), amorphous	Aerosil 380 F	Evonik, Essen Germany (10/15/2013)	112945-52-5 [SiO_2]	Fumed, nanoscale powder	nr[c]	380	5.5
Titanium dioxide (TiO_2)	Aeroxide P25	Evonik, Essen Germany (02/09/2014)	13463-67-7 [TiO_2]	Fumed, nanoscale powder	20 (diameter)[a]	50	7.2
Silver nanoparticles	nr	Quantum Sphere, Inc., Santa Ana, CA (05/24/2007)	7440-22-4 [Ag]	Nanoscale powder	20-40 (diameter)	nr	0.4
Carbon nanotubes (CNT)	Single-walled CNT	Unidym Inc., Sunnyvale, CA (02/08/2011)	nr	Nanoscale powder	0.8-1.2 (diameter); 100-1,000 (length)	508	31.8
Graphene	nr	Angstron Materials, Inc, Dayton, OH (05/08/2013)	1034343-98-0 [Graphene]	Nanoscale powder with <3 graphene layers	<10 (diameter); 1 (thickness); length nr	nr	nr[d]
Nanocellulose	Nanofibrillated fiber	Engineered Fiber Technologies, Shelton, CT (06/21/2007)	68442-85-3	Cellulose nanofibrils	100- 500 (diameter)	nr	nr[d]

nr: not reported

[a] As reported in Evans et al. (2012).

[b] Dustiness measured at 50% relative humidity (Evans et al. 2012).

[c] Not reported in Safety Data Sheet.

[d] Lack of published test data.

Table 2.

Hazard Banding Inputs for each material and tool evaluated.

Control Banding Tool	Hazard Input Parameters		SiO_2	TiO_2	CNT	Nanosilver	Graphene	Nanocellulose
CB Nanotool	Parent Material	Lowest Occupation Exposure Limit	6 mg/m^3	2.4 mg/m^3	3.5 mg/m^3	0.01 mg/m^3	2.5 mg/m^3	5 mg/m^3
		Carcinogen?	Yes	Yes	No	No	Yes[e]	Unknown[c]
		Dermal hazard?	Unknown[c]	No	No	No	Unknown[c]	Unknown[c]
		Asthmagen?	Unknown[c]	Unknown[c]	Yes	No	Yes[5]	Unknown[c]
	Nanoscale material	Surface reactivity	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]
		Particle shape	Unknown[c]	Unknown[c]	Tubular or fibrous	Unknown[c]	Anisotropic	Tubular or fibrous
		Particle diameter	Unknown[c]	Unknown[c]	1-10 nm	11-40 nm	1-10 nm	41-100 nm
		Solubility	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble	Insoluble
		Carcinogen?	No	Yes	Unknown[c]	Unknown[c]	No	No
		Reproductive hazard?	No	Yes	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]
		Mutagen?	No	Unknown	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]
		Dermal hazard?	No	No	Unknown[c]	Unknown[c]	Unknown[c]	Unknown[c]
		Asthmagen?	Unknown[c]	Unknown[c]	Unknown[c]	Unknown	Unknown[c]	Unknown[c]
Good Nano Guide		Hazard Group	C	B	B	C	C	C
		Potential for material release	free/unbound	free/unbound	free/unbound	free/unbound	free/unbound	free/unbound
ANSES	Preliminary Question	Does the product contain nanomaterials?	Yes	Yes	Yes	Yes	Yes	Yes
		Is the nano-substance already classified by a relevant authority?	No	No	No	No	No	No
		Is it a biopersistent fiber?	No, not a fiber	No, not a fiber	No, not a fiber	No, not a fiber	No, not a fiber	Yes, it is an insoluble fiber

Control Banding Tool	Hazard Input Parameters		SiO_2	TiO_2	CNT	Nanosilver	Graphene	Nanocellulose
		Is there a prelimary hazard band for the bulk material or most toxic analogous?	Yes[a]	Yes[a]	-	Yes[a]	Yes[a]	-
	Bulk material	Bulk Material: Substance dissolution time >1 hour	Yes, insoluble in water[b]	Yes, insoluble in water[b]	-	Yes, insoluble in water[b]	Yes[b,e]	-
		Bulk Material: Evidence of higher reativity than bulk/ analogous material?	Yes[e]	Yes[e]	-	Yes[e]	Yes[e]	-
ISO		OEL dust (8-hr TWA)	A	B	A	C	A	A
		Acute Toxicity	B[d]	B[d,e]	B[d]	B[d]	-	B[d]
		LD50 oral route mg/kg	-	A	-	-	-	A[b]
		LD50 dermal route mg/kg	-	A[e]	-	-	-	A[b]
		LC50 Inhalation 4H (mg/l) Aerosols/particles						A[b]
		Severity of acute (life-threatening) effects	C[d]	B[d]	B[d]	C[d]	B[d]	B[d]
		Sensitization	-	A[5]	-	C[d]	-	-
		Mutagenicity/genotoxicity	-	A[5]	-	-	-	-
		Irritant/corrosiveness	E[d]	A	A[d]	A[d]	A[d]	E[d]
		Carcinogenicity	E[d,e]	E[b,d,e]	C[d]	-	-	-
		Developmental/ repordactive toxicity	-	-	D[d]	-	-	-
EC Guidance	Concern Category	nanomaterial	Medium-high concern	Medium-low concern	High concern	Medium-high concern	Medium-high concern	Medium-low concern
	Dustiness Band	Dustiness	High	High	High	High	High[k]	High[k]
Precautionary Matrix		Size of primary particles (free, bound, aggregated or agglomerates)	1-500 nm	1-500 nm	1-500 nm	1-500 nm	1-500 nm	1-500 nm
	Nanorelevance	Do the nanoparticles/rods form agglomerates >500 nm?	No[f]	No[f]	No[f]	No[f]	No[f]	No[f]
	Potential Effect	Redox Activity or catalitic activity of nanparticles/	Not known[c]	Not known[c]	Not known[c]	Not known[c]	Not known[c]	Not known[c]

Control Banding Tool	Hazard Input Parameters		SiO_2	TiO_2	CNT	Nanosilver	Graphene	Nanocellulose
		rods present in the nanomaterial						
		Stability (half life) of the NPRs present in the nanomaterial in the body	Not known[c]	Not known[c]	Not known[c]	Not known[c]	Not known[c]	Not known[c]
Stoffenmanager Nano		Product appearance	Powder	Powder	Powder	Powder	Powder	Powder
		Dustiness	High (>150-500) mg/kg[L]	High (>150-500) mg/kg[L]	Very high (>500) mg/kg[L]	Medium (50-150) mg/kg[L]	Unknown	Unknown
		Moisture	Dry product (<5% moisture content)	Dry product (<5% moisture content)	Dry product (<5% moisture content)	Dry product (<5% moisture content)	Dry product (<5% moisture content)	Dry product (<5% moisture content)
		Concentration of the nanocomponent in the product	100%	100%	50-99%	99.90%	50-99%	50-99%
		Does the product contain fibers/fiber-like particles?	No	No	Yes	No	No	Yes
		Length: diameter of the fiber (aspect ratio)	No	No	Yes	No	No	No
		Hazardous properties	Unknown	Carcinogenic (not mutagenic),	Toxic, corrosive and/or respiratory allergens	Unknown[c]	Unknown[c]	Unknown[c]
Nanosafer		CAS Number	112945-52-5	13463-67-7	-	7440-22-4	1034343-98-0	68442-85-3
		Is the material coated? (Y/N)	No	No	No	No	No	No
		Morphology	Unknown	No	Tube	No	Flake/Plate/ Tabular/Clay	Fibre
		Solubility in Water	Insoluble (<1g/L)	Insoluble (<1g/L)	Insoluble (<1g/L)	Insoluble (<1g/L)	Insoluble (<1g/L)	Insoluble (<1g/L)
		Shortest dimension (nm)	-	-	0.8 nm	20 nm	1 nm	50 nm
		Middle dimension (nm)	-	-	-	-	-	-
		Longest dimension (nm)	-	-	1000 nm	40 nm	1000 nm	500 nm
		Average size (nm)	-	-	-	-	-	-
		Density (g/cm^3)	2.2 g/cm^3	4.1 g/cm^3	1.6 g/cm^3	0.25 g/cm^3	2.2 g/cm^3	1.5 g/cm^3
		Surface area (powder material) (m^2/g)	380 m^2/g[g]	15 - 50 m^2/g[g,j]	144m^2/g or 508m^2/g[g,j]	5 - 25 m^2/g[j]	800 m^2/g[h,j]	284 m^2/g[i,j]

Control Banding Tool	Hazard Input Parameters		SiO_2	TiO_2	CNT	Nanosilver	Graphene	Nanocellulose
		Respirable dustiness index	187.5 mg/kg	187.5 mg/kg	937.5 mg/kg	7.5 mg/kg	937.5 mg/kg	937.5 mg/kg

Dash (−) indicates that no information was found for this specific parameter.

[a]Created using Table 1 of ANSES

[b]GESTIS

[c]Interpreted as unknown as no proper option available

[d]ECHA C&L

[e]Toxnet

[f]Not known if de-agglomeration of agglomerates (or aggregates) to primary nanoparticles/rods or agglomerates <500 nm occurs in the body

[g]Reported in Evans et al. (2012)

[h]Technical data sheet/safety data sheet for material

[i]Sehaui, Zhou, Berglund (2011)

[j]Multiple numbers provided and larger number used

[k]Method provides no option for "unknown" therefore "high"

[L]Stoffenmanager Nano dustiness levels are medium, high and very high and unknown.

Table 3.

Exposure Band parameters for each tool and levels of each category.

Control Banding Tool	Information/ Scenario	Materials					
		SiO_2	TiO_2	CNT	Nanosilver	Graphene	Nanocellulose
All tools	Substance emission potential/physical form	Dry Powder					
	Activity emission potential/amount handled per day	50 grams					
	Task duration	1-4 hours per day					
	Task frequency	5 days per week					
	Volume of the working room	108 m^3 per nanosafer					
CB Nanotool	Dustiness	5.5%[a] Medium	7.2%[a] Medium	31.8%[a] High	0.4%[a] Low	Unknown	Unknown
	Number of employees with similar exposure	≤ 5 employees					
Good Nano Guide	Exposure Duration	Medium					
ANSES	Emission Potential (High/Moderate +1 Band)	EP3 - powder	EP3 - powder	EP3 - powder	EP3 - powder	EP3 - powder	EP3 - powder
	Manufacturing/ Handling process	Handling Powder					
ISO	Exposure band for Dust Generation/ Dustiness	EB2	EB2	EB2	EB2	EB2	EB2
	Manufacturing/ Handling process	Material in powder form - Manufacturing use and handling - Amount used >0.1g - Low potential of dust					
EC Guidance	Level of Exposure	High					
Stoffenmanager Nano	Task characterization	Handling of products in small amounts (up to 100 gram) or in situations where only low quantities of products are likely to be released					
	Is the task carried out at the breathing zone of the employee (distance person product <1m)?	Yes					
	Is there more than one employee carrying out the same task simultaneously?	Yes					
	Is the working room being cleaned daily?	Yes					
	Are inspections and maintenance of machines/ancillary equipment being done at least monthly to ensure good condition and	Yes					

Control Banding Tool	Information/ Scenario	Materials					
		SiO_2	TiO_2	CNT	Nanosilver	Graphene	Nanocellulose
	proper functioning and performance?						
	Ventilation of the working room	Mechanical and/or natural					
	Local control measures at the source	No control measures					
	Is the employee situation in a cabin?	No					
	Is personal protective equipment applied?	No					
Nanosafer	Energy level	H3 (0.50): Moderate energy (e.g. Pour 5-30 cm drop height, blending of powder in liquid medium)					
	Air exchanges	8 per hour					
	Mass handled per cycle	0.025 kg					
	Length x Width x Height of workroom (meters)	6x6x3					
	Cycle Duration	60 minutes					
	Time to perform work cycle	15 minutes					
	Amount of product used per work cycle	0.1 kg					
	How many times is the cycle repeated daily?	4					
	Activity level of room	Low quiet					

[a]Reported in Evans et al. (2012); categories assigned here are based on judgement: 0.1-1% low, 1-10% medium, >10% high.

Table 4.

Sources of information for control banding tools and model inputs.

Source Information	Source	Content Description	Website Address
OEL Guidance	US Occupational Safety and Health Administration (OSHA)	Permissable Exposure Limits	https://www.osha.gov/
	US National Institute for Occupational Safety and Health (NIOSH)	Recommended Exposure Limits	http://www.cdc.gov/niosh/
	American Conference of Governmental Industrial Hygienists (ACGIH)	Threshold Limit Values	http://www.acgih.org/
Online Databases	Institue for Occupational Safety and Health of the German Social Accident Insurance	Substance Database (GESTIS)	http://gestisen.itrust.de/nxt/gateway.dll/gestis_en/000000.xml?f=templates$fn=default.htm$3.0
	US National Library of Medicine	Toxicology Data Network (TOXNET)	http://toxnet.nlm.nih.gov/
	European Chemicals Agency (ECHA)	Classification & Labeling Inventory	http://echa.europa.eu/information-on-chemicals
Control banding Methods	Lawrence Livermore National Laboratory	Control Banding Nanotool	http://controlbanding.net/
	US National Institute for Occupational Safety and Health (NIOSH) Oregon Nanoscience and Microtechnologies Institute (OMAMI) Oregon State University (OSU)	GoodNanoGuide	https://nanohub.org/groups/gng

Source Information	Source	Content Description	Website Address
	French Agency for Food, Environmental and Occupational Health & Safety (ANSES)	Development of a specific Control Banding Tool for Nanomaterials	https://www.anses.fr/sites/default/files/documents/AP2008sa0407RaEN.pdf
	International Organization for Standardization (ISO)	Nanotechnologies -- Occupational risk management applied to engineered nanomaterials -- Part 2: Use of the control banding approach TS 12901-2:2014	http://www.iso.org/iso/catalogue_detail.htm?csnumber=53375
	National Research Centre for the Working Environment, Copenhagen, Denmark	NanoSafer	http://www.nanosafer.org/
	Schweizerische Eidgenossenschaft - Federal office of Public Health	Precautionary Matrix	http://www.bag.admin.ch/nanotechnologie/12171/12174/12175/index.html?webgrab_path=aHR0cDovL3d3dy5iYWctYW53LmFkbWluLmNoL25hbm9yYXN0ZXIvcG9ydGFsX2VuLnBocD9tb2Q9YSZsYW5nPWVu&lang=en
	Dutch Ministry of Social Affairs and Employment (SAE), TNO, Arbo Unie, BECO(EY)	Stoffenmanager nano	https://nano.stoffenmanager.nl/
	European Agency for Safety and Health at Work (EU-OSHA)	Guidance on the protection of the health and safety of workers from the potential risks related to nanomaterials at work	https://osha.europa.eu/en/news/eu-safe-use-of-nanomaterials-commission-publishes-guidance-for-employers-and-workers
Guidance/ Literature	US National Institute for Occupational Safety and Health (NIOSH)	Occupational Exposure to Carbon Nanotubes and Nanofibers	http://www.cdc.gov/niosh/docs/2013-145/pdfs/2013-145.pdf
	US National Institute for Occupational	Occupational Exposure to Titanium Dioxide	http://www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf

Source Information	Source	Content Description	Website Address
	Safety and Health (NIOSH)		
	Varies depending on material	Material Safety Data Sheets	Specific to the material used

Table 5.

Summary of Control Banding Tool Results.

		Nanomaterial					
		SiO_2	TiO_2	CNT	Nanosilver	Graphene	Nanocellulose
CB Nanotool	Severity Score	45.5	59	60	56	60	53
	Exposure Probability Score	65	65	80	57.5	72.5	72.5
	Control Band	Risk Level 2 - **Fume hoods or Local Exhaust Ventilation**	Risk Level 3 - **Containment**	Risk Level 4 - **Seek Specialist Advice**	Risk Level 3 - **Containment**	Risk Level 3 - **Containment**	Risk Level 3 - **Containment**
GoodNanoGuide		Hazard Group C - Limited Data CB - 3 **Seek Specialist Advice**	Hazard Group B - NIOSH CIB TiO2 CB - 3 **Containment**	Hazard Group B - NIOSH CIB CNT/F CB - 3 **Containment**	Hazard Group C - Limited Data CB - 4 **Seek Specialist Advice**	Hazard Group C - Limited Data CB - 4 **Seek Specialist Advice**	Hazard Group C - Limited Data CB - 4 **Seek Specialist Advice**
ANSES		Hazard Band 5 + Emission Potential 4 = Control Level 5: **Full containment and review by a specialist required: seek expert advice**	Hazard Band 5 + Emission Potential 4 = Control Level 5: **Full containment and review by a specialist required: seek expert advice**	Hazard Band 5 + Emission Potential 4 = Control Level 5: **Full containment and review by a specialist required: seek expert**	Hazard Band 5 + Emission Potential 3 = Control Level 5: **Full containment and review by a specialist required: seek expert advice**	Hazard Band 5 + Emission Potential 4 = Control Level 5: **Full containment and review by a specialist required: seek expert advice**	Hazard Band 5 + Emission Potential 4 = Control Level 5: **Full containment and review by a specialist required: seek expert advice**
ISO		Hazard Band E - Severe Hazard + Exposure Band 2 = Control Band 5 **Full containment and review by a specialist: seek expert advice**	Hazard Band E - Severe Hazard + Exposure Band 2 = Control Band 5 **Full containment and review by a specialist: seek expert advice**	Hazard Band E - Severe Hazard + Exposure Band 2 = Control Band 5 **Full containment and review by a specialist: seek expert advice**	Hazard Band E - Severe Hazard + Exposure Band 2 = Control Band 5 **Full containment and review by a specialist: seek expert advice**	Hazard Band E - Severe Hazard + Exposure Band 2 = Control Band 5 **Full containment and review by a specialist: seek expert advice**	Hazard Band E - Severe Hazard + Exposure Band 2 = Control Band 5 **Full containment and review by a specialist: seek expert advice**
EC Guidance		Medium-high concern + High level of exposure = Risk level 4 **Risk assessment performed by an expert + it is essential that measures specifically designed for the processes in question to be adopted**	Medium-low concern + High level of exposure = Risk level 3 **Risk assessment performed by an expert + closed systems or containment must be used.**	High concern category + High level of exposure = Risk level 4 **Risk assessment performed by an expert + it is essential that measures specifically designed for the processes in question to be adopted**	Medium-high concern + High level of exposure = Risk level 4 **Risk assessment performed by an expert + it is essential that measures specifically designed for the processes in question to be adopted**	Medium-high concern + High level of exposure = Risk level 4 **Risk assessment performed by an expert + it is essential that measures specifically designed for the processes in question to be adopted**	Medium-low concern + High level of exposure = Risk level 3 **Risk assessment performed by an expert + closed systems or containment must be used.**
Precautionary Matrix		All numbers > 20 **Precautionary need warranted**	All numbers > 20 **Precautionary need warranted**	All numbers > 20 **Precautionary need warranted**	All numbers > 20 **Precautionary need warranted**	All numbers > 20 **Precautionary need warranted**	All numbers > 20 **Precautionary need warranted**

		Nanomaterial					
		SiO_2	**TiO_2**	**CNT**	**Nanosilver**	**Graphene**	**Nanocellulose**
Stoffenmanager	Time & Frequency Weighted:	E - Extreme hazard class 2 - Average exposure potential I - **High risk priority**	D - Very high hazard class 3 - High exposure potential II - **Medium risk priority**	E - Extreme hazard class 2 - Average exposure potential I - **High risk priority**	D - Very high hazard class 2 - Average exposure potential II - **Medium risk priority**	E - Extreme hazard class 2 - Average exposure potential I - **High risk priority**	E - Extreme hazard class 2 - Average exposure potential I - **High risk priority**
Nanosafer	Estimated Hazard Level	0.59	1	0.59	0.761	0.539	0.488
	Near Field	Acute: 0.1267 RL2: Low toxicity/Low exposure potential EB2: Low exposure potential	Acute: 0.0777 RL4: High toxicity/ High exposure potential EB1: Very low exposure potential	Acute: 1.056 RL5: Very high toxicity/ Moderate to very high exposure potential EB5: Very high exposure potential	Acute: 0.0227 RL4: High toxicity/ High exposure potential EB1: Very low exposure potential	Acute: 3.2 RL5: Very high toxicity/ Moderate to very high exposure potential EB5: Very high exposure potential	Acute: 0.3873 RL4: High toxicity/ High exposure potential EB3: Moderate exposure potential
		Daily: 0.1275 RL2: Low toxicity/Low exposure potential EB2: Low exposure potential	Daily: 0.0782 RL4: High toxicity/ High exposure potential EB1: Very low exposure potential	Daily: 1.063 RL5: Very high toxicity/ Moderate to very high exposure potential EB5: Very high exposure potential	Daily: 0.0229 RL4: High toxicity/ High exposure potential EB1: Very low exposure potential	Daily: 3.22 RL5: Very high toxicity/ Moderate to very high exposure potential EB5: Very high exposure potential	Daily: 0.3899 RL4: High toxicity/ High exposure potential EB3: Moderate exposure potential

Table 6.

Control Banding Recommendations for the Nanomaterials Evaluated, Compared to Recommendations that Align with Proposed Occupational Exposure Limits (OELs).

Control Banding Tool	**Recommended Control Bands and Performance-based Exposure Ranges***		
	Seek Specialist Advice/ Adopt special measures	***Containment***	***Engineering Controls (fume hoods or LEV)***
	<1 ug/m^3	**1-10 ug/m^3**	**10-1000 ug/m^3**
Recommended Control Approaches by Control Banding Tool			
CB Nanotool	Carbon nanotubes	Graphene Nanocellulose Silver Titanium dioxide	Silica (amorphous)
GoodNanoGuide	Graphene Nanocellulose Silica (amorphous) Silver	Carbon nanotubes Titanium dioxide	
ANSES	Carbon nanotubes Graphene Nanocellulose Silica (amorphous) Silver Titanium dioxide		
ISO	Carbon nanotubes Graphene Nanocellulose Silica (amorphous) Silver Titanium dioxide		
EC Guidance	Carbon nanotubes Graphene Silica (amorphous) Silver	Nanocellulose Titanium dioxide	
NanoSafer	Carbon nanotubes Graphene	Nanocellulose Silver Titanium dioxide	Silica (amorphous)
Recommended Control Approaches that Align with OELs†			
	Silver	Carbon Nanotubes	Carbon Nanotubes Silica (amorphous) Titanium dioxide

*Estimated from control banding approaches shown in Figure 1; these correspond to the OEL concentration ranges (also called Occupational Exposure Bands, OEBs) associated with the hazard categories in the ANSES (2010) and ISO (2014) control banding tools. Note that some control band categories (CL2 and CL3) have been combined for ANSES and ISO to make the control bands results consistent between tools. And the control recommendations provided by NanoSafer differ from categories provided here (e.g. LEV, containment, special precautions) and include recommendations on respiratory protection-see Figure 2).

†Based on proposed OELs (Table S-1) and corresponding performance-based exposure ranges shown in this table.

LEV: Local exhaust ventilation.