Original Articles

Understanding Workplace Processes and Factors that Influence Exposures to Engineered Nanomaterials

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There is a critical need to understand the factors that influence engineered nanomaterial (ENM) exposures in the workplace. Such an understanding would aid in: identifying and prioritizing control measures; targeting future exposure measurements; and predicting worker exposures for work scenarios. This information could also be used in epidemiological studies. We propose a multitiered model in which information on exposure factors can be obtained at the macrolevel (examining differences in exposures between different ENM sectors or product types); the midlevel (examining differences in exposures between workplaces within the same ENM sector or product type); and the microlevel (examining differences in exposure between tasks or between ENM types during the same task). Further, within the microlevel, potential exposure factors are defined by a source-receptor model. We recommend that auxiliary data be collected systematically, along with exposure measurements, to enable analysis of exposure factors as well as the pooling of data across studies. *Key words*: nanoparticle; engineered nanomaterial; exposure; occupational exposure; exposure determinants; exposure factors; exposure controls; epidemiology; nanomanufacturing.

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INTRODUCTION

Engineered nanomaterials (ENMs) are materials designed and produced with at least one dimension ≤ 100 nm. Engineered nanomaterials can be classified by their chemical/atomic properties into a number of categories including pure metals, oxides, carbon-based nanoparticles, quantum dots, macromolecules, and self-assembled molecules.[1] Engineered nanomaterials can be heterogeneous in morphology and chemical composition. They can be present in a combination of size, shape, composition, surface charge, crystallinity, solubility, surface functionalization, and impurities, all of which can lead to different toxicological effects.[2]

Funding in nanotechnology reached $18.2 billion worldwide in 2008 and it continues to grow.[3] The Woodrow Wilson Center's Project on Emerging Nanotechnologies currently has over 1000 manufacturer-identified nanotechnology-based consumer products listed in their database.[4] Some ENMs that have widespread commercial value, such as carbon blacks, nanosilver, and titanium dioxide, are currently being produced in large quantities (millions of tons/year), while other ENMs, such as carbon nanotubes (CNTs) and nanofibers, are being produced in hundreds of tons per year.[5–8] However, there is no data available on amounts used in the manufacture of ENM-enabled consumer products or in the production of non-consumer-based ENM-enabled products, despite the fact that these are growing sectors of nanotechnology. Although much of the current investment by governments and corporations remains in research and development at the laboratory or pilot plant scale, it is expected that by 2015 nanotechnology will represent an estimated $3.1 trillion in manufactured goods worldwide.[3] In February of 2009 the US National Nanotechnology Initiative (NNI) hosted a workshop on Human and Environmental Exposure Assessment of Nanomaterials (Bethesda, MD, USA). One of the topic areas identified as a key research gap was: "Understanding workplace processes and factors that determine exposure to nanomaterials." Yet, for this and other environmental and occupational health and safety (EOHS) issues, only $350 million (~3%) of the cumulative $12 billion US NNI budget since 2001, including the proposed Federal 2010 budget, has been targeted for federally funded projects relevant to EOHS.[9] In order to make headway on this research, a greater public and private investment is necessary.

The life cycle of an ENM or ENM-containing product includes a research/discovery phase in the labora-

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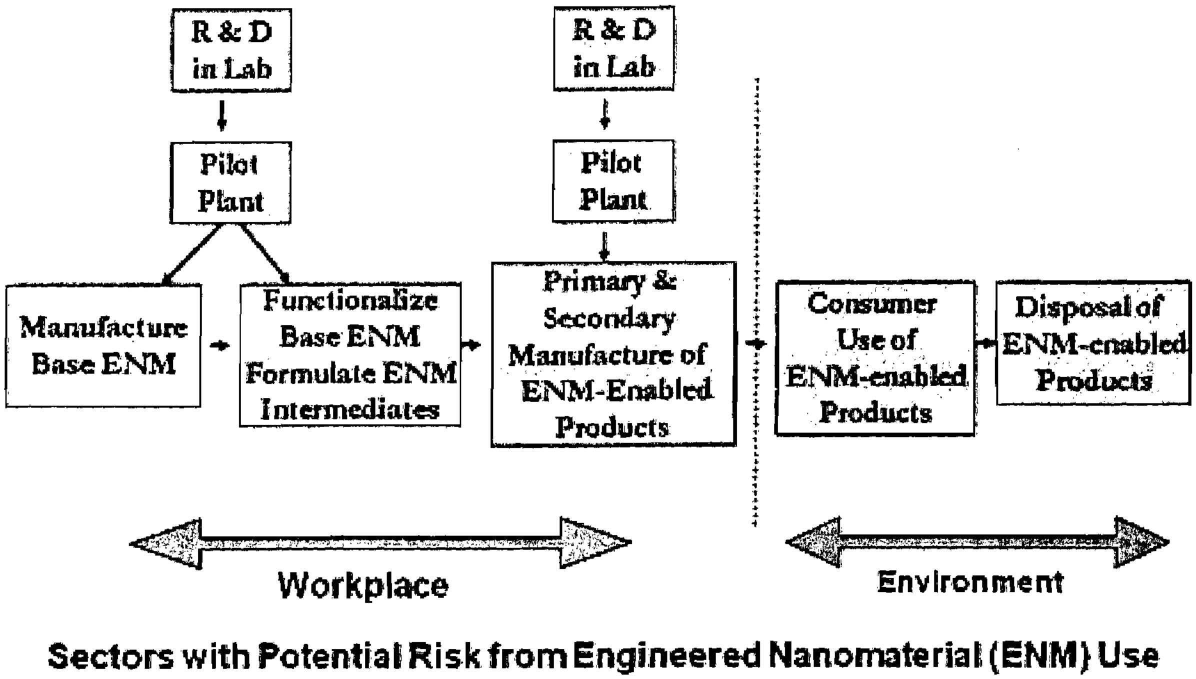

Figure 1—Classification of engineered nanomaterial (ENM) workplaces.

tory, a development phase where products are scaled up and processes developed for production (pilot project phase), and a manufacturing phase where products are made, packed, stored, and shipped in large quantities. Following manufacture, there is the end- use of the product and the eventual disposal of the product.[10] For ENMs, there are sectors of production that focus on the manufacturing of raw or base ENMs, and these can be the same or separate from those that focus on the functionalization or further customization of the base material. Eventually, the ENMs are used in formulations, intermediates, or end products. All of these sectors occur first in a research and development setting, then in a pilot plant setting, and finally in a manufacturing setting (Figure 1).

To understand the potential for exposure to ENMs, it is useful to first describe how the wide array of materials might be classified in order to elucidate whether exposures may be influenced by the base material. Six major categories of ENMs were suggested by the international council on nanotechnology (ICON) based on chemical/atomic properties:[11]

1. Oxides: titanium dioxide (TiO_2), zinc oxide (ZnO), cerium oxide (CeO_2), iron oxide (Fe_3O_4), manganese dioxide (MnO_2), and silicon dioxide (SiO_2);
2. Metals: silver (Ag), cobalt (Co), nickel (Ni), iron (Fe), platinum (Pt), palladium (Pd), rhodium (Rh), gold (Au), aluminum (Al), and copper (Cu);
3. Carbon-based nanoparticles: raw and functionalized nanotubes (single-, double-, and multiwall); nanohorns; fullerenes (buckyballs); nanofibers; graphene sheets; carbon black;
4. Quantum dots: fluorescent crystalline semiconductors;
5. Macromolecules: branched polymeric organic molecules;
6. Self-assembled molecules: lipids, metal oxides, and organic molecules which self-organize due to inherent physical properties.

Note that these six categories were based on knowledge at the time of the ICON survey; however, as science and technology evolves, this classification strategy may need to be amended. For example, nanophase powders such as silicon carbide, boron nitride, and tungsten carbide/cobalt represent a category of materials that are increasingly being produced and have industrial relevance, but do not fit neatly in any of these six categories.

The toxicity of nanoparticles (NPs) is influenced by the interplay of several factors including chemical composition, surface chemistry and reactivity, crystallinity, shape and morphology, phase purity, catalytic impurities, biopersistence, and surface charge in the biological milieu.[12–15] As such, simply classifying the base material may not be enough to categorize the potential hazard of an ENM.[16]

Most of the measurements made to date of ENM operations are area samples rather than personal samples and focus on short periods of time when tasks are being done. Some have termed these emission measurements; however, source emissions are typically reported as mass/unit time while ambient ENM levels, which represent potential worker exposures, are reported in concentration units. By contrast, in order to estimate a worker's potential dose of ENM it would be necessary to also incorporate other variables, such

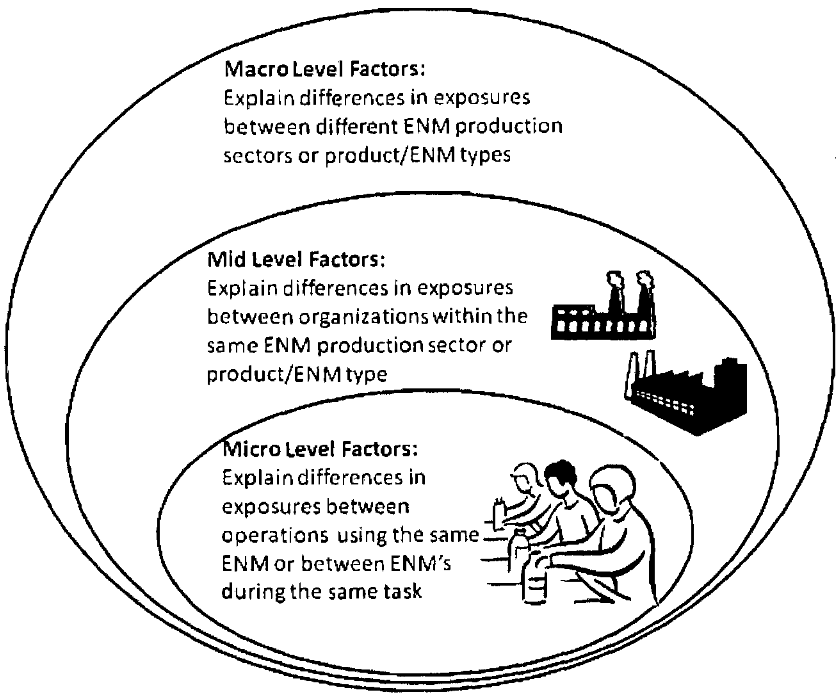

Figure 2—Factors at the macro-, mid-, and microlevel may influence/explain differences in engineered nanomaterial (ENM) exposures and may be used to help target exposure monitoring efforts and exposure interventions and to predict worker exposures for epidemiologic studies.

as use of personal protective equipment (PPE), personal breathing rate, and exposures over longer periods of times. This paper is focused on factors that may influence the potential exposure of a worker to ENM, rather than the more narrow source emissions or the more inclusive dose estimation.

It should be noted that multiple metrics may need to be used when evaluating potential occupational exposures to ENM. Some of the equipment and testing procedures needed to fully evaluate the potentially relevant exposure metrics in an epidemiological study of health effects can be quite expensive, complex, and difficult to use in field studies.[17,18] However, a semiquantitative method has been recommended by the National Institute of Occupational Safety and Health (NIOSH).[19] In all cases, it is crucial that an evaluation of potential nanoscale particle exposures resulting from incidental sources (including byproducts of combustion or hot processes such as vehicle exhaust, compressors, photocopiers, and cleaning operations) which may interfere with processes of interest also be evaluated so that actual exposure to the ENM of interest can be associated with the relevant process.[20,21]

A SYSTEMATIC APPROACH TO INVESTIGATING ENM EXPOSURE FACTORS

When auxiliary information on potential exposure factors is systematically collected along with each exposure measurement, it is possible to examine the extent, direction, and strength of the relationship between the presence or level of these auxiliary variables and the exposure level through statistical modeling. Typically, in such models the outcome (dependent variable) of the model is the exposure metric, and predictors (independent variables) can be either grouped (categorical) or continuous (numerical) indicators of the exposure factors. Such models can then be used to predict exposures for unmeasured combinations of exposure factors for use in epidemiological studies and to prioritize and target exposure monitoring and control efforts.

Potential influential exposure factors for ENM occur at the macro-, mid-, and microlevels (Figure 2; Tables 1–3). At the macrolevel, the focus is on factors which may be able to explain differences in ENM exposure levels between different ENM production sectors or product/ENM types (including characteristics of an industry sector such as the number of years in operation or experience with the technology). Next is the mid-level where exposure differences may occur between organizations within the same ENM production sector, product type, or ENM type. For example, for metal oxides, factors such as the manufacturing method—whether it is flame pyrolysis or colloidal synthesis—may play an important role in the nature and extent of exposures. Finally, at the microlevel (job/task), exposure differences may occur between operations using the same ENM or between different ENMs during the same task (such as bagging CNTs versus bagging titanium dioxide). Here, a source-recep-

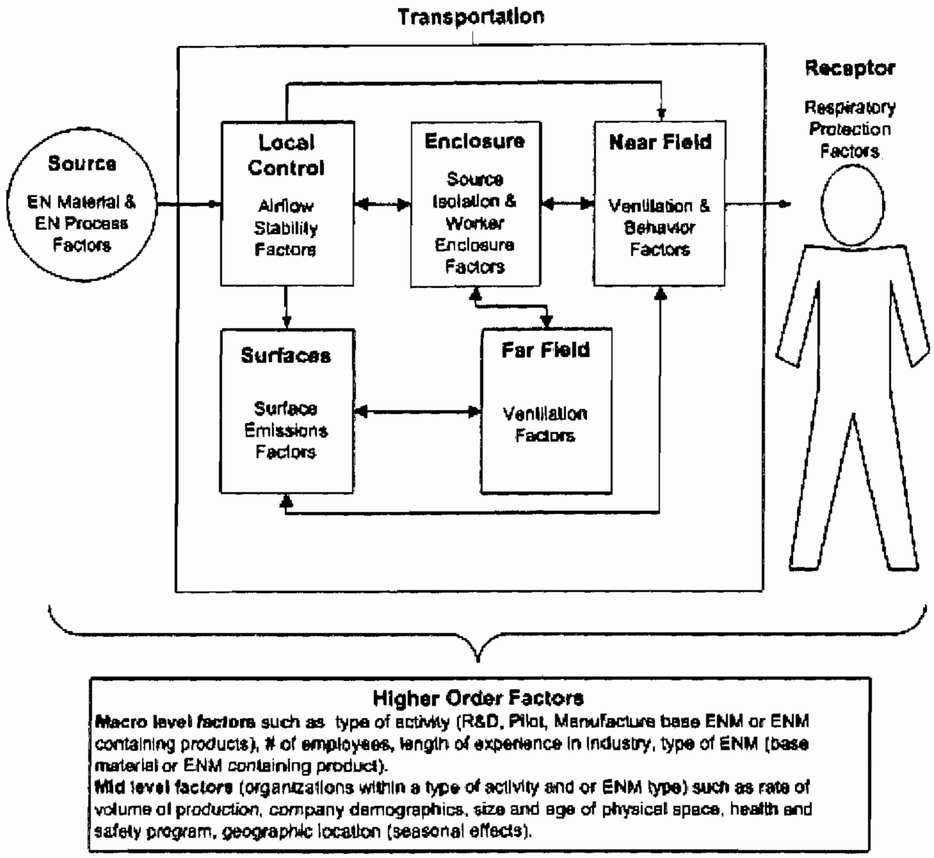

Figure 3—Source receptor model adapted from Tielemans et al.[22] The microlevel factors are contained within the source, transport, and receptor compartments and their subcompartments.

tor model is used to describe the physical pathway of a source emission through different compartments and mechanisms resulting in human exposure (Figure 3). The three main compartments in this model are the source compartment, the transport compartment, and the receptor compartment.

The key component of the source-receptor model is the source, where process-related variables such as the physical and chemical aspects of the potential contaminant, including vapor pressure, dustiness, quantity, reactivity, system temperature, and pressure come into play in influencing the emission rates from the source compartment. Once emitted into the transport compartment, a complex set of processes including dilution, distance, and direction to receptors (that is, workers) as well as mitigating factors (exhaust ventilation) or enhancing factors (other sources of emissions) may impact whether the contaminant reaches the receptor compartment worker. Receptor/worker factors that influence the dose received from an inhalation exposure can include time, distance, use of PPE, work practices, and training. Figure 3 (adapted from Tielemans et al.)[22] includes macro- and mid-level factors as "higher order factors." Consistent with the emphasis in existing literature on airborne nanomaterials, many of these factors explore the impact on airborne (inhalation) exposures to ENM. However, in the future, consideration should also be given to factors that influence potential dermal contact with ENM, which is also a plausible exposure pathway.[23]

MACROLEVEL EXPOSURE FACTORS

Macrolevel factors are those that examine data from all sectors and/or ENM types in order to evaluate differences between sectors and ENM types. By sectors we mean research and development, manufacturing of base or functionalized ENMs, or manufacturing of ENM-enabled products (Figure 1). By ENM types we mean the categories of base ENMs described above or products containing ENM such as composites, coatings, and textiles. The purpose of a macroanalysis would be to target exposure evaluation, training, or control efforts to specific sectors or ENM types that have the potential to result in worker exposures. Potential macrolevel factors that could account for substantial differences in exposure include the year of sampling (calendar time), whether the work was done indoors or outdoors, worker unionization status, employment size of the sector being evaluated, and the nature of technology in use (Table 1). To date, very little exposure factor data analysis at this level has been published.

The ICON survey of current practices in the nanotechnology workplace looked at a variety of organizations using ENMs.[1,24] Results of the survey indicate that the most common activity of organizations is research and development, followed by manufacturing of ENMs, and then manufacturing of ENM-enabled products. In general these research and development organizations are small, having less than 50 employees, and tend to be new to the industry, with 56% being less than 10 years old and 86% having used ENMs for less than 10 years. As noted previously, ICON developed six basic categories of ENMs. However, in their survey 45% of users reported working with metal oxides or pure metals, 45% with carbon nanotubes, 19% with fullerenes, 14% with quantum dots, and 20% with nanopolymers or dendrimers. Clearly, at this time, certain types of ENMs are being used more frequently than others for commercial purposes, and different technologies are at different stages in their path to commercialization.

Additional information on macrolevel factors comes from a recent survey of Swiss manufacturing companies in the Swiss National Accident Insurance Fund.[25] In that survey 0.6% of companies and 0.08% of the manufacturing workforce in Switzerland were reported to be potentially exposed to NPs. The percentage of companies dealing with ENMs increased with company size. The survey did not identify any manufacturers of ENMs, though only a "handful" exist in the country. The greatest fraction of companies and workers with potential exposures to ENMs were in the chemical industry, electrotechnics (electronic technology manufacturing), automobile work (repair, bodywork, and painting), and the trade sector (beverage manufacturing, recycling, fuel trade, construction materials, farming and livestock trade, as well as the steel and metal trade). They also reported on three groups of NP types, as well as yearly turnover (usage), which was an average of 1426 kg for inorganic NPs, 365 kg for organic NPs, and 500 l for metallic NPs in liquid (only one company reported liquid NPs).[25]

To summarize what we know about macrolevel factors and potential ENM exposures: (1) there currently exists little data linking macrolevel factors to actual exposure measurements. This gap could be filled by the development of a collaborative ENM exposure measurement database. (2) If information on high frequency of use is applied as a criteria for prioritizing future exposure monitoring efforts and/or preventative control interventions, then based on the ICON survey, the priority should be in research and development, base ENM manufacturing, small and young organizations, and organizations that use carbon-based NPs, metal oxide NPs, or pure metal ENM. By contrast, the Swiss data suggest that the priority in manufacturing should be placed on large companies in the chemical industry, especially those using inorganic NPs.

A potential problem with using macrolevel data on industry without any consideration of toxicity information is that such an approach can only target high-use materials or sectors for future exposure assessment or control efforts. This is problematic because, by not accounting for the relative toxicity of an ENM, materials that may be more hazardous, though less commonly used, will not be high in the priority list for measurement or intervention.

To assist in setting priorities for ENM health effects research and standards development it is essential that concurrent data on macrolevel factors and exposure measurements be collected in order to provide a thorough demographic overview of industrial ENM exposures. In addition, future epidemiological studies are likely to include very diverse workplaces (both in terms of sectors and ENM types) in order to obtain sufficient numbers of ENM-exposed subjects to conduct a study. Therefore, information that can aid in comparing exposures across the diverse array of workplace ENM use scenarios would be very useful.

MID-LEVEL EXPOSURE FACTORS

Mid-level factors that could influence ENM exposures compare organizations within a given ENM sector, such as research and development, ENM manufacturing, or manufacturing of ENM-enabled products. Potential mid-level factors might include: the type of product; the rate or volume of production; company or site level demographics; descriptors of the physical worksite (such as size and age); ratings of worksite health and safety programs; geographic location (which could include seasonal effects); the production and/or synthesis method; or the target sales and consumer audiences (Table 2). Note that many of these mid-level factors can identify opportunities to control exposures at the emission source through use of engineering or administrative controls following the conventional occupational hygiene hierarchy of controls.[26,27] Evaluation of the importance of these factors in differentiating ENM exposure levels could inform determinations of the utility of various EHS program interventions as well as help EHS managers focus their resources for exposure sampling efforts.

To date, only a few studies have investigated these mid-level factors and compared airborne levels of nanoscale particles at different sites producing the same ENM. Kuhlbusch et al.[28,29] investigated exposures during two common operations of ENM manufacturing (reactor synthesis and ENM pelletizing and packaging for shipment) in three different nano-carbon black production plants. A unique feature of these studies was that repeat sampling was performed on the same process at each plant, which permitted reporting of both a mean level and a measure of the variance (the 25th to 75th percentile) for the particle counts for each of the operations at each of the plants (thereby addressing the midlevel factor: company/site specific demographics). In addition, the authors collected ambient measurements outside the plant. Their results show that for plant 1 there was no number concentration difference between inside and outside air or between the reactor areas or the pelletizer areas for particles in the 10 to 100 nm size range. In plant 2 there was also no inside-to-outside difference, but overall particle counts were higher, which they attributed to the plant being nearer to an incidental source of nanoscale particles from automobile traffic. Plant 3 had significantly higher inside (vs. outside) particle number concentration differences for both the reactor and the pelletizer operations. The authors analyzed filters for organic and elemental carbon and found high levels of organic carbon, and thus surmised that some of the nanoparticle exposure may have come from process leaks (such as oil and flue gases).

Methner et al.[30] reported several exposure metrics associated with processes and tasks for carbon nanofibers, multiwalled carbon nanotubes (MWCNTs), and several metals and metal oxides from twelve facilities (mid-level factor: type of product/production method). However, because the measurements were made as a part of range-finding evaluations to determine if an emission from a process/task occurred, no attempt at statistical inference was made. Although this limits the utility of this work for evaluating within-ENM type exposure factors, it does suggest that future studies could use the technique for evaluating exposures in combination with the collection of additional data on potential exposure factors to develop a database for statistical evaluation.

Lee et al.[31] reported results for exposure monitoring conducted at seven facilities manufacturing and handling MWCNTs in the research and manufacturing phases. Although the researchers reported characteristics of the workplaces such as type of facility (research or manufacturing), material manufactured, processes, controls, and PPE usage (mid-level factors: type of product/production method), the only comparison of the results across the various facilities were tables listing the number (frequency) of measurements with increased NP exposures during various processes and the range of particle counts measured for those processes.

Demou et al.[32] investigated the impact of production techniques on total number concentration of NPs at four research laboratories using flame spray pyrolysis production techniques. Changes in the production system such as the flame distance or strength as well as the number of flames were found to have an impact on exposure levels (mid-level factor: production method).

To summarize, few studies have compared exposures within a sector but across sites. Those that have evaluated few macro-, mid-, or microlevel factors that could explain differences in levels. The studies by Kuhlbusch[28,29] are noteworthy in their use of statistical methods to report the data.

MICROLEVEL (JOB/TASK) EXPOSURE FACTORS

At the microlevel, the specific tasks/ activities associated with a job/operation are what determine a worker's potential exposure to ENMs. Since a worker's daily exposure is proportional to the sum of the task exposure intensity and duration for an entire day's tasks, it is important to understand the factors that influence the exposure levels of each specific task within a job or operation. In fact, to date most exposure monitoring of ENMs has been at the task/activity level rather than attempting to estimate a worker's daily average exposure, as is more typically done for both compliance and health hazard assessments.

Common operations that should be examined for task-level factors include: receipt and unpacking of ENMs; laboratory and research and development operations; manufacturing and finishing steps in production; packaging, storage, and shipping; maintenance and repair; waste management; and spill and emergency procedures. Workers who may directly or indirectly come into contact with ENMs during these tasks include operators, maintenance workers, janitorial staff, supervisors and quality assurance/quality control inspectors, emergency responders, and/or bystanders (workers, visitors, or contractors not directly involved in the process). Note that microlevel factors are highly dependent on individual tasks and worker activities. As such, exposure mitigation efforts at this level are dependent upon engineering controls as well as administrative controls (such as the redesign of the workflow for particular tasks) and the use of PPE.

The following discussion summarizes our understanding of the microlevel factors that influence exposures to ENMs (Table 3). For simplicity, this literature review is organized by tasks and activities in the base production of ENMs, the functionalization of ENMs, and manufacture of ENM-enabled products. Since the this review focuses on factors that can differentiate exposure levels, rather than attempting a complete review of the study findings, readers are referred to earlier reviews[33,34] as well as the papers themselves for additional study details .

Task-Level Factors: Manufacturing Base ENMs

Base ENMs are generally produced though processes that are enclosed and engineered to minimize emissions during normal operation. As such, exposures are more likely to occur during other tasks associated with the manufacture of these base materials, such as setting up and running reactors; unloading reactors; finish processing such as drying, maintenance, or cleaning;

packaging and shipping; or handling accidental spills or waste product. To date, only a few studies have investigated task-level exposure factors in the base ENM manufacturing industry.[31,32,35–39]

Tsai et al.[39] looked at emissions from the production of MWCNTs and single-wall carbon nanotubes (SWCNTs) in a laboratory setting. The authors observed that a greater quantity of NPs was released during synthesis of MWCNTs and that low injection temperatures decreased the NP emissions while increasing nanotube production (microlevel category: source process).

Yeganeh et al.[35] performed a study at a reactor in a fullerene manufacturing plant. The authors observed that the tasks technicians performed were: (1) vacuuming residual nanomaterials from previous runs in the reactor; (2) placing fresh graphite rods inside the reactor; (3) sealing the reactor; (4) running the arc to produce fullerenes; and (5) opening the reactor to remove the product by sweeping it into a jar. The monitoring of these tasks suggests that the vacuuming process produced the highest concentration of nanoscale particles which were < 100 nm and could be measured both at the reactor and two meters away. The authors also noted that some days there were high particle counts during sweeping of the fullerenes into jars (microlevel category: operations/tasks). Unfortunately, although the authors monitored 12 production runs, they did not use a statistical presentation of the exposures during these tasks, so we do not have a real sense of the mean and variance in particle counts per task.

Methner et al.[36] measured exposures to nanoscale metal catalytic materials (manganese, silver, and cobalt) during cleanout of a gas-phase condensation vapor deposition reactor with and without the use of local exhaust ventilation (LEV). The LEV reduced airborne mass concentration emission levels during the reactor cleanout by an average of 88% (microlevel category: local control).[27] Similarly, Han et al.[27] reported large reductions in exposure levels of MWCNTs by implementing engineering controls such as ventilation and process isolation (microlevel category: local control). Fujitani et al.[37] also investigated emissions at a fullerene production facility and reported that the particle count in the size range of 10 to 50 nm increased during bagging/weighing and vacuum cleaner use. They also reported that although the number of large (> 2000 nm) particles did not increase, the volume of these particles did increase during the bagging and vacuuming operations, suggesting that agglomeration of the fullerenes was occurring (microlevel category: operations/tasks and far field/ambient).

Bello et al.[38] investigated emissions during chemical vapor deposition (CVD) growth of nanotube forest films. The authors reported no exposures to CNTs or other nanoscale particles during the growth of nanotube forest films, their removal from the furnace, or removal from their support film. However, micron-sized clumps of carbonaceous material were measured in air during furnace opening (microlevel category: operations/tasks). Lee et al.[31] reported total number concentration during manufacture and handling of MWCNTs by CVD. They reported timelines of activities and tasks during monitoring at selected facilities, which they use to explain the patterns on total number concentration plots for the day. The study reported highest exposures associated with catalyst preparation, followed by opening the door to CVD, wafer heating, opening the cover of spray, and ultrasonic operations (micro level category: operations/tasks).

Demou et al.[32] measured total ENM number, mass concentrations, and particle size distributions at a pilot plant manufacturing metal-based NPs embedded in a porous oxide matrix. The authors characterized emission sources by monitoring at different locations (near and far field/ambient) from the reactor over 25 days, and assessed spatial and temporal variations in concentrations. The authors also noted changes in operations and employee activities and tasks such as reactor maintenance and cleaning, adjustments to reactor system, powder handling and packaging, and workplace cleanup on data logging sheets to help interpret exposure data. The results of the total number concentration measurements showed increasing exposure levels and variability as production progressed from background to reactor cleaning, followed by a rapid decline before starting the reactor, a rapid increase after the start of reactor, a steady state during production marked by reduced variability, and an end-phase marked by declining exposure levels and increasing variability to the background level marked by low exposure and variability (microlevel category: operations/tasks). Such a trend was not observed with the mass concentration measurements. During the steady state, little spatial variation was observed, however, on a shorter time scale, such as during reactor cleanup, large differences were observed between locations (microlevel category: far field/ambient). Chemical and morphological analysis of the ENM was not conducted, thus limiting the complete characterization of exposure.

In another study of the manufacture of different types of NPs using the flame spray pyrolysis production technique in research laboratories, Demou et al.[32] reported similar results of NP number concentration tracking with the production events. High number concentrations above the background was observed during cleaning followed by a steady increase during production and decline after production had stopped (microlevel category: operations/tasks). As in their earlier study, the mass concentration did not track well with the production events.

In summary, what we know about microlevel exposure factors for manufacturing base ENMs is primarily focused on the differences between various operations/tasks, with little data available to evaluate other potential exposure factors. The studies to date suggest that: (1) unloading an ENM reactor can produce measureable exposures; (2) most studies do not report elevated emissions from properly operating closed-system reactors, but elevated total number concentrations have been reported during the production phase; (3) maintenance and cleaning of reactors can be a source of exposure; (4) the potential exists for exposure from drying operations adjacent to a pelletizing operation (suggested by anecdotal information from one study); (5) packaging of final products can be a potential source of exposure to ENMs (indicated by two studies); and (6) all available microlevel task/operation data for base manufacturing is for carbon-based ENMs with none of the other five categories identified by ICON having yet been studied in this fashion.

Task-Level Factors: Functionalization of ENMs

Once base ENMs have been produced, they are often functionalized or modified to enhance their properties or make them more useful for product development (Figure 1), among other things. Note that the chemical functionalization of ENMs is often performed to purposefully modify the surface of a material for enhanced performance; however, within the context of this section, functionalization is taken to mean activities that use base ENMs to produce an ENM-enabled product or intermediate material. Much of the work for functionalizing ENMs is performed in research and development laboratory settings. In these laboratory settings there is significant potential for personal contact with ENMs during tasks such as mixing and pouring, cleaning equipment and apparatus, weighing, ultrasonic agitation, and preparing ENMs for quality assurance/quality control testing. The need to understand microlevel factors during functionalization activities in research and development work settings is especially critical because ICON reports that only 47% of laboratories that handle dry powder use a fume hood. As with base manufacturing, only a few studies have investigated task-level exposure factors in workplaces that focus on laboratory activities and/or functionalization of ENMs.[40–42]

Johnson et al.[41] reported that ENMs may become airborne during common laboratory activities such as weighing and transferring carbon-based ENMs and probe sonication of materials in open vials (microlevel category: operations/tasks). Lee et al.[31] monitored a research facility where CNTs were weighed, dispersed by ultrasonic agitation (probe sonication), and chemically treated with sulfuric acid. Nanoparticles were emitted during the probe sonication task (microlevel category: operations/tasks).

In another study, Methner et al.[42] investigated emissions at a university-based research laboratory using carbon nanofibers to produce composite materials. Although they only measured total airborne carbon mass concentrations, during some tasks, including weighing and mixing, air concentrations were significantly higher compared to background (microlevel category: operations/tasks).

Use of a laboratory fume hood is a potentially important factor modifying ENM exposure concentrations. Tsai et al.[40] investigated the efficacy of two types of hoods, a conventional laboratory ventilation hood and a bypass lab ventilation hood, during transfer and pouring of nanoalumina. The authors reported their results after subtracting out the background particle counts. When the hoods were running at their recommended face velocity of 100 to 150 ft/min, the bypass hood better controlled particle release. However, even in a conventional hood the number concentrations at the peak particle size of about 10 to 20 nm was only about 5000 particles above background (microlevel category: local control/operations/tasks). While these data indicate that use of fume hoods appears to be a very effective control technology in terms of nanoscale particle number concentrations, ENM could be measured 1 meter outside the laboratory hood for up to eight minutes after completion of pouring or transferring activities involving nanoalumina. Additionally, particle counts outside the hood were elevated during cleanup activities inside of the hood, though they dropped relatively quickly to near background (microlevel category: far field/ambient). Thus, for high-hazard ENMs, fume hoods alone may not provide adequate worker protection from source emissions, and additional engineering controls may be necessary.

To summarize, as with manufacturing base ENMs, what we know about microlevel exposure factors during functionalization of ENMs in laboratory settings is primarily focused on the differences between various operations/tasks, although even there we have limited data. The work by Tsai et al.[40] provides important information on the impact of local controls (such as ventilation) on these tasks. More such work is needed since 23% of organizations surveyed by ICON used ENM as a dry powder only, 37% used ENM in dry powder form and in suspension, and, as reported previously, only a minority used these materials inside a laboratory hood.[1] These statistics are particularly troublesome because the range of functionalized ENM types encountered in research environments is so vast that occupational hygienists will need to collaborate with toxicologists to target those functionalized nanomaterials of greatest concern. In addition, more work needs to be done to evaluate other types of hood designs as well as to examine other tasks inside the hood, including those that add thermal load to the ventilation demands.

Task-Level Factors: Manufacturing of ENM-Enabled Products

The final sector for evaluating workplace exposure factors is in the manufacturing and formulation of ENM-enabled products (Figure 1). Currently, much of this work is performed in research environments where, as noted above, there is significant potential for exposure to workers. Over time, many of these processes are expected to be scaled-up to high-quantity throughput, which will require additional consideration of factors at the mid- and macrolevel.

A current area of active research is the enhancement of composite material performance through using ENMs. One type of nanoenabled composite material is referred to as a hybrid material because it incorporates CNTs between substrates (graphite or alumina cloth) to form a "sandwich" of material held together with epoxy resins. Another type of nanoenabled composite material uses a compounding process where a heated extruder is used to mix plastic polymers with nanoscale alumina powder.

Tsai et al.[43] investigated whether different methods of adding nanoscale alumina to an extrusion process made a difference with respect to process emissions. In one method, the nanoscale alumina was premixed with the polymer, and in the other methods the alumina was added at various downstream locations through separate ports in the extruder. The premix method produced higher particle counts than the other methods (microlevel category: source process). Despite having the highest emission level, the fabrication engineers opted to continue to use this process because it resulted in a more even distribution of the alumina throughout the polymer product, which was an important feature for product performance. This highlights the need to work with engineers to enhance health and safety through "prevention by design" in order to avoid reliance on less preferable "after-the-fact" control techniques to protect workers from unintended exposures.

Bello et al.[44,45] investigated exposures associated with machining activities on hybrid composite ENM-enabled materials (microlevel category: source material). All composites, when cut, produced significantly higher particle number concentrations than those measured in background. Exposure levels were strongly dependent on the composite type and its thickness. Thinner composites produced considerably less exposures than thicker composites. Single ply CNT-alumina hybrid composites produced very low total particle number concentrations compared to machining the same type of composite material without CNTs. For much thicker composites, more notable differences were observed in the size distributions and composition of airborne aerosols, whereas carbon composites had much higher number concentrations of small (< 10 nm) particles.[44] The authors also investigated emissions from dry cutting versus wet cutting. As might be expected, dry cutting produced much higher particle number concentrations than wet cutting (microlevel category: source process). In addition to particle number concentrations, the authors also collected replicate samples for analysis by electron microscopy. The authors did not find free or aggregated CNTs, but observed considerable amounts of nanofiber. Using a method for counting asbestos fibers, the authors determined that respirable-sized fibers were present in air at concentrations of 1.6 to 3.8 fibers/ cm^3. Cutting the carbon nanotube-alumina composite produced fewer numbers of fibers than the CNT-carbon composite. (microlevel category: source material). In addition, the distance from the source was identified as a significant factor in exposure level (microlevel category: far field/ambient) .

Solid core drilling on these same composites produced notably different findings, suggesting that a simple change in the process can profoundly alter the nature and intensity of exposures to nanoscale particle and fibers during the processing of advanced composites.[45] Compared to dry cutting, drilling generated airborne CNT aggregates that were not observed while saw-cutting similar composites (microlevel category: source process). In addition, an ultrafine (< 5 nm) aerosol originating from thermal degradation of the composite material was identified during drilling. While Bello et al.[45] found fewer nano- and respirable-sized fibers in the dry cutting aerosol than in the drilling aerosol, they found similarly high NP concentrations. Exposures in drilling operations were less dependent than the cutting operations on composite thickness (microlevel category: source material/source process).

To summarize, unlike studies of manufacturing base ENMs and functionalization of ENMs, studies of manufacturing ENM-enabled products have focused on exposure factors rather than just differences between operations/tasks. Nevertheless, we know very little about most of the tasks encountered during production of hybrid composites. To date, most of the work has focused on products containing CNTs or nanoalumina, rather than any of the other ENM types identified by ICON.

CONCLUSION

In conclusion, exposure information is missing on many tasks within each sector of ENM production and ENM-enabled product manufacture. Basic information on many of the six basic types of ENMs identified by ICON is missing, and many subgroups within each of those basic categories have received little attention. Very little data has been published examining the differences in exposures due to exposure factors at the macro-, mid-, or microlevel, though available studies support the importance of gathering this detailed information as part of any exposure assessment and measurement strategy for ENMs. Few studies have reported on ENM exposures and very few potential exposure factors have been examined or reported within each study, in part likely due to a lack of varia-

TABLE 1 Preliminary List of Macro-level Exposure Factors

Macrolevel Category	Macrolevel Factors for Data Collection during Exposure Sampling
Sector	• Research and development • Manufacturing base engineered nanomaterials (ENMs) • Functionalizing ENMs • Formulating ENM intermediates • Manufacturing ENM products for use in consumer/commercial products • Manufacturing consumer/commercial market products
ENM type	• Oxides: TiO_2, ZnO, CeO_2, Fe_3O_4, MnO_2, SiO_2 • Metals: Ag, Co, Ni, Fe, Pt, Pd, Rh, Au, Al, Cu • Carbon-based nanoparticles: raw and functionalized nanotubes (single-, double-, and multiwall); nanohorns; fullerenes; nanofibers; graphene sheets; carbon black • Quantum dots: fluorescent crystalline semiconductors • Macromolecules: branched polymeric organic molecules • Self-assembled nanomolecules: lipids, metal oxides, organic molecules that self-organize due to inherent physical properties
Organization demographics	• Number of employees • Business volume (financial) • Age of organization and/or technology • Unionization status • Health and safety culture/infrastructure
Business category	• North American Industry Classification System (NAICS) • Swiss National Accident Insurance Fund Industry Code • Other EU industry coding systems
Location	• Country • Geographic area

tion in tasks within a facility. Also, the number of exposure measurements collected within studies has been few, limiting opportunities for statistical analyses. This review of the literature suggests that additional information on the potential factors that may determine differences in exposure levels can be learned from pooling the existing exposure auxiliary data from different sources. The pooling of data is a common practice used in occupational exposure assessment and has been previously used to evaluate the variation in inhalation exposures within and between workers;[46] to evaluate dermal exposures within and between workers;[47] and to evaluate factors affecting laboratory fume hood performance.[48] Data pooling requires a consistent approach to collecting information on potential exposure factors. The preliminary lists of macro-, mid-, and micro-level factors (Tables 1–3) and the source-receptor model (Figure 3) represent an approach that can unify data collection on exposure factors and facilitate pooled data analyses. This type of database could also be extremely useful in risk assessment, standards development, and epidemiological studies.

TABLE 2 Preliminary List of Mid-level Exposure Factors

Mid-level Category	Mid-level Factors for Data Collection during Exposure Sampling
Type of product	• Plastic composite • Nanoemulsion • Base engineered nanomaterials
Production method	• Top down ENM production • Bottom up ENM production • Melt processing of nanocomposites • In situ polymerization of nanocomposites
Rate or volume of production	• Volume of ENM produced per year • Volume of ENM-enabled product produced per year • Frequency of production cycles (continuous vs. batch production)
Company/site specific demographics	• Public vs. private ownership • Profitability (Standard and Poor rating) • Size of physical space • Age of physical space • Site EHS program rating • Location relative to other potential nanomaterial exposure

TABLE 3 Preliminary List of Microlevel Exposure Factors Associated with Compartments and Mechanisms Identified in a Source-Receptor Exposure Model Adapted from Tielemans et al.[22]

Microlevel Category	Microlevel Factors for Data Collection during Exposure Sampling
Operations/tasks	• Receipt and unpacking of engineered nanomaterials (ENMs) • Laboratory tasks (weighing, transferring materials, sonication) • Manufacturing ENMs (e.g., moving product, installing rods) • Finishing steps in production (e.g. drilling, grinding, sawing) • Packaging, storage, and shipping • Maintenance and repair • Waste management • Spill and emergency procedures • Task frequency and duration
Source material	• Physical and chemical properties • Bulk ENM characteristics • ENM phase (solid vs. liquid) • Intrinsic dustiness
Source process	• Input energy • Generation rate (mass, volume) • Cycle frequency • Tendency for generation of ENM • Possibility for aerosolization (e.g. sonication of open vs. closed vessels) • Process characteristics • Source strength • Source mobility • Source scale (pilot vs. commercial scale) • Number of sources
Local control	• Local exhaust ventilation • Airflow patterns • Time source active • Reactivity/stability • Hood type and conditions
Surfaces	• Contamination level • Disturbances of surfaces • Degree of worker contact • Housekeeping practices and culture • Work area hygiene
Enclosure	• Enclosure characteristics • Maintenance and repair routines/frequency • Openings/leaks • Time in enclosure or time enclosure remains open • Built-in controls
Far field (ambient)	• Distance from source • Density of sources • General exhaust ventilation or dilution • Emission direction • Work area size • Work environment conditions • Air flow patterns
Receptor (worker)	• Personal protective equipment use • Training and health and safety awareness • Safety culture • Job title • Tasks, time, and frequency • Personal anthropometric features • Body orientation relative to and distance from point-source of emissions • Experience

For future exposure characterization and assessment of ENMs, a consistent approach to data collection is needed, including near-field, far-field/ambient, and outdoor measurements routinely collected before and after each sampling exercise as well as the collection of key auxiliary data (Tables 1–3). Measurements should routinely include particle size distribution and concentration data, as well as morphological and compositional analysis. Repeat sampling of the same tasks within and between organizations is also needed to understand variability in processes and exposures. Near real-time particle count data, both total and size-fractioned, should be summarized using statistical methods that account for the autocorrelation in these measurements and that utilize proper summary statistics (see, for example Pfefferkorn et al.[49] and Bello et al.[45]), rather than only showing simple time plots of exposure. Real-time data collected in conjunction with exposure factors may yield better explanatory and predictive models and offer opportunities for better utilization of current data for future epidemiological analysis and descriptions of exposure trends, as well as for more effectively targeting controls.[50] Since sample time can impact the variance of exposures, a common approach for selecting sampling times would aid in comparisons between studies. For example, when investigating continuous processes exposure data may best be summarized in intervals of 15, 30, or 60 minutes, whereas for intermittent peak exposures, data may best be summarized in intervals of just a few seconds or for the duration of the tasks. Internationally agreed-upon guidance documents or best practices would strengthen the utility and comparability of data and facilitate comparison of study results, thereby improving overall data quality and risk assessment decision-making.

Finally, Paik et al.[51] propose a control banding tool for working with ENMs as offering a simple and practical solution for controlling worker exposures. A clearer understanding of the macro-, mid-, and microlevel factors affecting ENM exposures will likely enable better characterization of exposure factors and control recommendations provided in such guidance tools. Understanding these factors could also improve exposure assessments for future epidemiological studies that will likely draw their study populations from numerous workplaces due to small workforce size at any given facility.

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