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StandardGuide for Handling Unbound Engineered Nanoscale Particles in Occupational Settings[1]

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INTRODUCTION

Nanometer-scale particles are encountered in nature and in industry in a variety of forms and materials. Engineered nanoscale particles as a class comprise a range of materials differing in shape, size, and chemical composition, and represent a broad range of physical and chemical properties. Workers within some nanotechnology-related industries and operations have the potential to be exposed to these engineered nanoscale particles at levels exceeding ambient nanoscale particle concentrations through inhalation, dermal contact and ingestion when not contained on or within a matrix (unbound). Occupational health risks associated with manufacturing, processing and handling unbound nanoscale particles, agglomerates or aggregates of nanoscale particles are not yet clearly understood. Dominant exposure routes, potential exposure levels and any material hazard are expected to vary widely among particular nanoscale particle materials and handling contexts. Additional research is needed to understand the impact of these exposures on employee health and how best to devise appropriate exposure monitoring and control strategies. Until clearer understandings emerge, the limited evidence available suggests caution when potential exposures to unbound engineered nanoscale particles (UNP) may occur.

1. Scope

1.1 This Guide describes actions that could be taken by the user to minimize human exposures to unbound, engineered nanoscale particles (UNP) in research, manufacturing, laboratory and other occupational settings where UNP may reasonably be expected to be present. It is intended to provide guidance for controlling such exposures as a cautionary measure where neither relevant exposure standards nor definitive hazard and exposure information exist.

1.2 *General Guidance*—This Guide is applicable to occupational settings where UNP may reasonably be expected to be present. Operations across those settings will vary widely in the particular aspects relevant to nanoscale particle exposure control. UNP represent a vast variety of physical and chemical characteristics (e.g., morphology, mass, dimension, chemical composition, settling velocities, surface area, surface chemistry) and circumstances of use. Given the range of physical and chemical characteristics presented by the various UNP, the diversity of occupational settings and the uneven empirical knowledge of and experience with handling UNP materials, the purpose of this Guide is to offer general guidance on exposure minimization approaches for UNP based upon a consensus of viewpoints, but not to establish a standard practice nor to recommend a definite course of action to follow in all cases.

1.2.1 Accordingly, not all aspects of this Guide may be relevant or applicable to all circumstances of UNP handling. The user should apply reasonable judgment in applying this Guide including consideration of the characteristics of the particular UNP involved, the user's engineering and other experience with the material, and the particular occupational settings where the user may apply this Guide. Users are encouraged to obtain the services of qualified professionals in applying this Guide.

1.2.2 *Applicable Where Relevant Exposure Standards Do Not Exist*—This Guide assumes that the user is aware of and in compliance with any authoritative occupational exposure standard applicable to the bulk form of the UNP. This Guide may be appropriate where such exposure standards do not exist, or where such standards exist, but were not developed with consideration of the nanoscale form of the material.

1.3 *Applicable Where Robust Risk Information Does Not Exist*—This Guide assumes the absence of scientifically sound risk assessment information relevant to the particular UNP involved. Where sound risk assessment information exists, or

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comes to exist, any exposure control measures should be designed based on that information, and not premised on this Guide. Such measures may be more or less stringent than those suggested by this Guide.

1.4 *Materials within Scope*—This Guide pertains to unbound engineered nanoscale particles or their respirable agglomerates or aggregates thereof. Relevant nanoscale particle types include, for example, intentionally produced fullerenes, nanotubes, nanowires, nanoropes, nanoribbons, quantum dots, nanoscale metal oxides, and other engineered nanoscale particles. Respirable particles are those having an aerodynamic equivalent diameter (AED) less than or equal to 10 µm (10 000 nm) or those particles small enough to be collected with a respirable sampler (**12**, **34**, **36**).[2] The AED describes the *behavior* of an airborne particle and is dependent upon the particle density, shape, and size—for instance, a particle with a spherical shape, smooth surface, density of 1.0 g/cc and a physical diameter of 4 µm would have an AED of 4 µm, whereas a particle with a spherical shape, smooth surface, density of 11.35 g/cc and a physical diameter of 4 µm would have an AED of 14 µm and would therefore be of a nonrespirable size. Respirable fibers are those having physical diameters less than or equal to 3 µm (3000 nm) or those fibers small enough to be collected with a thoracic sampler (**65**, **66**).

1.5 *Materials Beyond Scope:*

1.5.1 UNP may be present in various forms, such as powders or suspensions, or as agglomerates and aggregates of primary particles, or as particles dispersed in a matrix. This Guide does not pertain to UNP incapable, as a practical matter, from becoming airborne or be expected to generate or release UNP in occupational settings under the particular circumstances of use (e.g., UNPs dispersed or otherwise fixed within a solid, strongly bonded to a substrate or contained within a liquid matrix such as aggregated primary crystals of pigments in paints). This guide does not pertain to aggregates or agglomerates of UNP that are not of a respirable size.

1.5.2 This Guide does not pertain to materials that present nanoscale surface features, but do not contain UNPs (e.g., nanoscale lithography products, nanoelectronic structures or materials comprised of nanoscale layers).

1.5.3 This Guide does not pertain to UNPs which exist in nature which may be present in normal ambient atmospheres or are unintentionally produced by human activities, such as by combustion processes. Nor does it pertain to materials that have established exposure control programs (e.g. safe handling protocols for nanoscale biological agents) or published exposure limits such as occupational exposure limits for welding fumes.. See Appendix X1.

1.6 *Handling Considerations Beyond Scope*—The use of this Guide is limited to the scope set forth in this section. This Guide generally does not address actions related to potential environmental exposures, nor to exposures potentially arising at disposal or other end-uses.

1.7 *Not a Standard of Care*—This ASTM standard Guide does not necessarily represent the standard of care by which the adequacy of a set of exposure control measures should be judged; nor should this document be used without consideration of the particular materials and occupational circumstances to which it may be applied. The word "standard" in the title means only that the document has been approved through the ASTM consensus process.

1.8 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[3]

E2456 Terminology Relating to Nanotechnology

3. Terminology

3.1 *Definitions*—Refer to Terminology E2456 for definitions of terms used within this guide.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *aerodynamic equivalent diameter (AED), n*—the diameter of a smooth, unit density [$\rho_o = 1$ gram per cubic centimeter (g/cm^3)] sphere that has the same terminal settling velocity as the actual particle (**26**).

3.2.2 *agglomerate, n—in nanotechnology*, a group of particles held together by relatively weak forces (e.g., van der Waals or capillary.) and which may break apart into smaller particles upon processing.

3.2.3 *aggregate, n—in nanotechnology*, a discrete group of particles in which the various individual components are not easily broken apart, such as in the case of primary particles that are strongly bonded together (for example, fused, sintered, or metallically bonded particles).

3.2.4 *control principle, n*—the principle establishes in this guide that, as a cautionary measure, occupational exposures to unbound, engineered nanoscale particles (UNP) should be minimized to levels that are as low as is reasonably practicable.

3.2.5 *nanoscale, adj*—having one or more dimensions on the order of 1 to 100 nanometers.

3.2.6 *particle, n—in nanotechnology*, a small object that behaves as a whole unit in terms of transport and properties.

3.2.7 *program, n*—a management policy to minimize occupational UNP exposures together with the procedures and actions to meet that objective.

3.2.8 *respirable, adj*—airborne particles which are small enough to enter the alveolar (gas-exchange) region of the lung.

3.2.9 *inhalable, adj*—airborne particles which are small enough to enter the head airways through the nose and/or mouth during inhalation.

[2] The boldface numbers in parentheses refer to the list of references at the end of this standard.

[3] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

3.2.10 *should, aux., v—as used in this guide*, indicates that a provision is not mandatory but is recommended as a good practice.

3.2.11 *ultrafine particle, n*—a particle smaller than about 0.1 micrometer (100 nanometers) in diameter.

3.2.12 *unbound, adj—with reference to engineered nanoscale particles*, those nanoscale particles that are not contained within a matrix under normal temperature and pressure conditions that would reasonably be expected to prevent the particles from being separately mobile and a potential source of exposure. An engineered primary nanoscale particle dispersed and fixed within a polymer matrix, incapable as a practical matter of becoming airborne, would be "bound," while such a particle suspended as an aerosol would be "unbound".

3.3 *Acronyms:*

3.3.1 *HEPA*—high efficiency particulate air

3.3.2 *MSDS*—material safety data sheet(s)

3.3.3 *PPE*—personal protective equipment

3.3.4 *UNP*—unbound engineered nanoscale particles

4. Summary of Guide

4.1 This Guide presents the elements of an UNP handling and exposure minimization program including considerations and guidance, based on a consensus of viewpoints, for establishing such a program. The six principal elements are: *(a)* establishing management commitment to the control principle; *(b)* identifying and communicating potential hazards; *(c)* assessing potential UNP exposures within the worksite; *(d)* identifying and implementing engineering, and administrative controls consistent with the control principle for all relevant operations and activities; *(e)* documentation; and *(f)* periodically reviewing its adequacy.

4.2 *The Control Principle*—Exposure control guidance in this Guide is premised on the principle (established in this guide) that, as a cautionary measure, occupational exposures to UNP should be minimized to levels that are as low as is reasonably practicable. This principle does not refer to a specific numerical guideline, but to a management objective, adopted on a cautionary basis, to guide the user when *(a)* assessing the site-specific potential for such exposures; *(b)* establishing and implementing procedures to minimize such exposures; *(c)* designing facilities and manufacturing processes; and *(d)* providing resources to achieve the objective. Additional discussion of the application of the control principle is set forth in Annex A1.

5. Significance and Use

5.1 This Guide is intended for use by entities involved in the handling of UNP in occupational settings. The Guide covers handling principles and techniques that may be applied, as appropriate, to the variety of UNP materials and handling settings. These settings include research and development activities, material manufacturing, and material use and processing. The Guide may also be used by entities that receive materials or articles containing or comprising nanoscale particles fixed upon or within a matrix (i.e., bound nanoscale particles), but whose own processes or use may reasonably be expected to cause such particles to become unbound.

6. Establishing a Program to Implement the Control Principle

6.1 *Process for Establishing Program*—To attain the integrated effort needed to minimize UNP exposures consistent with the *control principle*, the user should develop a *program* that addresses the efforts in all management, planning and operational phases of the enterprise to be taken to achieve that objective. The principal topics of this Guide outline an iterative process typical of many occupational safety regimes the user of this Guide may adopt for the initial establishment and implementation of an effective *program* to minimize occupational UNP exposures.

6.2 *Management Commitment*—A formal, written management policy should be established committing to minimizing potential occupational UNP exposures to levels that are as low as is reasonably practicable. The policy and commitment should be regularly communicated throughout the organization and reflected in *(a)* written administrative procedures, instructions and training materials for operations and contingencies potentially involving occupational UNP exposures, *(b)* facilities design, and *(c)* instructions to designers, vendors and user personnel specifying or reviewing facility design, systems, operations or equipment.

6.3 *Organization of Personnel and Responsibilities*—Responsibility and authority for implementing a minimization program consistent with this Guide should be assigned to an individual with organizational freedom to ensure appropriate development and implementation of the *program*. This *program* manager would be responsible for coordinating efforts among the several functional groups (e.g., operations, housekeeping, maintenance, engineering, safety, human resources, sales, and shipping) that may be involved or impacted by the *program*, and should have the authority, or direct recourse to an authority, to timely resolve questions related to the conduct of the *program*. The *program* manager should be knowledgeable, or adequately supported by persons who are knowledgeable, concerning the characteristics of the UNP involved, all aspects of the organization's processes and worker activities involving UNP, relevant engineering exposure control methods, and the organization's best information concerning the potential occupational safety and health risks of relevant UNP exposure.

6.3.1 Responsibilities of the *program* manager should include to *(a)* establish and maintain a *program* that implements the management commitment to the control principle, including specific goals and objectives; *(b)* ensure the development of appropriate procedures and practices by which the specific goals and objectives will be met; *(c)* ensure the resources needed to achieve the goals and objectives are made available as deemed appropriate; *(d)* regularly communicate progress and status information to the user's management.

6.3.2 Responsibilities of all supervisory personnel should include to *(a)* communicate the management commitment to the control principle to user personnel at all levels; *(b)* ensure that the persons within their respective areas of supervisory responsibility have received requisite training in the *program*;

(c) ensure support from personnel for attaining exposure minimization objectives, including compliance with applicable work rules related to the *program* ; *(d)* ensure personnel and facilities are properly equipped consistent with *program* requirements; *(e)* participate in design and process reviews and development of procedures in connection with the *program* to the extent affecting or involving their areas of supervisory responsibility; and *(f)* support the *program* manager in formulating and implementing the *program*.

6.4 *Training and Supervision*—The *program* should include instructing all personnel (including contractor personnel) whose duties may involve potential exposure to UNP, or who direct the activities of others whose duties may involve potential exposure to UNP. Personnel who do not ordinarily enter work areas containing UNP may also require limited instruction in the user's workplace exposure minimization *program* (e.g., to respect any access restrictions or personal protective equipment requirements). Personnel should receive initial training and periodic refresher training.

6.4.1 Training should emphasize the importance of UNP exposure minimization as a management objective. The training should be commensurate with duties and responsibilities of those receiving the instruction, as well as the magnitude of the potential exposure that might reasonably be expected. Training should include instruction on relevant hazard information, instruction on the exposure minimization work rules, work practices, operating procedures and emergency response procedures developed and implemented at the facility. Copies of these rules and procedures should be available to those receiving instruction.

6.4.2 Personnel (including contractor personnel) who direct the activities of others should have the authority and responsibility to implement the *program*. During operations in UNP work areas, adequate supervision should be provided to ensure that appropriate procedures are followed, that planned precautions are observed, and that all potential exposure circumstances that develop or are recognized during operations or incidents are addressed in a timely and appropriate manner.

6.5 *Documentation of Program*—The user's *program* should be recorded in a written form and should contain sections that address each of the principal topics presented in this Guide.

6.5.1 The objectives for preparing and maintaining such documentation should be to *(a)* record the management commitment to the *control principle*; *(b)* provide an ongoing means to demonstrate to user management that the *control principle* is being applied; *(c)* provide the basis for efficient and informed future periodic evaluations of the potential need to amend the *program* by documenting the practicable engineering and administrative controls adopted and the rationale for their selection among other options; and *(d)* serve as a training and operational reference for the various user personnel responsible for implementing aspects of the *program*.

6.5.2 The extent and form(s) of the documentation should be tailored to the user's individual circumstances consistent with *(a)* meeting the foregoing documentation objectives; *(b)* practical utility; *(c)* updating the documentation over time; and *(d)* the scale and extent of the user's relevant operations. Depending on the user's individual circumstance, documentation to be prepared, maintained and updated (as applicable) may include:

6.5.2.1 Allocation of organizational responsibilities for the *program*;

6.5.2.2 Material characterization and safety information (including underlying basis documentation where the user developed the data or analysis);

6.5.2.3 Documentation of qualitative and/or quantitative exposure assessments, risk assessments and hazard analysis;

6.5.2.4 Relevant engineering and other analyses supporting selection of equipment and operating parameters, including the manufacturer's performance and other specifications for such equipment and alternatives considered;

6.5.2.5 Work rules, work practices, standard operating procedures, policies, and response plans adopted to implement the control principle;

6.5.2.6 Employee training materials and initial and refresher training schedules;

6.5.2.7 Schedules and procedures for periodic substantive review and modification of the program as appropriate, updating program documentation, and reporting results; and

6.5.2.8 Equipment maintenance, certification and calibration schedules.

6.6 *Periodic Review of Program*—At least annually the *program* should be reviewed to ensure that the *program* design, scope and implementation continue to be effective in meeting the management objective of the *control principle*. Amendments to the *program* should be based on the results of any more current empirical research in relevant disciplines (e.g., toxicology, epidemiology, exposure measurement, and exposure control and prevention), the development or amendment of relevant and authoritative occupational exposure limits and test methods, changes in workplace processes or personnel, the results of workplace monitoring, lessons learned from any unplanned exposure or potential exposure incidents (e.g., accidental spills, releases), the results of any medical surveillance, any worker observations or complaints relevant to the program and the results of any new job hazard or process safety analyses.

6.6.1 Additional program reviews of relevant scope should be conducted in connection with any proposed process changes potentially impacting UNP exposure control, and indicated by the results of incident or accident follow-up investigation such as failure analysis in relation to any unplanned UNP exposure or potential exposure incidents.

6.6.2 The results of *program* reviews should be documented and any amendments to the *program* determined to be warranted should be implemented in a reasonable time frame in view of the circumstances. Any changes to one aspect of the *program* should be carried through to other relevant components (e.g., training, material safety data sheets or other documentation, and monitoring protocols).

7. Hazard Assessment and Evaluation

NOTE 1—The user should assess the UNP material anticipated to be present in the workplace to identify, to the extent practicable, any physical or health hazards the UNP may present in the event of acute or chronic exposure based upon review of either *(a)* any material safety data sheets provided by the supplier or *(b)* the available, statistically significant, scientific evidence from studies conducted in accordance with established scientific principles and that are otherwise relevant and reliable indicators of hazard. The assessment should evaluate the UNP in the condition or form in which it would be expected to be found in the workplace (e.g., dispersed individual particles or as aggregates/agglomerates of primary particles). Where no substance-specific data are available, a qualitative assessment should be made based upon reliable data (as above) and authoritative standards for analogous materials (bulk or nanoscale) as an indication of potential hazards. The method and results of the assessment, even if indeterminate, should be documented.

7.1 *Scientific Uncertainty Concerning Most Significant Characteristics for Assessing Hazard Potential:*

7.1.1 There is little consensus for the relative significance of the physical and chemical characteristics of UNP as an indicator of toxicity. However, current research indicates that particle size, surface area, and surface chemistry (or activity) may be more important metrics than mass and bulk chemistry (**1**).

7.1.2 A number of sources have indicated physical and chemical characteristics that may have important health implications (**28, 52-55**). The toxicity and health risk may be a factor of the following properties, all or some of which may be significant, or not, and whereby some properties may enhance the overall toxicity:

7.1.2.1 Size and size distribution;

7.1.2.2 Shape (e.g., fiber diameter, length, and aspect ratios for individual nanotubes and bundles/ropes);

7.1.2.3 Agglomeration state;

7.1.2.4 Biopersistence/durability/solubility;

7.1.2.5 Surface area: "biologically available surface area," "specific surface area," "external (geometric surface area)," and "internal (if material is porous)." Microporous or mesoporous powders exhibit much higher surface areas than nonporous powders;

7.1.2.6 Porosity;

7.1.2.7 Surface chemistry: "surface composition," "surface energy/wettability," "surface charge," "surface reactivity," "adsorbed species," and "surface contamination";

7.1.2.8 Trace impurities/contaminants (e.g., metal catalysts, polycyclic aromatic hydrocarbons, etc.);

7.1.2.9 "Chemical composition, including spatially averaged (bulk) and spatially resolved heterogeneous composition";

7.1.2.10 Physical properties (e.g., density, conductivity, etc.); and

7.1.2.11 Crystal structure/crystallinity.

7.2 *Occupational Exposure Limits*—Currently, there are no published regulatory occupational exposure limits (OEL) for airborne exposures specific to UNP as a general class of particulates. Occupational exposure limits do exist for nuisance particles (insoluble or poorly soluble) not otherwise classified and may exist for particles of similar physical and chemical composition to the UNP of interest. Refs (**10-13, 38, 47**) identify sources of exposure limits for airborne contaminants that may be considered in selecting target exposure limits for comparative UNP materials. It is essential that the documentation used to derive such values be consulted, since the nanoscale form may have not been considered in its development, and therefore such limits may not be relevant or adequate for poorly-soluble or insoluble nanoscale particles.

7.2.1 *Interim Occupational Exposure Limits*—In the absence of definitive occupational exposure limits, it is prudent to control exposures to "as low as is reasonably practicable." The following are examples of interim occupational exposure limits that one might consider to evaluate the effectiveness of UNP exposure controls. These are provided as examples, only, and professional judgment must be exercised as to the appropriateness of such interim limits for the specific UNP in question.

7.2.1.1 *General:*

(1) ACGIH believes that all particles (insoluble or poorly soluble) not otherwise specified (PNOS) should be kept below 3 mg/m^3, respirable particles, and 10 mg/m^3, inhalable particles, until such time as a TLV is set for a particular substance (**12**). These recommendations apply only to particles that *(a)* Do not have an applicable TLV, *(b)* Are insoluble or poorly soluble in water (or, preferably, in aqueous lung fluid if data are available); and *(c)* Have low toxicity (i.e., are not cytotoxic, genotoxic, or otherwise chemically reactive with lung tissue, and do not emit ionizing radiation, cause immune sensitization, or cause toxic effects other than by inflammation or the mechanism of "lung overload." It is important to note that the ACGIH PNOS exposure limits were not based on nanoscale materials and are not likely to be appropriate to apply to nanoscale particles as a general rule.

(2) The U.S. Environmental Protection Agency (EPA) has set National Ambient Air Quality Standards for particle pollution (**72**). Scientific studies have found an association between exposure to particulate matter and significant health problems, including: aggravated asthma; chronic bronchitis; reduced lung function; irregular heartbeat; heart attack; and premature death in people with heart or lung diseases. These outdoor air pollution standards were set to protect public health, including the health of "sensitive" populations such as asthmatics, children, and the elderly. Though not intended for application in occupational environments, such limits may still be useful in assessing exposures in occupational settings. The limitations of using these values include *(1)* the physical-chemical composition of outdoor air pollution is likely to be different than with engineered nanoscale particles, *(2)* those employed in the workplace are generally considered a less sensitive population, *(3)* the averaging times for the EPA standards are based on either 24-hour or annual averaging times, whereas averaging times in the workplace are usually 8-hours per day, 5-days per week. Therefore, even if the physico-chemical composition was similar, an argument could be made that these values should be adjusted for application in an occupational environment. For fine particles, otherwise known as $PM_{2.5}$ (particulate matter of 2.5 µm in aerodynamic diameter and smaller), the EPA standard is 35 µg/m^3 (0.035 mg/m^3) as a 24-hour average, and 15.0 µg/m^3 (0.015 mg/m^3) as an annual arithmetic mean. A $PM_{2.5}$ air sampler collects particulate matter that can penetrate into the deep part of the lung referred to as the pulmonary region (alveolar region where gas exchange takes place). Sources of fine particles in outdoor air pollution include forest fires; diesel and gasoline engines; high-temperature industrial

processes, such as smelters and steel mills. For PM_{10} (particulate matter of 10 µm in aerodynamic diameter and smaller), the EPA standard is 150 µg/m^3 (0.150 mg/m^3) as a 24-hour average. A PM_{10} air sampler collects particulate matter than could penetrate into either the upper part of the lung referred to as the tracheobronchial region (conducting airways of the lung) or into the deep part of the lung (pulmonary region).

7.2.1.2 *Titanium Dioxide*—There are occupational exposure limits for titanium dioxide, but they do not currently distinguish between nanoscale and larger particles. The 2006 ACGIH 8-hour TWA for titanium dioxide is 10 mg/m^3, as "total" dust. Because nanoscale titanium dioxide is more potent (due to increased surface area) than larger sized titanium dioxide, NIOSH has proposed a 10-hour TWA of 0.1 mg/m^3 for ultrafine titanium dioxide (**40**). However, findings by Warheit et al. on nanoscale titanium dioxide rods and dots run counter to the postulation that, because of increased surface area, nanoscale titanium dioxide will always have increased toxicity compared to larger sized particles of similar composition (**69**). Additionally, crystalline structure may make a difference in toxicity. For instance, anatase nano titanium dioxide was found to be 100-times more cytotoxic than rutile nano titanium dioxide leading Sayes et al. (**68**) to conclude that size as a parameter was far less important than the crystal phase composition of titanium dioxide. Warheit et al. indicates that it remains to be determined whether similar results reported by Sayes et al. will be measured under in vivo conditions (**69**).

7.2.1.3 *Carbon Nanotubes (CNT)*—The 2006 ACGIH 8-hour TLV-TWA for carbon black is 3.5 mg/m^3, as "total' dust. Carbon black is composed of disordered graphite sheets and differs from the continuous graphitic sheet nature of the nanotube surface. The 2006 ACGIH 8-hour TLV-TWA for respirable graphite (all forms except graphite fibers) is 2 mg/m^3. The appropriateness of applying the carbon black or graphite occupational exposure limits for carbon nanotubes has been questioned (**49, 50, 52**). With regard to carbon nanotubes, occupational exposure limits for mass, number, and surface area might be considered. There may also be trace contaminants that may be present and the specific occupational exposure limits for these contaminants may need to be considered, as well.

(1) Mass—Some forms of Single Wall Carbon Nanotubes (SWCNT) have been found to be as toxic as quartz on a mass basis (**49, 50**), which have lead some to recommend applying occupational exposure limits for crystalline silica (e.g., quartz), at least in the interim, until SWCNTs are further characterized (**49, 50**); therefore, for at least some forms of SWCNT, the 8-hour time-weighted occupational exposure limit of 25 ug/m^3 (i.e., the ACGIH 2006 TLV-TWA for respirable crystalline silica) may be more appropriate than a respirable synthetic graphite OSHA PEL-TWA of 5000 ug/m^3 or 2006 ACGIH TLV-TWA of 2000 ug/m^3. However, applying the quartz exposure limit measure for SWCNT may not necessarily be appropriate in all instances, because the toxicity may vary depending on various factors (e.g., agglomeration state, functionalization, trace impurities/contaminants, etc.).

(2) Number—Donaldson et al. cites a study that demonstrated that Multi Walled Carbon NanoTubes (MWCNT)s were highly fibrogenic and inflammogenic, being roughly equivalent to a chrysotile asbestos control and recommended that until better information becomes available, that they should be considered in the same way other biopersistent fibers in workplace risk assessments, using similar assessment approaches (e.g., fiber counts) (**52**). However, this approach may be questionable and difficult given that carbon nanotubes agglomerate and mechanically entangle into complex structures/clumps. The 2006 ACGIH 8-hour TLV-TWA for respirable chrysotile fibers is 0.1 fibers per cubic centimeter; 0.2 f/cc for respirable refractory ceramic fibers; and 1 f/cc for glass wool fibers. Some organizations apply an 8-hour TWA occupational exposure limit of 1 f/cc for respirable carbon fibers; however, CNTs are distinct from carbon fibers, which are not single molecules but strands of layered graphite sheets.

(3) Surface Area—Donaldson et al. indicates that CNT number concentration, alone, may not be a suitable metric, and that a surface area metric might be more appropriate (**52**).

(4) Trace Contaminants—Trace contaminants may include organics (such as carbon black and polycyclic hydrocarbons) and metals. Cobalt, iron, nickel, and molybdenum are the most commonly used metals in CNT synthesis (**52**). The ACGIH has established occupational exposure limits for these metals based upon either the inhalable fraction, the respirable fraction, or as "total dust" (**12**). It is conceivable that, in the future, the ACGIH may have exposure limits for some metals that are based upon the thoracic deposition fraction.

8. Exposure Assessment and Exposure Risk Evaluation

NOTE 2—The specific elements of an exposure minimization program (e.g., engineering and administrative controls, work practices and any personal protective equipment) should be determined based upon the assessment of the potential UNP physical or health hazards outlined in Section 7 of this Guide, and the assessment of potential occupational exposure outlined in Section 8.

8.1 *Potential UNP Exposure Routes*—As with other particles, workers may potentially be exposed to UNP by way of inhalation, ingestion, injection and dermal contact (including eyes and mucus membranes).

8.1.1 The most common route of exposure to UNP in the workplace is anticipated to be by inhalation.

8.1.2 Ingestion can occur from unintentional hand to mouth transfer of materials; ingestion may also accompany inhalation exposure because particles that are cleared from the respiratory tract may be swallowed.

8.1.3 Some studies suggest that UNP could also enter the body through the skin or eyes during occupational exposure. Research is ongoing to determine whether this is a viable exposure route for UNP (**1**).

8.2 The nature and extent of any UNP exposure will be dependent on the physical characteristics of the material.

8.2.1 *Solids*—Handling of solid materials (e.g., nanocomposites) where UNP are bound on or within a solid matrix should pose no risk of exposure during normal handling; however, machining, or combustion of such materials may or may not generate UNP. Like deposition of other types of ultrafine airborne particles, nanoscale particle agglomerates greater than 500 nm in diameter are deposited in the respiratory tract according to their aerodynamic equivalent diameter (AED) (**22**), which is a function of the particle density, shape, and diameter (**26**). Diffusion is the predominant deposition mechanism in the respiratory tract for UNP and nanoscale particle agglomerates < 500 nm in diameter and is governed by geometric physical diameter rather than AED (**22**). The dustier (ability to become airborne) the material, the more it is likely to become aerosolized and become inhaled, inadvertently ingested, or for there to be contact with the skin, eyes, and mucous membranes.

8.2.2 *Liquids*—UNP suspended in liquids may pose potential exposure risks, including inhalation, ingestion or skin absorption if suspensions are either physically contacted (skin, eye, or mucous membrane) or if the suspensions are aerosolized and subsequently inhaled.

8.3 *Inventory of Potential Exposure Locations*—The exposure assessment should begin with assembling a complete inventory of work processes and activities where the potential for exposure to UNP may reasonably be expected to exist. Relevant activities at a facility may include material receipt and unpacking; all manufacturing and finishing processes; lab operations; storage, packaging and shipping; waste management activities; maintenance and housekeeping activities; reasonably foreseeable upset circumstances; and other movements of goods and employees in and out of UNP work areas. Annex A2 provides additional guidance for identifying specific processes and operations that may be a source of UNP and may present a risk of occupational exposure by inhalation, ingestion, and/or dermal penetration.

8.4 *Qualitative Exposure Assessments*—A qualitative assessment of the potential for direct and indirect occupational exposure to UNP should be made for all phases of each activity identified in the inventory. The assessment should include full consideration of the properties of the UNP material at the different process locations, the quantity of material present in each process, the design and performance characteristics of relevant process equipment, any existing engineering controls, and the effect of any existing administrative exposure controls. The method and results of the assessment should be documented. Appendix X2 provides additional guidance for assessing UNP exposure risk.

8.4.1 For new operations, exposure assessments are ideally performed at the pre-design stage so that facilities and process may be designed and constructed to present an inherently low risk of UNP exposure. Assessments should be repeated prior to the start-up of a new task or operation, prior to the re-start of a task or operation following a change, periodically even in the absence of changes in accordance with section 6.6 of this Guide, and any other circumstances where the exposure potential needs to be confirmed or reestablished.

8.5 *Quantitative Exposure Assessments:*

8.5.1 Quantitative UNP exposure measurements may be useful for a variety of occupational health and system safety purposes including *(a)* evaluating UNP metrics against standards for analogous materials, *(b)* qualitatively assessing the effectiveness of containment controls, work practices, or the effect of changes to processes or controls; *(c)* identifying sources, patterns and direction of releases, distributions of exposure, *(d)* and estimating exposure levels as a function of process.

8.5.2 *Technical Constraints*—Quantitative and qualitative assessment of potential UNP exposure in occupational setting presents a number of technical challenges. In general there is no consensus regarding: *(a)* the relative importance of the different exposure metrics that might be used; *(b)* the best way to characterize and differentiate exposures against available metrics; or *(c)* the best measurement techniques to monitor exposures in the workplace. Depending on the metric selected, background concentrations of non-target nanoscale particles may significantly interfere with obtaining relevant and meaningful results, and it may not be possible to control for this interference. The direct and indirect sampling and analysis techniques and the commercially available instruments for measuring airborne nanoaerosols vary widely in complexity, accuracy and selectivity depending on the metric to be assessed.

8.5.3 Appendix X2 and Refs (**1**, **29**, **41-43**, **59-61**, **71**) provide additional guidance for employee and workplace UNP aerosol exposure assessments.

8.6 *Exposure Assessment for Materials and Devices Containing Bound Engineered Nanoscale Particles:*

8.6.1 Devices, such as integrated circuits, that contain bound, engineered nanoscale particles or nanoscale features pose a minimal risk of releasing UNP during handling. Likewise, large-scale composite articles which contain nanoscale particles typically do not present significant exposure potential as the nanoscale particles are bound within the matrix of the composite. Absent reason to believe that these materials shed UNP at the exposed surfaces no precautionary measures are warranted.

8.6.2 The risk of UNP exposure from handling or processing materials containing nanoscale particles is greater, however, if the composite matrix is subject to disintegration in the course of foreseeable use or handling (e.g., the matrix is brittle or disintegrates), or if the materials or devices are otherwise used or handled in such a manner that that they may generate UNP (e.g., machining, saw cutting, drilling, or grinding). The user should evaluate the use of materials containing nanoscale particles for their potential to release UNP in the course of reasonably foreseeable use and handling. This evaluation should be based on information provided by the supplier or manufacturer and the user's circumstances of use or processing of the nanoscale particle containing material. If the result of the assessment indicates a significant risk that UNP may be generated or released, then the user should establish work practices to minimize UNP exposure consistent with the scale of the relevant operations and this Guide.

9. Exposure Minimization Methods

9.1 *Generally*—This section of the Guide provides information and guidance concerning a variety of exposure control methods potentially available to the user. Not all of the noted control methods will be relevant or necessary to meet control objectives at a given facility. See section 1.2. References (**1**) and (**59**) provide additional guidance regarding exposure minimization methods.

9.2 *Types of Controls*—Occupational exposure control methods can be generally grouped as one of three types: *(a)* engineering controls (e.g., process modification to eliminate toxic material usage, closed manufacturing systems, ventilation systems, and work area enclosures.), *(b)* administrative controls (e.g., work practices and rules to prevent circumstances of potential exposure) and *(c)* personal protective equipment (e.g., gloves, protective clothing and respirators). Engineering controls are the preferred method of control. Personal Protective Equipment should be used when practicable engineering and administrative controls do not sufficiently minimize exposure.

9.3 *Engineering Controls*—For most processes and job tasks, the control of airborne exposure to UNP can be accomplished using a wide variety of engineering control techniques similar to those used in reducing exposures to more common airborne particulates, gases, and/or vapors. Based on what is known of nanoscale particle motion and behavior in air, control techniques such as source enclosure (i.e., isolating the generation source from the worker) and local exhaust ventilation systems should be effective for capturing and containing airborne UNP. Engineering controls eliminate or reduce exposure by the use of machinery or equipment. General examples from industry include ventilation systems, process enclosures, sealed process piping, robotic applications of hazardous materials, interlocks and machine guards.

9.3.1 *Isolation*—Employees may be isolated from hazardous operations, processes, equipment, or environments by distance, by physical separation, barriers, control rooms, isolation booths, and by capture ventilation. UNP contained within closed systems or containers present minimal risk of exposure. Most UNP synthesis, product recovery, processing, transfer and other handling activities can be designed to occur within totally enclosed process equipment. All UNP handling systems should be designed to operate in an enclosed manner to the extent reasonably practicable (e.g., sealed reactor vessels, closed storage containers or vessels, pumps enclosures, valve isolation, glove boxes (**30**, **31**) may be practicable for some operations).

9.3.2 *Fixation Strategies*—Processing UNP in solutions verses handling dry powders may help reduce UNP exposures during handling and processing activities. Processes may be designed to collect nanoscale particles in well-adapted liquids or dust suppression mists to minimize particle releases may be utilized.

9.3.3 *Waste Minimization Strategies*—Processes may be designed and optimized to minimize the quantity of UNP-containing waste generated.

9.3.4 *Ventilation Strategies:*

9.3.4.1 Removing UNP from workplace air by well engineered ventilation systems is an effective and important method for minimizing the potential for inhalation of UNP. Ventilation systems should be designed, tested, and maintained using applicable guidance (e.g., Refs (**8**, **9**, **30**, **31**, **62**)). Current scientific knowledge regarding the generation, transport, and capture of aerosols suggests that capture ventilation control techniques should be effective for controlling airborne exposures to UNP (**1**).

9.3.4.2 Ventilation control systems that capture emissions at or very near the source (local exhaust ventilation) exist in a variety of designs that are applicable to most occupational circumstances. Local exhaust ventilation systems include *(a)* total enclosures, such as a glovebox; *(b)* partial enclosure hoods, such as laboratory chemical hoods, low-flow vented compounding pharmacist workstations, or low-flow vented balances; *(c)* weigh hoods for dry materials; and *(d)* exterior hoods, which are located adjacent to particle source areas but do not enclose them, such as a receiving hood which catches particles that rise or are thrown into them, and draft hoods, which draw in particles. When using local ventilation to manipulate dry powders, consideration should be given as to avoiding excessive air velocities across the powders that may generate aerosols unintentionally. Preventing inadvertent aerosolization of dry powders may require the use of low-velocity laboratory chemical hoods, cabinets, balance enclosures, gloveboxes, etc. Enclosures and glovebags may also be useful inside higher-velocity hoods in that they will isolate/shield the powder from the high velocities inside the hood.

9.3.4.3 Facility comfort heating, ventilation and air conditioning systems (HVAC) for UNP work areas, including make-up and exhaust air, should be designed, installed and maintained so that UNP do not migrate from production areas to adjacent workspaces. Clean room work areas, if used for UNP containment, should be at a negative pressure differential relative to the surrounding work areas to prevent introduction of UNP in to the surrounding areas.

9.3.4.4 Filters, traps, baffles, and clean-outs or other containment and control technologies should be used to prevent buildup of UNP within ventilation exhaust systems. HEPA filters are an effective filter medium for nanoscale particulates. Safe change systems (i.e. ability to change out exhaust system filters without release of UNP into work environment) may be used where filtration is installed in equipment or ventilation systems.

9.4 *Administrative Controls:*

9.4.1 *General Administrative Controls*—Administrative controls are work practices and operating procedures established to, directly or indirectly, avoid or reduce occupational exposures to substances of concern. Examples from general industry include safety policies, rules, supervision, and training. Administrative controls can form an important supplement to engineering controls. This section of the Guide provides information and guidance concerning a variety of administrative control methods available to the user.

9.4.2 *Administrative, Housekeeping Controls to Minimize UNP Aerosolization*—Work practices in all phases of operations should include measures to minimize accumulation of UNP-containing dusts (surface contamination) and to minimize any re-aerosolization of settled UNP or UNP agglomerates through effective housekeeping techniques. Corresponding administrative housekeeping controls may include:

9.4.2.1 Vacuuming in UNP work areas with only HEPA-filtered vacuum equipment and systems. Non-HEPA filtered vacuums may release and aerosolize UNP and increase airborne concentrations of UNP. The use of portable vacuums within UNP work areas should be evaluated to ensure the vacuum exhaust does not aerosolize UNP materials adjacent to the vacuum unit itself.

9.4.2.2 Prohibition of dry mopping, sweeping, dusting and other dry cleaning methods.

9.4.2.3 Prohibition of cleaning using compressed air or blow downs of work areas using portable blowers or fans.

9.4.2.4 Use of surfactants with wet drilling or cutting methods and maintaining good process controls to prevent dust generation.

9.4.2.5 Prohibition of the accumulation of dusts on equipment in UNP work areas and requiring regular and frequent removal of such dusts (e.g., daily);

9.4.2.6 Requiring UNP work area surfaces, equipment and furniture to be constructed of smooth, non-porous material that will allow easy cleaning (e.g., no fabrics or rough surfaces).

9.4.3 *Administrative Controls to minimize Inadvertent Exposure and Unintended Removal of UNP From Work Areas*—Administrative controls to minimize inadvertent ingestion or removal of UNP may include:

9.4.3.1 Prohibiting eating, drinking, smoking, or applying cosmetics in UNP work areas;

9.4.3.2 Requiring hand washing and other good hygiene practices prior to leaving UNP work areas or the work site; and

9.4.3.3 Limiting access to UNP work areas to those persons with an operational need to be present.

9.4.4 *Administrative Controls To Assure Process Integrity (Process Safety)*—Process safety measures may be important to assure that engineering controls (and associated processes) operate as intended, and do not result in exposures from unanticipated releases of UNP to the worksite. Both experimental (pilot) and production units should reflect proper planning and design. Process flow diagrams, instrument and piping diagrams, even for batch units, should be made. Process safety administrative controls should include:

9.4.4.1 Before start-up, preparing written operating procedures that have been reviewed and approved by all relevant departments;

9.4.4.2 For both pilot and production units, identifying and installing the instrumentation necessary to maintain good process control, including at least a simple control scheme on all independent process variables that can be directly measured, and provide adequate safety condition monitoring and shut down processes to identify and safely shut down systems that may generate release of UNP in the event hazardous/upset operating conditions are detected;

9.4.4.3 Evaluating production and processing practices to identify any flammable or explosive conditions during operations or maintenance activities, and installation of appropriate engineering controls to control any identified fire or explosion risks. Nanoscale combustible material may present a higher risk of explosion or fire than coarser material of similar composition and quantity (**1**). Explosion risk can increase significantly for some metals as particle size decreases (**1**). It is possible that relatively inert materials may become highly combustible when in the nanoscale (**1**).

9.4.4.4 Conducting appropriate pressure testing before pressurized processes are initiated;

9.4.4.5 Conducting regular and timely inspection of process, manufacturing, operational and exposure control equipment and ancillary systems (including ventilation and filtration equipment), and regular and timely preventative and corrective maintenance and repair of such equipment. The frequency and extent of the maintenance program and schedule of service should be greater for those operations with greater potential for physical harm and occupational exposure;

9.4.4.6 Evaluating the effect, if any, on ventilation and other engineering control system performance resulting from each facility or operational change;

9.4.4.7 Establishing equipment lock-out procedures for work on equipment, electrical circuits, or piping that may, directly or indirectly, result in loss of UNP containment or control;

9.4.4.8 Providing sufficient operational training to those personnel who operate systems or perform other operational or maintenance tasks with the potential to result in loss of UNP containment or control if performed improperly;

9.4.4.9 Establishing procedures to assure continuous good process control, such as establishing and testing safe operating envelopes; and

9.4.4.10 Periodically evaluating the ventilation and other engineering controls to ensure they are operating and functioning as designed.

9.4.5 *Medical Surveillance*—For guidance on medical surveillance of UNP workers consult the NIOSH Nanotechnology homepage (**48**).

9.4.5.1 Whether a medical surveillance program is warranted is a management decision to be made in consideration of a number of factors including; whether there is good reason to believe that adverse health effects may occur as a result of the contemplated exposure; the invasiveness of the surveillance procedures, the benefits, risks and costs of the surveillance method; and the utility of the information reasonably expected to be generated by the surveillance program.

9.4.5.2 Any medical surveillance program should be developed and implemented only with medical, industrial hygiene and legal professional consultation, and under the direction of a physician experienced in medical surveillance programs with a high level understanding of the available information concerning the UNP and potential exposure circumstances.

10. Exposure Minimization and Handling in Particular Occupational Settings

NOTE 3—This section describes actions that could be taken by the user to minimize occupational UNP exposures in particular occupational settings where UNP may reasonably be expected to be present. These actions are intended to supplement the general exposure controls guidance in Section 9. Not all of the noted actions and considerations will be relevant or necessary to meet control objectives at a given facility. See section 1.2.

10.1 *Manufacturing*—Gas phase processes have the potential to cause exposure to primary UNP during the synthesis stage of nanomaterials. All process phases (liquid, solid, gas) may give rise to exposure to agglomerated UNP during recovery, handling, and product processing. The probability and potential exposure level will differ according to the specific processes and the stages of the process. The optimum strategy to control employee exposures and the efficacy of the control methods utilized will likewise differ depending on the specific process and phase matrix. Annex A2, Table A2.1 summarizes the potential pathways of exposure in nanoscale particle production and recovery.

10.2 *Laboratory Operations*—The general guidance provided elsewhere in this Guide is applicable to laboratory occupational settings. Good laboratory safety practices should be employed when handling UNP in research and development or other laboratories. Appropriate guidance for UNP may be found in or supplemented by a laboratory Chemical Hygiene Plan Refs (**2-4**, **30**, **31**, **63**) are sources of general laboratory safety guidance.

10.2.1 Where there is a potential for exposure to the body, effective protective lab clothing should be worn within the work area if not already addressed by personal protective equipment to minimize street clothing contamination. Care should be exercised during donning and doffing of protective lab clothing to prevent aerosolization of UNP. Outer personal protective clothing when worn for contamination control should not be worn outside the work area.

10.3 *Maintenance, Housekeeping, Commissioning, Decommissioning and Non Routine Activities:*

10.3.1 Housekeeping, maintenance and repair, commissioning, decommissioning, demolition and non routine activities are likely to present a greater risk of exposure to UNP than normal manufacturing or other routine process operations, and may warrant particular focus and exposure risk evaluation. Based upon this evaluation, operating procedures to minimize UNP exposures during these types of activities should be developed. Personnel who have the responsibilities to perform these types of activities (which may include operations personnel) should be trained in those procedures. Engineering and administrative control strategies to minimize or prevent exposure during these operations may include:

10.3.1.1 HEPA filtration systems with safe-change systems (i.e., containment of filters and/or bags during removal or replacement);

10.3.1.2 Negative air enclosures designed to minimize dispersal of UNP from UNP worksite areas to other areas, with consideration given for a waste load-out area, such as a two-chamber air lock, to inhibit the release of UNP into other areas;

10.3.1.3 Maintenance and housekeeping activities should be performed in such a manner as to minimize the number of persons potentially exposed during non-routine operations;

10.3.1.4 Decontaminating equipment (instruments, piping, duct work, HVAC units, process units and other miscellaneous facilities) that may have been contaminated with visible or suspected UNP prior to repair or removal from UNP work areas. Use of Clean In Place (CIP) technologies may be used to eliminate the opening of process vessels and reduce the potential for UNP releases during cleaning operations. Marking decontaminated equipment as "clean" (e.g., by identification tags or other practicable marking) after decontamination is complete will aid in properly identifying equipment that has been decontaminated. This is especially prudent when UNP contamination may not be visible.

10.3.1.5 Developing written housekeeping procedures that specify cleanliness standards and the frequency and method of cleaning, based on the assessed need to minimize aerosolization and migration of UNP within the worksite.

10.3.1.6 Requiring all surfaces where UNP may have settled to be maintained as free as practicable of any accumulation of visible dust or waste, including prompt collection and containment of all spills, scrap, debris and waste that may contain or be a source of UNP exposure; and

10.3.1.7 Establishing procedures for appropriate design, integrity, and construction of containers potentially containing UNP waste or residuals, to ensure those containers do not react with, deteriorate, or spill UNP waste under normal handling and conditions.

10.3.2 Minimization of maintenance activities by task planning (identification of required tools, replacement parts etc) may help reduce exposure time by shortening maintenance times.

10.4 *Transferring Material Between Containers and Processes*—The potential for exposure to UNP exists whenever closed vessels or containers containing UNP are open to the atmosphere, repacked, or UNP are added or removed from the container. Examples of potential UNP release operations during transfer operations include, for example, transfers from enclosed manufacturing equipment to subsequent processing equipment or storage containers or from storage containers to transportation containers or opening of containers containing UNP or product packaging. The extent of UNP release and potential exposures will depend on the properties of the particular UNP-containing material, the transfer method used and the engineering and administrative controls employed. Engineering, work practice, and administrative controls should be developed to minimize any release of UNP to the worksite ambient air for all operations where UNP will be transferred. Established material transfer techniques used in analogous small particle production or processing industries (e.g., fumed material or carbon black) may provide useful guidance for safe handling, spill control, and decontamination processes.

10.4.1 Processes should be designed to minimize the number of necessary transfers between containers and other equipment.

10.4.2 Vacuum conveyance is preferred method for transferring UNP from one vessel to another (e.g., from a process vessel to a storage vessel). The conveying air moving through the intermediate vessel should discharge to atmosphere. Sufficient engineering controls (such as exhaust filtration) should be employed to prevent the release of UNP from conveying air discharge.

10.4.3 Where vacuum transfers are not practicable, transfers should be conducted within a fully or partially enclosed exhaust hood or an exterior hood where an enclosed hood is not practicable.

10.4.4 Vessel or container openings should not be larger than is necessary to transfer material from the container, and receiving containers. Openings between the containers should