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ENVIRONMENT DIRECTORATE
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THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

HARMONIZED TIERED APPROACH TO MEASURE AND ASSESS THE POTENTIAL EXPOSURE TO AIRBORNE EMISSIONS OF ENGINEERED NANO-OBJECTS AND THEIR AGGLOMERATES AND AGGREGATES AT WORKPLACES

Series on the Safety of Manufactured Nanomaterials
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IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate

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No. 29, *Current Development/ Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 8th Meeting of the Working Party on Manufactured Nanomaterials (2011)*

No. 30, *Regulated Nanomaterials: 2006-2009(2011)*

No. 31, *Information Gathering Schemes on Nanomaterials: Lessons Learned and Reported Information (2011)*

No. 32, *National Activities on Life Cycle Assessment of Nanomaterials (2011)*

No. 33, *Important Issues on Risk Assessment of Manufactured Nanomaterials (2012)*

No. 34, *Current Development/ Activities on the Safety of Manufactured Nanomaterials: Tour de table at the 9th Meeting of the Working Party on Manufactured Nanomaterials (2012)*

No. 35, *Inhalation Toxicity Testing: Expert Meeting on Potential Revisions to OECD Test Guidelines and Guidance Document (2012)*

No. 36, *Guidance on Sample Preparation and Dosimetry for the Safety Testing of Manufactured Nanomaterials (2012)*

No. 37, *Current Developments in Delegations on the Safety of Manufactured Nanomaterials - Tour de Table at the 10th Meeting of the WPMN (2012)*

No.38, *Co-Operation on Risk Assessment: Prioritisation of Important Issues on Risk Assessment of Manufactured Nanomaterials - Final Report (2013)*

No. 39, *Environmentally Sustainable Use of Manufactured Nanomaterials - Workshop held on 14 September 2011 in Rome, Italy (2013)*

No. 40, *Ecotoxicology and Environmental Fate of Manufactured Nanomaterials: Test Guidelines (2014)*

No.41, *Report of the OECD Expert meeting on the Physical Chemical Properties of Manufactured Nanomaterials and Test Guidelines (2014)*

No.42, *Report of the questionnaire on regulatory regimes for manufactured nanomaterials 2010-2011 (2014)*

No.43, *Genotoxicity of Manufactured Nanomaterials: Report of the OECD expert meeting (2014)*

Nos. 44-54, These items are the dossiers derived from the Testing Programme on Manufactured Nanomaterials which are located at:
http://www.oecd.org/chemicalsafety/nanosafety/testing-programme-manufactured-nanomaterials.htm

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The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 34 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

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The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

The OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology (the Joint Meeting) held a Special Session on the Potential Implications of Manufactured Nanomaterials for Human Health and Environmental Safety (June 2005). This was the first opportunity for OECD member countries, together with observers and invited experts, to begin to identify human health and environmental safety related aspects of manufactured nanomaterials. The scope of this session was intended to address the chemicals sector.

As a follow-up, the Joint Meeting decided to hold a Workshop on the Safety of Manufactured Nanomaterials in December 2005, in Washington, D.C. The main objective was to determine the "state of the art" for the safety assessment of manufactured nanomaterials with a particular focus on identifying future needs for risk assessment within a regulatory context.

Based on the conclusions and recommendations of the Workshop [ENV/JM/MONO(2006)19] it was recognised as essential to ensure the efficient assessment of manufactured nanomaterials so as to avoid adverse effects from the use of these materials in the short, medium and longer term. With this in mind, the OECD Council established the OECD Working Party on Manufactured Nanomaterials (WPMN) as a subsidiary body of the OECD Chemicals Committee in September 2006. This programme concentrates on human health and environmental safety implications of manufactured nanomaterials (limited mainly to the chemicals sector), and aims to ensure that the approach to hazard, exposure and risk assessment is of a high, science-based, and internationally harmonised standard. This programme promotes international co-operation on the human health and environmental safety of manufactured nanomaterials, and involves the safety testing and risk assessment of manufactured nanomaterials.

The work on this document was led by the Business and Industry Advisory Committee to the OECD especially: Michele Ostraat, *Aramco Research Center*, Boston; Stefan Engel, *BASF SE*; Keith A. Swain, *DuPont*; Thomas A. J. Kuhlbusch and Christof Asbach, *Institute of Energy and Environmental Technology e.V.* (IUTA).

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology of the OECD.

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1. TABLE OF ABBREVIATIONS

AFM	Atomic Force Microscopy
AIHA	American Industrial Hygiene Association
BET	Brunauer, Emmett and Teller
CEA	Commissariat a l'energie atomique et aux energies alternatives
CEN	European Committee for Standardization
CNF	Carbon Nanofibres
CNT	Carbon Nanotubes
CPC	Condensation Particle Counter
EC	Elemental Carbon
EDS	Energy Dispersive X-Ray Spectroscopy
EDX	Energy Dispersive X-Ray
EELS	Electron Energy Loss Spectroscopy
ELPI	Electrical Low Pressure Impactor
EM	Electron Microscopy
ESP	Electrostatic Precipitator
FMPS	Fast Mobility Particle Sizer
HVAC	Heating, Ventilation and Air Conditioning
ICP-AES	Inductively Coupled Plasma - Atomic Emission Spectroscopy
ICP-MS	Inductively Coupled Plasma - Mass Spectroscopy
INERIS	Institut National de l'Environnement Industriel
INRS	Institut National de la Recherche et de la Securite
ISO	International Organisation for Standardisation
LSL	Lower Size Limit
MMAD	Mass Median Aerodynamic Diameter
MOUDI	Micro-Orifice Uniform Deposit Impactor
MNO	Manufactured Nano-Object
MSDS	Material Safety Data Sheet
NEAT	Nanoparticle Emission Assessment Technique
NIOSH	National Institute for Occupational Safety and Health
NOAA	Nano-Objects and their Aggregates and Agglomerates
NSOM	Near-Field Scanning Optical Microscopy
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
OPC	Optical Particle Counter
PIXE	Particle Induced X-ray Emission
PM_1	Particle size fraction with $dp_{50} < 1$ µm diameter
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
REL	Recommended Exposure Limit
SEM	Scanning Electron Microscope
SMPS	Scanning Mobility Particle Sizer
SOP	Standard Operating Procedure
SPM	Scanning Probe Microscopy
TEM	Transmission Electron Microscopy
TEOM	Tapered Element Oscillating Microbalance
TP	Thermal Precipitator
TR	Technical Report
TWA	Time Weighted Average
TXRF	Total Reflection X-Ray Fluorescence Spectroscopy
WHO	World Health Organization
VCI	Verband der chemischen Industrie
XRD	X-Ray Diffraction

2. EXECUTIVE SUMMARY

Engineered nano-objects (<100nm) and their agglomerates and aggregates (> 100nm) (NOAA) are handled today in workplaces that span broad occupational environments from research to production to use and applications in work processes. Applications for NOAA also encompass many industrial sectors that include and extend beyond the chemical industry. As with all materials, including engineered NOAA, validated control of workplace exposure must be implemented, verified, and monitored to protect the workforce. The primary goal of this document is to describe a reliable formal methodology for conducting consistent exposure related measurements and assessments of aerosols containing engineered NOAA in workplace operations. The approach suggested here is aimed at finding and defining a common framework. Hence, this document presents a harmonized tiered approach that is systematic, consistent, practical, and flexible for conducting field-based, real-time workplace release and exposure measurement and assessment to airborne NOAA and off-line analyses of measurement samples. The level of details to the different tiers described here is seen to be adequate for the framework but details have to be further discussed and defined in Guidelines or Standard Operation Procedures. For the purposes of this document, nano-objects refer to solid, engineered particulates with a primary particle size range of 1 nm to 100 nm.

The three-tiered approach is described in Section 5. This Harmonized Tiered Approach is based upon a systematic evaluation of the similarities and differences among 14 currently used or proposed approaches, including initiatives and published documents on measurement strategies. Tier 1 focuses on gathering information on the occupational workplace under consideration, including workplace activities and the materials handled. This information is analyzed and used to determine whether additional assessment is required. Tier 2 focuses on conducting a basic exposure or release assessment using a straightforward approach for determining whether releases of or an exposure to engineered nano-objects may occur. The approach utilizes easy-to-use, portable equipment for a) release-related site investigations or for b) monitoring workplaces for a longer period, both linked by applying up-to-date knowledge. Tier 3 focuses on obtaining as much information as possible on airborne nano-objects in the workplace in order to a) determine whether or not exposure to engineered nano-objects has the potential to occur, b) identify the level of exposure, and c) determine the need for additional risk management steps. In Tier 3, all possible detection and measurement strategies should be used, including direct-reading instruments, integrated samplers for area and personal assessment where relevant, and analytical measurement techniques in order to provide a definitive conclusion regarding the presence of airborne NOAA in the occupational environment.

The three-tiered approach described in this document is not intended to be a risk assessment strategy, which would also require a health based strategy to assess the toxicity of the material. This three-tiered approach can, however, be part of a risk management and mitigation strategy. Importantly, it can also be utilized to assess the effectiveness of risk mitigation measures. Users of the approach are highly encouraged to publish their data and findings in international journals or to share them with other users of the approach in order to identify and address shortcomings and improve the degree of harmonization in approaches.

3. BACKGROUND AND OBJECTIVES

1. Engineered nano-objects (<100nm) and their agglomerates and aggregates (including structures that are > 100nm) (NOAA) are handled today in workplaces that span broad occupational environments from research to production including industrial sectors that extend beyond the chemical industry. The International Organisation for Standardisation (ISO) defines nano-objects as materials with one, two, or three external dimensions with size range from approximately 1 nm to 100 nm (ISO, 2010). Industrial hygienists and occupational health and product safety professionals are interested in the characterization, measurement, and assessment of the exposure to the inhalable and respirable NOAA in such environments. Currently, there is an absence of health based regulatory OELs for the various NOAA. Therefore, implementing, verifying and monitoring measures to control exposures in the workplace are critical to protect the workforce.

2. Efforts have been undertaken by various organizations to understand the issue of workplace air emissions and possible exposure to NOAA by monitoring potentially affected workplaces. The focus of these efforts has been generally tailored to Research and Development (R&D) projects (NanoValid, nanoGEM, etc.). Recently, several organizations, projects, and initiatives have proposed varied approaches for workplace exposure assessment, which are meant to improve the practicability for and acceptance by practitioners in the field. Although they all follow a similar structure, they differ significantly in their details and do not provide a harmonized approach for exposure assessment.

3. The primary goal of this document is to present a harmonized, tiered approach that is systematic, consistent, practical, and flexible and that addresses the need for a methodology for conducting field-based workplace exposure measurement and assessment of airborne NOAA released in the workplace. For the purposes of this document NOAA refers to solid, insoluble, engineered nano-objects (<100nm) and their agglomerates and aggregates (including structures ≥100nm). This tiered approach can be widely used by small, medium and large enterprises as one component of an occupational health risk management program. It is foreseen to be broadly applicable to assess general exposure potential and as an approach to more specific exposure measurement assessment. Additionally it may also be used to study of the effectiveness of risk management measures, such as local ventilation or suction, by utilizing both field-based, real-time techniques and supporting off-line (e.g., Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), X-Ray Diffraction (XRD), etc.) instrumentation. The aim of this document is to harmonize various approaches to exposure characterization to enable efficient and effective use of limited resources. When used in conjunction with other analyses, this approach can enhance workplace risk management across a wide variety of occupational environments and situations.

3.1 Scope

4. The scope of this guidance focuses on a standard methodology for conducting field-based workplace exposure measurement and assessment to airborne NOAA released in the workplace for solid, insoluble, engineered nano-objects (<100nm) and their agglomerates and aggregates (including structures ≥100nm). However, this guidance could apply to nano-objects comprised of particles, fibres, or plates as long as a combination of realtime and off-line instrumentation could facilitate the reliable measurement and characterization of non-spherical nano-objects. In reality, the ability of currently available hand-held, real-time aerosol instruments applicable for areal monitoring are only suitable for measurement of specific size-ranges of airborne spherical structures.

4. MEASUREMENT AND ASSESSMENT OF AIRBORNE NANO-OBJECTS

5. This section begins with key scientific questions that are as yet unresolved and that impact exposure characterization and measurement strategies for airborne NOAA in occupational environments. Incomplete scientific knowledge about health implications of exposure to airborne NOAA and the lack of health based regulatory OELs for many NOAA complicates exposure measurement and characterization. Consequently, occupational assessment of these materials must be broad to capture as much potentially relevant data as possible. Once more specific scientific understanding is developed, exposure measurement strategies and characterization may become more streamlined. The key scientific unknowns regarding occupational exposure and their impact on measurement strategies and/or exposure characterization for airborne NOAA include the following:

6. **Lack of health based regulatory OELs**

a) Because no exposure limits exist for the majority of engineered nano-objects and the metric (number, surface area, mass) by which the limit should be quantified, a combination of qualitative and a quantitative assessment must be applied to determine if release of engineered nano-objects has occurred. In its simplest form, such qualitative assessments typically include comparing particle concentrations at the emission source with background particle concentrations coupled with a qualitative means for determining whether existing measures are adequate for controlling nano-object emissions or if additional controls are needed.

b) A frequently employed (and conservative) approach (e.g. BekGS 527) to address the lack of OELs for nano-forms is to apply a safety (or assessment) factor to the existing OEL for non-nano forms, This however causes considerable problems in identifying exactly when relevant elevated concentrations occur.

c) Results from a qualitative assessment are not indicative of actual worker exposure. They will not be comparable to possibly upcoming OELs.

d) Because most existing occupational exposure assessment strategies presuppose the existence of OELs, the absence of OELs for nano-objects provides no regulatory motivation to conduct NOAA-specific exposure monitoring.

7. **Lack of appropriate exposure metrics**

a) The reason for choosing an exposure relevant metric is threefold: choosing i) a health relevant metric, ii) a sensitive metric detecting nanomaterials, iii) a conservative metric to link release with exposure and hence facilitate risk management. Measured exposure metrics are currently mostly mass-based, and conversion to particle number or surface area will be difficult due to erroneous and/or conflicting assumptions, for example due to agglomeration and non-uniform particle shape, mixtures, and unknown effective particle densities and primary particle sizes.

b) A link to conventional knowledge about occupational exposures expressed in mass-based units might not be applicable to NOAA of the same or similar composition.

c) A proper error discussion in the measurement software of most measurement tools is also lacking. Error margins to the measurement values would potentially increase the trust in those values.

8. **Behaviour of airborne NOAA**

a) Additional issues in measurement strategies and exposure characterization arise due to the behavior of airborne NOAA and particularly their differences when compared to larger aerosol particles. These deviations often require substantial modifications compared to more conventional occupational assessments and strategies. They typically require a minimum knowledge set about airborne NOAA behaviour as a function of time and environmental conditions.

b) Nano-object aerosols are dominated by viscous rather than inertial forces and are also subjected to significant diffusion forces. As such, nano-object aerosols will typically follow fluid streamlines when they are present. Practically speaking, this means that airborne NOAA are more influenced by airflows and pressure differentials generated by Heating, Ventilation and Air Conditioning (HVAC) systems, by air movements generated when people walk, or by doors opening and closing. For these reasons, it is important to record workplace activities and noting when and where measurements are taken. Furthermore, any assessment of true exposure should be based upon personal monitoring.

c) As nano-objects have very low mass, airborne nano-objects are typically not influenced by gravity. The residence time in air due to their low gravimetric settling rate can reach or even exceed several days. When also considering the dominance of diffusion in the distribution of these airborne nano-objects, more traditional occupational assessments that rely on gravity, such as gravity settling collectors, will be ineffective for NOAA assessment.

d) Airborne nano-objects interact with other aerosol materials as well as with any other surfaces. For example, aggregation of nanoparticles with larger aerosol particles may cause individual nanoparticles to be undetected in real-time number and size-distribution measurements. Therefore, it is important to utilize measurement strategies that examine the spatial and temporal variation of airborne NOAA as these interactions with other aerosol materials are strongly time dependent. From a practical perspective, these variations require measuring in possible exposure zones close to the emission source as well as at distances from the sources to generate an accurate exposure assessment of the airborne NOAA while also taking other workplace and ambient aerosol sources into consideration.

e) Airborne nanosized particles can originate from naturally occurring and incidental sources in addition to the engineered particle sources typically of interest in occupational environments. They are usually termed "ultrafine particles." For these reasons, background particle concentrations can be highly dependent upon such factors as diurnal and seasonal variations, proximity to roadways, and workplace activities (such as forklifts, machine operation, oil mist, condensation of chemicals or reaction products, or water condensation by rapid fall in temperature) that can generate incidental nanosized particles. Therefore, it is highly important to understand the different particle sources and background characteristics to be able to distinguish engineered nano-objects from background.

9. This guidance document draws upon significant international activity in developing exposure characterization and measurement strategies for airborne NOAA, including studies from peer reviewed journal articles, review articles, workshop reports, national guidance documents, and international standards organization documents (Table 1). These publications discuss and present data using different measurement methods and strategies from which a successful approach can be developed. Section 4.1 begins with a high level summary of the key points of each of these resources in tabular form. Section 4.2 discusses key similarities and differences in the recommendations for exposure characterization. Section 4.3 discusses the similarities and differences in the recommendations of measurement strategies. Sections

4.2 and 4.3 conclude with an outline of the main recommendations from the comparisons. For those publications that describe a complete exposure measurement and characterization strategy, the measurement strategy is summarized. The content in Section 5 draws upon the similarities and differences identified in Section 4 to develop a harmonized, tiered approach.

Table 1: Summary of International Activity

Section	Abbreviation	Reference	Document Type
4.1.1	nanoGEM	C. Asbach, T.A.J. Kuhlbusch, H. Kaminski, B. Stahlmecke, S. Plitzko, U. Götz, M. Voetz, H. J. Kiesling, D. Dahmann, 2012: nanoGEM Standard Operation Procedures for assessing exposure to nanomaterials, following a tiered approach, httv://www.nanosem.de/cms/nanosem/uvload/Veroeffentlichungen/nanoGEM SOPs TieredApproach.pdf	Project Deliverable Report
4.1.2	VCI	BAuA, BG RCI, IFA, IUTA, TUD, VCI (2011) Tiered Approach to an Exposure Measurement and Assessment of Nanoscale Aerosols Released from Engineered Nanomaterials in Workplace Operations. www.vci.de/downloads/tiered-approach.pdf	Brochure
4.1.3	French INRS, INERIS, CEA	O. Witschger, O. Le-Bihan, M. Reynier, C. Durand, D. Charpentier (2012): Préconisation en matière de caractérisation et d'exposition des potentiels d'emission et d'exposition professionnelle aux aerosols lors d'operations nanomateriaux	Journal Article
4.1.4	NIOSH NEAT	M. Methner, L. Hodson, C. Geraci (2009): Nanoparticle Emission Assessment Technique (NEAT) for the identification and Measurement of Potential Inhalation Exposure to Engineered nanomaterials - Part A, Journal of Occupational and Environmental Hygiene, *7:3*, 127-132.	Journal Article
4.1.5	NIOSH Approaches	Approaches to Safe Nanotechnology: Managing the Health and Safety Concerns Associated with Engineered Nanomaterials: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2009-125. www.cdc.gov/niosh/docs/2009-125/pdfs/2009-125.pdf	National Guidance Document

Section	Abbreviation	Reference	Document Type
4.1.6	NIOSH CNT and CNF	Current Intelligence Bulletin 65: Occupational Exposure to Carbon Nanotubes and Nanofibers. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2013-145. www.cdc.gov/niosh/docs/2013-145/pdfs/2013-145.pdf	National Guidance Document
4.1.7	NIOSH TiO_2	Current Intelligence Bulletin 65: Occupational Exposure to Titanium Dioxide. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2011-160. www.cdc.gov/niosh/docs/2011-160/pdfs/2011-160.pdf	National Guidance Document
4.1.8	TNO Brouwer	D. Brouwer, M. Berges, M.A. Virji, W. Fransman, D. Bello, L. Hodson, S. Gabriel, E. Tielemans (2012): Harmonization of Measurement Strategies for Exposure to Manufactured Nano-Objects; Report of a Workshop. Annals of Occupational Hygiene 56(1):1-9.	Journal Article
4.1.9	OECD: Australian	P. McGarry, L. Morawska, H. Morris, L. Knibbs, A. Capasso (2012): Strategies, Techniques and Sampling Protocols for Determining the Concentrations of Manufactured Nanomaterials in Air, Draft report for OECD WPMN Steering Group 8	International
4.1.10	ISO TR - Workplace Atmospheres	Workplace atmospheres - Ultrafine, nanoparticle and nano-structured aerosols - Inhalation exposure characterization and assessment; ISO/TR 27628:2007(E)	International
4.1.11	OECD #11	OECD (2009) Series on the Safety of Manufactured Nanomaterials Number 11, Emission Assessment for Identification of Sources and Release of Airborne Manufactured Nanomaterials in the Workplace: Compilation of Existing Guidance	International

Section	Abbreviation	Reference	Document Type
4.1.12	NEW Group	Ramachandran, G., M. Ostraat, D.E. Evans, M.M. Methner, P. O'Shaughnessy, J. D'Arcy, C.L. Geraci, E. Stevenson, A. Maynard, and K. Rickabaugh. 2011. A strategy for assessing workplace exposures to nanomaterials. Journal of Occupational and Environmental Hygiene 8(11):673-685	Review Article
4.1.13	Exposure Review PFT	T.A.J. Kuhlbusch, C. Asbach, H. Fissan, D. Göhler, M. Stintz (2011): Nanoparticle exposure at nanotechnology workplaces - A review. Particle Fibre Toxicology 2011, 8:22 http://www.particleandfibretoxicology.com/content/8/1/22	Review Article
4.1.14	ICEMN Review	M.L. Ostraat, J.W. Thornburg, Q.G.J. Malloy. 2013. Measurement Strategies of Airborne Nanomaterials; Environmental Engineering Science 30(3) 126-132	Review Article

4.1 Summarized Initiatives on Measurement Strategies and Approaches

10. This section provides a brief summary for each of the 14 documents listed in Table 1, including a list of key similarities and differences for each document that are further articulated in Sections 4.2 and 4.3.

4.1.1 nanoGEM

High Level Summary	Key Similarities	Key Differences
A three-tiered approach is introduced and described in detail. The tiers are established logically, starting from a “paper”-based assessment, followed by a second step with low-budget measurements to assess possible release to decide if a third step with full scale measurements is needed. The tiered approach includes longer-term monitoring strategies. This measurement strategy was developed by industry, public bodies and research institutions together and hence has gained high acceptance. It has been tested internationally in several European projects and was introduced to the Organisation for Economic Co-operation and Development (OECD).	A three tier approach comparable to some other proposed approaches is suggested. Multi-instrumental use is proposed in the second and especially in the third tier. Electron Microscopy (EM) is needed for ultimate identification of the nano-object.	Detailed descriptions of the three tiers including different ways of assessing background nanoscale particle contributions are given. Measurement strategy is extended by Standard Operating Procedures (SOPs) also taking statistical evaluations into account. A described monitoring strategy allows for long term assessment and facilitating safety monitoring. Agreement to this approach by different stakeholder groups from industry public bodies and research like the Verband Der Chemischen Industrie (VCI) approach.

4.1.2 VCI

High Level Summary	Key Similarities	Key Differences
The VCI tiered approach, published in 2011, was the nucleus of the previously described nanoGEM approach. It basically consists of the same three tiers (excluding monitoring) as an additional option in tier two.	Tiered approach is suggested as well as the use of a set of different measurement techniques. Chemical analysis and EM are needed for the identification of the nano-object.	This approach was developed by a consortium consisting of industry, public bodies, and research institutions only comparable to nanoGEM approach.

4.1.3 French approach: INRS, INERIS, CEA

High Level Summary	Key Similarities	Key Differences
The paper describes a joint effort of French groups at Institut National de la Recherche et de la Securite (INRS), Institut National de I'Environnement Industriel (INERIS) and Commissariat a l'energie atomique et aux energies alternatives (CEA) to define a harmonized approach for exposure assessment. The strategy foresees five phases during the exposure assessment: Phase 1: "Situation study" Phase 1 only defines, based on criteria given in the document, whether or not the materials used are indeed nano-objects. Phase 2: "Initial Assessment" If Phase 1 did not deliver conclusive results, material samples have to be characterized in phase 2 by using e.g. EM and Brunauer, Emmett and Teller (BET) analysis. If nano-object involvement is confirmed in Phase 1, it has to be checked whether release of and exposure to the materials can be excluded. If this is not the case, the situation requires more detailed analysis in phase 3. Phase 3: "In-situ preparatory visit" Phase 3 foresees a visit to the workplace under consideration mainly as preparation for measurements in phase 4. Phase 3 measurements do not contain exposure measurements, but only an assessment of local air flow situations as well as the background concentration. If deemed to be necessary, the potential for	Although the apparent structure of the approach looks different, it basically follows the same logical structure as the aforementioned approaches. This document suggests a very elaborate protocol for defining whether the handled materials are nano-objects. This is done in three phases, which when combined, are similar to Tier 1 in the VCI and nanoGEM approaches. The measurement steps foresee two levels, a basic and an expert assessment. These are basically identical with Tier 2 and Tier 3 in the aforementioned approaches. Data gathering to determine worker exposure is similar to other approaches.	The approach is sub-divided into five phases instead of three tiers. Phases 1 to 3 resemble what is done in a Tier 1 in the VCI and nanoGEM approaches, but the procedures described here are certainly more detailed than in any other approach. The approach described here is also the only one that suggests experiments to be conducted in a laboratory to clarify whether nanomaterials may be released. The measurement phase is similarly structured as Tier 2 and Tier 3, but unlike other approaches, no clear decision criteria are provided to move from one tier to another. No clear instructions for data analysis are given.

nanomaterial release may be studied in the laboratory, e.g. through dustiness testing. Phase 4: "In-situ measurement campaign" The in-situ measurements are divided into two levels. Level 1 foresees a simple assessment of the particle concentration in the workplace, e.g. by handheld condensation particle counters and particle sampling. Level 2 measurements are an expert assessment including a wide range of measuring equipment. Phase 5: Results analysis Data from the measurement and the contextual information gathered are analyzed.		

4.1.4 NIOSH NEAT

High Level Summary	Key Similarities	Key Differences
Nanoparticle Emission Assessment Technique (NEAT) is an approach used by the National Institute for Occupational Safety and Health (NIOSH) nanotechnology field research team when conducting on-site evaluations of the potential for both airborne release of nanomaterials and worker exposure in facilities where engineered nanomaterials are produced and/or handled.	Multiple instruments utilized, including real-time methods to detect releases of airborne nano-objects and off-line methods for particle identification and chemical speciation. Multi-metric approach to determine particle size, surface area, and number concentrations and composition. Multistage approach to measurement strategy: 1) identify potential sources of emissions; 2) conduct particle number concentration sampling; 3) collect filter-based samples.	Instrument selection more broad compared with other guidance and may not be readily field deployable – Tapered Element Oscillating Microbalance (TEOM) and diffusion charger as examples. Includes concept of breathing zone analysis.

4.1.5. NIOSH Approaches to Safe Nanotechnology

High Level Summary	Key Similarities	Key Differences
The report covers the whole range of issues related to safe nanotechnology: Health concerns, safety concerns, working with nanomaterials, exposure assessment and characterization, precautionary measures and	The report refers to the NEAT publications and the publication by Brouwer et al. 2004 for sampling strategies and exposure assessment.	The need for the identification of sources is much more in focus of this report. There is one section dealing specifically with release processes, linking this to exposure and

occupational health surveillance. Only the section on exposure assessment and characterization present and discusses issues for this document. The focus of this report is on measurement techniques rather than test strategies and approaches.	The need to include background particles in the assessment is clearly stated and similar approaches named as in other reports strengthening this issue. Particle number concentration mapping is discussed in detail.	reduction measures. It is clearly stated in view of toxicity and exposure that "mass and bulk chemistry may be less important than particle size and shape, surface area, and surface chemistry (or activity) for some nanostructured materials." Personal sampling is stressed and pointed out should be used to "ensure accurate representation of the worker's exposure". Area sampling is less usable for exposure assessment. An extensive overview of measurement methods is given in this report extending also to the non-nanometer size range.

4.1.6 NIOSH CNT and CNF

High Level Summary	Key Similarities	Key Differences
NIOSH has prepared nano-object-specific guidance on carbon nanotubes (CNTs) and carbon nanofibres (CNFs) due to recent animal studies that indicate that these materials may pose a respiratory hazard and adverse lung effects at relatively low-mass doses. NOTE: The link to human health has not been established but the results from animal studies indicate a need to minimize worker exposure.	A multi-tiered exposure assessment is recommended. Airborne Elemental Carbon (EC) concentrations are compared relative to background for CNF and CNT exposure to identify if exposure may be present.	Materials specific characterization can be used as an indicator of CNT and/or CNF presence, specifically using EC or metals that are present in the catalyst particles used during synthesis. The combined measurement of chemical composition (EC, catalyst), diameter, length, specific surface area is recommended. The approach follows a specific NIOSH method to determine EC (NIOSH Method 5040) and an international guidance that is tailored for fibrous materials (but is not specific to nano-objects). The approach includes a Recommended Exposure Limit (REL) of 1 microgram/m^3 elemental carbon as a respirable mass 8-hour time-weighted average (TWA) concentration that was determined using data from nonmalignant pulmonary data from CNT animal studies.

4.1.7 NIOSH TiO_2

High Level Summary	Key Similarities	Key Differences
NIOSH has prepared TiO_2-specific guidance that includes both nano and non-nano forms of TiO_2.	A multi-tiered exposure assessment is recommended. It includes remarks to distinct between primary particles and agglomerates/aggregates – and suggests a calculation to determine the percent of fine and ultrafine particles based upon the measurement of primary particles, including aggregates of primary particles.	This approach emphasizes the relationship between particle surface area dose and toxicity as the scientific evidence supports surface area as the critical metric for occupational inhalation exposure to TiO_2. Following measurements and information are needed for a good assessment: Mass Median Aerodynamic Diameter (MMAD), geometric standard deviation, specific surface area, possible coatings and crystal structure. It includes a discussion of crystal-dependent toxicity. The NIOSH Method 0600 is recommended for work environments where exposure to different types of aerosols occurs or when the size distribution of TiO_2 is unknown, along with the use of NIOSH Method 7300 for offline characterization with electron microscopy and EDS. The approach includes a suggestion for an REL of 0.3 mg/m^3 ultrafine (including engineered nanoscale) as a TWA concentration for up to 10 hours per day during a 40 hour work week – from chronic inhalation studies in rats to predict lung tumor risks in humans.

4.1.8 TNO Brouwer

High Level Summary	Key Similarities	Key Differences
The paper presents a summary of the *First International Scientific Workshop of Harmonization of Strategies to Measure and Analyze Exposure to Manufactured Nano-Objects (MNO) in Workplace Air*. The workshop was held in December 2010 and gathered 25 experts in the field from Europe, United States, Japan, and South Korea. The workshop participants discussed topics ranging across measurement strategy, data	A multi-metric approach is recommended for workplace exposure analysis, but in certain cases a limited assessment based on a single metric may be sufficient. This leads to the use of a tiered approach, which is also discussed and considered as favourable. A minimum set of harmonized contextual information has to	The urgent need for a database is stressed throughout the paper. Such a database should be the foundation for exposure modeling, compliance testing and epidemiological studies. The database needs to have a structure different from conventional exposure databases, because of the different type of instruments (time and size resolved) used for nano-objects.

evaluation, data and contextual information reporting, and the need for a (multi-purpose) database. The workshop produced several recommendations. The paper recommends that European Committee for Standardization (CEN) and OECD may take a lead in developing a harmonization effort. (Nevertheless, three more of such workshops have been held in the meantime, 2011 in Helsinki, 2012 in Boston and 2013 in Nagoya).	be defined for data pooling and storage and is to be gathered and delivered along with the measurement data. EM analysis of particle samples is seen as necessary due to a lack of specificity of existing direct-reading instruments for nano-objects. However, clear strategies and guidelines for sampling, counting, and evaluation of the particles are lacking, also taking into account the inhomogeneity of most samples. The paper points out the necessity for instrument comparison, which are essential for comparing measured exposure data.	A need for guidance on statistical analyses is pointed out, because commonly used methods, such as autoregressive integrated moving average may be out of the field of an occupational hygiene practitioner. Although geometric mean and geometric standard deviation are widely accepted as summary statistics, the paper describes the need for other analyses, such as arithmetic mean and peak concentration, because disease mechanisms are not yet fully understood.

4.1.9 OECD: Australian Approach

High Level Summary	Key Similarities	Key Differences
This OECD document provides extensive information on the measurements of airborne nano-objects by utilizing previous documents and material from the international community. Although the goal of this document is not to provide harmonized guidance, it does provide a comprehensive analysis of available methodologies as well as recommendations for appropriate measurement strategies under various scenarios. The document concludes with some significant recommendations, many of which are also included in this harmonization guidance document.	It describes a three-tiered assessment process. It includes recommendations of real-time and off-line instruments as well as the use of complimentary instruments that can be used to gather information on temporal and spatial variations. Discusses importance of background measurements and how they should be conducted.	It provides various measurement strategies based upon the objective of the study. It advocates for a wide range of measurement equipment to characterize workplace exposure and evaluate the effectiveness of emission controls (including for mass, number, surface area, and off-line) because of the different toxicology pathways arising from the diversity of nano-object physico-chemical traits.

4.1.10 ISO TR – Workplace Atmospheres

High Level Summary	Key Similarities	Key Differences
The stated purpose of this Technical Report (TR) is to provide generally accepted definitions and terms, as well as guidelines on measuring occupational exposure of airborne nano-objects against a range of metrics due to the reality that nanotechnology is introducing new processes and materials into occupational environments. This document is also responding to evidence which points toward a particle-related health risk following inhalation exposure to some occupational aerosols that is not appropriately reflected by mass concentration alone. Therefore, there is a need to establish the means by which exposure can be measured against different metrics in order to develop a deeper understanding of the association between aerosol exposure and health effects using a range of exposure metrics.	A combination of instruments for real-time (in situ) and off-line analysis of samples is required for both chemical and physical characterization. Spatial and temporal variations need to be understood in an assessment. The determination of the background concentrations is essential.	Since no single device is available to determine all relevant exposure characteristics, so both static and portable devices should be used. Characterizing sample location with respect to source, air movement, and position of the worker is essential for relating results to personal exposure. Additional discussion on identifying appropriate sampling location for fixed monitors, determining air flow patterns, and considering workers' positions, activities, and behaviors in assessing exposure is included in this document.

4.1.11 OECD Number 11

High Level Summary	Key Similarities	Key Differences
This document focuses on assessing emissions from workplace processes, materials, and control technologies. Through international surveys, this document concludes that both the evaluation of instrumentation for characterization of nano-objects in workplace environments and emission assessment guidance to semi-quantitatively evaluate workplaces where release of engineered nano-objects may occur are available. However, because no exposure limits exist for the majority of engineered nano-objects, a qualitative assessment must be used to determine if release of engineered nano-objects has occurred. Such assessments are not necessarily representative of worker exposure.	It compares particle concentrations at the emission source with background concentrations as a qualitative evaluation of a workplace. It recommends a multiple instrument approach for real-time and off-line analysis. Background measurement methodologies are described and discussed. Results from work area samplers may not be indicative of worker exposure.	It discusses the measurement of the effectiveness of existing measures for controlling nano-object emissions as well as determining if additional controls may be needed. Methodologies for dust sampling from surfaces are included in this document.

4.1.12 NEW Group

High Level Summary	Key Similarities	Key Differences
The goal is to develop a tailorable exposure assessment strategy that enables effective and efficient exposure management while simultaneously requiring a modest level of resources to conduct the strategy. Motivation for developing this strategy is that because most existing occupational exposure assessment strategies presuppose the existence of OELs, their absence for nano-objects provides no regulatory motivation to conduct exposure monitoring. Therefore, the limited routine monitoring efforts that do exist do not follow a consistent strategy. Additionally, cost can be a factor in preventing assessments from being conducted.	The discussion around the appropriate exposure metric for nano-objects, with the recognition that the traditionnal mass metric may not be most appropriate for nano-objects. The need to use several instruments in an assessment to account for limitations of individual instruments and to prevent erroneous assumptions was identified. Direct reading and time-integrated instruments are both seen to be important to be used in combination. A tiered approach is suggested, but one tailored from American Industrial Hygiene Association (AIHA) guidance. The importance of background measurements is clearly identified. Until OELs are established, it is recommended to adopt a conservative approach and to include sufficient safety factors to ensure that the risk is not underestimated.	Discussions around acute and chronic exposures and their uncertainty remain open. “Costs” as a factor in preventing exposure assessments from being conducted need to be considered. The document mentions difficulties using Material Safety Data Sheets (MSDSs) as many do not distinguish between nano and bulk forms. One big challenge is related to the background measurements – the best measurement strategy is found to be situation specific. A prioritization for assessments is suggested by focusing the resources on groups with the highest hazard potential as a way to manage costs. The document recommends the establishment of a long term monitoring program to make sure workplace concentrations do not change on assessed.

4.1.13 Exposure Review PFT

High Level Summary	Key Similarities	Key Differences
The review presents the overview on measurement strategies linked to airborne nanomaterial measurement technologies, results from field investigations at nanotechnology workplaces and nanomaterial release studies based on peer reviewed journal articles. It is stated that several approaches differentiating background particles from those released by the process can be applied with different advantages and disadvantages. Secondly, the link between existing or available measurement technology and measurement strategy is discussed.	From the review it becomes evident that a multi-instrumental approach has to be used to be able to differentiate the released nano-object from background particles. It is also shown that a clear identification of product nano-objects was only possible using single particle analysis techniques, more specifically electron microscopy coupled with chemical analysis.	Due to the review character of this article no specific key differences from this paper compared to the other discussed papers in this section can be identified.

4.1.14 ICEMN Review

High Level Summary	Key Similarities	Key Differences
This review article discusses the measurement strategies and exposure characterization of airborne nano-objects as one part of a broader industrial consortium effort to characterize nano-objects in various environmental media and industries. Uncertainties in and costs associated with conducting exposure assessments for engineered nano-objects have led to the adaptation of a limited number of strategies that are typically multi-step or tiered approaches.	Although mass concentration has previously been regarded as the most appropriate exposure metric associated with health effects of particle exposure, its appropriateness for nano-objects is not clear. Number and surface area concentrations may be more suitable alternatives for nano-objects. The absence of OELs for nano-objects may hinder exposure monitoring efforts as could assessment costs. Current commercially available measurement technologies are inappropriate for assessing personal exposure to nano-objects. Multi-metric approaches, including real-time and off-line analysis are seen to be important. Differentiating the background from engineered nanomaterial exposure is also seen as important	

4.2 Guidance and recommendation on exposure characterization for airborne NOAA

11. To date, harmonized guidance of exposure characterization has not occurred, primarily because of the lack of suitable instrumentation, lack of appropriate exposure metrics, and lack of quantified exposure limits. For these reasons, the instrumentation used in exposure characterization often varies, creating a wide set of options for characterizing workplace environments for airborne nano-objects. This section describes the similarities and differences between the various guidance documents highlighted in Section 4.1 in order to provide harmonized guidance for conducting exposure characterization.

4.2.1 Noted similarities

Real-time and off-line instruments are routinely used

12. Because there is currently no single commercially available instrument capable of meeting all desired requirements of exposure characterization to airborne NOAA, a suite of instruments is typically used to conduct an exposure characterization of an occupational environment. Hence exposure characterization methodologies and measurement strategies often rely on multiple instruments, including real-time and offline instruments, in order to conduct an adequate exposure characterization. The most commonly reported combination of real-time and off-line instruments include direct-reading, handheld instruments (Condensation Particle Counter (CPC) and Optical Particle Counter (OPC)) to detect releases of airborne nano-objects coupled sampling (Electrostatic Precipitator (ESP), Thermal Precipitator (TP) or filter) and subsequent chemical and microscopic analyses (SEM or TEM with Energy Dispersive X-Ray Spectroscopy (EDS)) for particle identification and chemical speciation. A more comprehensive suite of

real-time and off-line instruments as well as the methods to collect off-line samples that are also reported for conducting exposure characterization are summarized below.

13. Real-time instruments and noted limitations include the following:

- Aerosol photometers to estimate mass concentration based upon an assumed density and particle size distribution
  - The lower particle size limit of >100 nm optical diameter has to be considered
  - Does not cover the size range of free primary nano-objects and their smaller agglomerates/aggregates
- OPC to measure particle size distributions
  - The lower particle size limit of approximately 300 nm optical diameter has to be considered
  - Does not cover the size range of primary nano-objects and their smaller agglomerates/aggregates
- CPC to measure total number concentrations
  - Upper number concentration limit (depends on specific device) may in some cases be too low
  - Not nanoscale specific as the range spans nm to µm
- Diffusion chargers to measure number concentration, lung deposited surface areas area concentration or mean particle size or a combination thereof
  - Low charging efficiencies of nano-objects smaller than ~ 10 nm
  - Accuracy only around ±30%
  - Increasing measurement error for particles >400 nm
  - Not nanoscale specific as the range spans nm to µm
- Electrical mobility analysis to measure submicron particle number size distributions (Scanning Mobility Particle Sizer (SMPS), Fast Mobility Particle Sizer (FMPS) as examples)
  - Limitation is requirement of peripheral equipment to generate usable data and potential use of radioactive chargers (some SMPS only) that render the instrument non-portable
  - SMPS requires size distributions and concentrations to be stable up to several minutes, i.e. not useable in dynamic processes
- Impactors (Electrical Low Pressure Impactor (ELPI), nano-Micro-Orifice Uniform Deposit Impactor (MOUDI) as examples)
  - Limitation is that impactors lack real-time data output (with the exception of the ELPI)

  - Lower size-resolution than electrical mobility analyzers

- TEOM for measuring particle mass concentration e.g. in the submicrometer range (PM1)
  - Only useable for mass concentrations approximately >5 μg/m^3
  - Not nanoscale specific

14. Off-line samples are collected using the following methods and instruments:

- Open-face sampling, filtration,
- Electrostatic or thermal precipitation,
- Size-selective collection-cyclones, elutriators, cascade impactors, e.g. nano-MOUDI
- Personal samplers: e.g., cascade impactor or respirable cyclone sampler
- Surface sampling and wiping

15. Off-line instruments include the following:

- EM with TEM and/or SEM with Energy Dispersive X-Ray (EDX) (most common)
- Atomic Force Microscopy (AFM)
- Electron Energy Loss Spectroscopy (EELS)
- Scanning Probe Microscopy (SPM)
- Near-Field Scanning Optical Microscopy (NSOM)
- Total Reflection X-Ray Fluorescence Spectroscopy (TXRF)
- Wet chemical analyses
- Inductively coupled plasma mass spectrometry (ICP-MS)

16. Please note that this list is meant to be indicative and not exhaustive and that this guidance could apply to nano-objects comprised of particles, fibres, or plates as long as real-time and off-line instrumentation allow sensible investigation and characterization of non-spherical nano-objects. In reality, the current availability of hand-held, real-time instruments appropriate for non-spherical structures is limited. For the performance of the specific devices, their advantages and draw-backs, refer to the corresponding literature Asbach et al. (2014) or Kaminski et al. (2013).

Desired functionality of commercially available instruments

17. Guidance documents often list instruments that are used in exposure characterizations along with their current limitation. Other guidance documents, including Ramachandran et al. (2011) and Ostraat et al. (2013), list some desired features of a commercially available instrument. These features include the following:

- Limited size resolution with 2 to 5 distinct size bins < 100 nm
- Simple to operate, including minimal training to collect and interpret data
- Portable
- Minimal maintenance and calibration
- Capable of area measurements over extended periods of time (~ 8 hours) with no supervision as well as targeted measurements with rapid time scanning (entire size distribution in < 1 minute)
- Reliable operation in wide variety of conditions, including high and low particle concentrations and broad particle chemistry insensitivity
- Ability to distinguish between background and incidental nano-objects and engineered nano-objects
- Robust and field deployable
- Inexpensive to purchase, operate, and maintain

Multi-metric approaches are reported

18. In addition to the utilization of real-time and off-line instruments for exposure characterization, another similarity among the documents tabulated in Section 4.1 includes the reporting of the measurement of various exposure metrics regarding airborne NOAA. This may be due to an instrument providing data on a specific exposure metric. It could also be due to the reality that the appropriate exposure metric for nano-objects has not yet been identified, so practitioners have selected the metric that is either most convenient or most relevant to their understanding of airborne NOAA and potential health implications. A listing of the common number-based, surface area-based, massbased, and size distribution techniques, challenges, and limitations are summarized above and are given in Kuhlbusch et al., 2011 (see 4.1.13). In general three different physics-based aerosol metrics can be differentiated, including particle number, surface area, and mass concentration. Depending upon measurement principles, all three metrics can be converted into each other if the particles are spherical and if the size distribution and density or optical parameters are known. Still, the metrics exhibit significantly different sensitivities to different size fractions and often cannot simply be converted since particles are usually non-spherical and the size distribution is often unknown. All metrics can be linked to specific toxicological mechanisms explaining some of the toxicity of the airborne particles.

- The number concentration is the only metric that is independent of particle size. Number based instruments, such as CPCs and OPCs, require broad detector sensitivities down to particle diameters of a few nanometers and up to microns if there is a need to determine aggregates and agglomerates for primary nano-objects. Although the CPC is the most widely used instrument for detecting airborne nano-objects, many references do not report using the CPC by itself. Often, the CPC is used with other instruments, typically with an SMPS, sometimes also with a diffusion battery, or often with an OPC to exploit different size ranges. Some instruments using diffusion charging techniques also apply electrometers to determine the particle number concentration down to the nanometer size range.
- The particle surface area is proportional to the particle diameter squared (in case of spherical particles). The definition for the surface area of an agglomerated or aggregated particle is still

under discussion, because it is unclear whether only the outer surface area or the entire surface area including all pores should be counted. For surface area based instruments, several techniques can be utilized. In one example, real-time diffusion chargers and electrometers infer the particle surface area. It is important to note that aerosol charging methods have shown good correlation with the fraction of the total particle surface area concentration of spherical particles that would deposit in the human lungs. Errors in case of agglomerated particles were reported to be small (Fissan et al., 2012). However, if the aerosol is already charged or if the probability of multiple charges per particle is high, erroneous results can be obtained (Qi et al., 2009). In a second example, some practitioners measure aerosol number and mass and then estimate surface area by assuming the geometric standard deviation for the assumed lognormal distribution. Although the method is simple and is gaining increasing application in workplace monitoring, errors associated with critical assumptions must be minimized or reported. As a third example, BET can be a useful off-line technique to measure surface area, but it requires a relatively large amount of material for collection and measurements are influenced by particle porosity and sample substrate.

- The particle mass concentration scales with the third power of the particle size and is additionally proportional to the particle density. For mass based instruments, a pre-separator may be required to remove particles of non-desired large sizes from the air stream as these high mass particles will dominate any measured mass due to the low mass inherent in nano-objects. Additionally, mass based instruments that enable offline sample collection, such as with nano-MOUDIs, require stationary, high flow pumps to collect samples with sufficient mass typically over longer time periods in order to increase the signal-to-noise ratio.

- For particle size distribution measurements, there are several choices for instrumentation, but most suffer from limitations that render them problematic in an occupational environment. Key instruments and their limitations include the following:

  - The SMPS is a widely used instrument for determining particle size distributions in the research laboratory by electrical mobility analysis, but major limitation result in workplace applications due to the SMPS size, cost, complexity of operation, the need for two or three instruments operating in parallel to measure wide aerosol size distributions, and reliance on radioactive chargers to neutralize incoming aerosol. Furthermore the particle size distribution needs to be stable during each scan of the size distribution, which usually requires several minutes. Only very recently (fall 2013) have SMPS systems been introduced that can accomplish a complete size scan within 10seconds. Despite these limitations, work is ongoing to advance SMPS to more portable, handheld versions from commercial sources.

  - Impactors allow for personal or static sampling with a range of particle size cut points. However, as with mass-based samplers, it is important to collect sufficient material on each stage to allow for adequate quantification without overloading the upper collection stages. In some instances, particle bounce could be an issue, reducing the resolution and accuracy of the size bins. Common approaches to avoiding particle overloading include using multiple-orifice collection stages, rotating collection substrates, and using coated and/or porous collection substrates. An additional advantage of impactors is that samples can be collected and further analyzed using off-line techniques.

  - The ELPI is an instrument that combines inertial collection with electrical particle detection to provide near-real-time aerosol size distributions for particles larger than 7 nm in diameter. Additionally, it is able to collect samples for off-line analysis, including EM and chemical speciation. One current limitation of the ELPI is that it lacks field portability and errors at the smallest particle sizes can be large if the incoming sample is not properly conditioned.

- Diffusion batteries are based on Brownian motion of aerosol particles. As such, these instruments are capable of continuous measurement, but they need to be operated with a particle counter to determine the number concentration before and after each diffusion stage.

Physical and chemical characterization of the nano-object is important, including particle size, surface area, and number concentrations as well as chemical composition

19. Current exposure characterization guidance focuses on both physical and chemical aspects of airborne NOAA. Physical characterizations of airborne NOAA, most commonly particle size, surface area, and/or number concentration measurements, are typically conducted using real-time, handheld instruments. Off-line instruments (most commonly with EM) allow additionally the characterization of the morphology as well as the chemical composition of the collected NOAA.

4.2.2 Noted differences

Expanding characterization to include important features of a nanomaterial

20. Differences in exposure characterization related to specific features or characteristics of airborne NOAA of interest to practitioners have been reported. For example, if fibrous airborne NOAA are of interest, the individual or aggregate fiber-length is often measured using off-line instruments, such as EM or AFM.

21. Furthermore, if there is scientific evidence that a physical or chemical parameter may influence the hazard level of an airborne NOAA, this parameter is often characterized as part of the exposure characterization. One example is that crystalline polymorph type can be measured for airborne NOAA of TiO_2.

22. Finally, as there are considerable differences in the possible toxicology pathways arising from the diversity of nano-objects, exposure characterization needs to be flexible with regard to measuring the physico-chemical traits most relevant to potential health implications. Thus, it is likely that no single measurement method for airborne particles will suit all nano-objects and, therefore, a wide range of measurement equipment should be used to characterize workplace exposure and evaluate the effectiveness of emission controls including for mass, number, surface area, and off-line characterization.

Chemical specific signatures of airborne NOAAs

23. As another example, if airborne NOAA are known to have a specific chemical signature, the chemical signature can be used as an indicator of airborne NOAA. In some cases, methods for quantification of these specific chemical signatures have been developed and can be used to guide exposure characterization. According to NIOSH Method 5040, occupational exposure to EC, including CNTs and CNFs, can be evaluated using this method which is specific to EC, when an elevated airborne elemental carbon concentration relative to background is detected, this event is a reasonable indicator of CNT or CNF exposure potential. When elevated background exposure to elemental carbon is possible, additional off-line analytical techniques may be required to better characterize exposures of the engineered NOAA. For example, analysis of airborne samples by EM with EDS can help to verify the presence of CNT and CNF and can distinguish this elemental carbon from that of soot or diesel exhaust. Furthermore, the presence of certain metal catalysts used to synthesize CNTs may not be prevalent in the background environment. As such, the detection of catalyst metals in samples can then be used as an indicator of the

presence of CNTs and can be measured using off-line instruments on collected samples, typically with Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) or Inductively Coupled Plasma-Mass Spectroscopy (ICP-MS) or with XRD and Particle Induced X-ray Emission (PIXE) (if one needs to avoid speculation about extraction efficiencies in preparation of ICP). The latter two methods are also two examples of an off-line analytical measurement method to determine the possible presence of metal or metal-oxide based NOAA.

4.3 Guidance and recommendation on measurement strategies of airborne NOAA

24. To date, the creation of harmonized guidance of measurement strategies has not occurred, primarily because the objectives of the corresponding study have determined the measurement strategy to be followed. Still, various measurement strategies have recently been used within other national projects leading to interest for their usability and comparability to develop a harmonized approach.

25. Additionally, confounding factors, including background readings, spatial and temporal variations, and measurement costs, have often been used to justify modifications to a given measurement strategy, which results in customized approaches. This section describes the similarities and differences between various guidance documents in order to provide harmonized guidance for measurement strategies of airborne NOAA.

4.3.1 Noted similarities

Justification for conducting measurements and developing measurement strategies

26. In general, there is agreement that examining the potential for airborne release of nano-objects and resultant potential worker exposure in facilities where engineered nano-objects are produced and/or handled is important. It is also generally recognized that the earliest and potentially the most significant exposures and risks to airborne NOAA will be in the occupational arena. This need is often further justified by summarizing studies that examine the health effects of nano-objects, particularly when potential harmful outcomes in animal studies are observed. Additionally, employers, workers, and researchers engaged in the production and use of engineered nano-objects have expressed an interest in determining whether nano-objects are hazardous and if the potential for worker exposure exists.

Background assessments are essential

27. As the prevalence of airborne ultrafine particles from naturally occurring and incidental sources can be common in an occupational environment, it is critical that the measurement strategy include a determination of background concentrations as part of an occupational exposure assessment. However, due to natural variations, including diurnal and season fluctuations, as well as activity variations, such as roadway proximity and traffic conditions, measurement of background airborne NOAA concentrations can be complicated. Furthermore, as current real-time instruments are generally unable to differentiate between naturally occurring, incidental, and engineered nano-objects, additional off-line characterization may be required.

28. Guidance documents recommend several general approaches for conducting background assessments that are situation specific. Several real-time measurement strategies are listed below.

- Measuring before and after processing or handling of nano-objects and comparing to measurements taken during processing or handling of nano-objects (time variance approach)

- Measuring simultaneously at a co-location not influenced by the investigate process and comparing the results to those from the occupational environment (spatial variance approach)

- Investigating the same work process with and without the nano-object (material variance approach)

- A combination of any of the above three approaches

- Measuring peak concentration values relative to background as a practical screening indictor for processes that may require additional control for particle emission

- Measuring at the intake of some process and comparing to the emission source

- Conducting simultaneous measurements in possible exposure zones closer to the possible emission source and at some distance from the emission source

- Conducting simultaneous measurement with process-related monitoring or pre-/post-process monitoring

29. In order to determine any temporal variations that have cycles longer than the measurement duration, long-term monitoring may be helpful in collecting more data for statistical inferences. Whatever approach is taken to conduct a background assessment, an activity-based analysis is required. Continuous spatial time-activity observations, with documentation, must be made for the length of the operation. Correlating the possible measurement contributions from the documented spatial activity based observations for the operation and for the surrounding area enables an effective means for understanding the primary contributors to nanoscale aerosols consisting of NOAA released and detected from the operation.

Strategies for temporal and/or spatial variations are provided

30. As mentioned previously, airborne NOAA readily follow fluid streamlines, are generally unaffected by gravity, and have high thermal mobilities (diffusion). Due to the high rate of diffusion, airborne nano-objects have a size and concentration dependent tendency to agglomerate with other aerosol particles, that may cause the nano-objects to no longer be detected at the nanoscale with real-time instruments. For these reasons, any measurement strategy must consider the temporal and spatial variations inherent in these airborne nano-objects, not just in looking at specific nano-objects emissions, but also in assessing the background concentration as discussed previously. These and points below are considered in the tiered approach suggested in Section 5.

31. Key implications on temporal and spatial variations for a measurement strategy include:

- Conducting real-time measurements in the possible exposure zones close to and away from potential sources to characterize the evolution of the size distribution over time.

- Using elevated concentration guidance criteria to evaluate the significance of temporal and spatial particle variation in relation to risk assessment to inform if particle concentration emissions and exposure are acceptable or if they require additional assessment

- Identifying appropriate sampling locations for fixed area monitors that are unaffected by HVAC, doorways, or other air flow patterns that could impact measurements.

- Documenting occupational events during measurements, including worker's positions, activities, and behaviours and other occupational activities, such as forklift traffic, doors opening and closing, and HVAC systems turning on and off.

Measurement strategies utilize tiered approaches

32. As guidance documents recommend a tiered or staged approach to conduct an exposure assessment, this discussion will be expanded upon in Section 5 of this document.

4.3.2 Noted differences

Measurement strategies may need to vary, depending upon the objective or study question

33. Some guidance documents indicate that measurement strategies will need to vary depending upon the objective of the study and whether the study is related to a personal exposure, a process, or a link to a toxicological and/or an epidemiological question. For example, the different objectives below would require a different measurement strategy:

- Determine processes and the fate of aerosols after emission
- Determine the effectiveness of a control measure
- Compliance measurements relative to a reference value
- Full risk assessment that requires a comprehensive exposure assessment
- Risk or concern driven tiered approach to support evidence-based decisions or actions to be taken
- Properties of nano-objects that influence measurement decisions-particle size; surface area and the reactivity of that surface area; particle number; solubility and biopersistence; shapes and fibers; primary particle size, aggregation, and agglomeration

34. It is the purpose of this document to define a harmonized measurement strategy that can be utilized independent of the study objective or question when a measurement strategy is not specified. Where measurements and/or methodologies are specified in regulatory instruments, those methodologies should be followed to ensure compliance.

5. HARMONIZED TIERED APPROACH

35. From the extensive literature review provided in Section 4.1, several common points emerged. All documents that discuss measurement strategies identify the need for a tiered approach to facilitate the assessment. Furthermore, this tiered approach should be easy to pursue, cost effective, based on established measurement methods, able to discriminate and quantify engineered nano-objects from background particles, and deliver comparable results independent from the workplaces under investigation.

36. A harmonized approach based on three tiers is presented in this section. Tier 1 is focused on the gathering of information prior to laboratory or field assessment in order to most effectively assess possible release of and exposure to nano-objects. If occupational exposure cannot be excluded following the Tier 1 analysis, a Tier 2 on-site investigation will occur. The focus of Tier 2 is to assess an occupational environment for possible release and detection of elevated particle concentrations by cost effective temporal and/or spatial screening methods. Tier 3 becomes necessary if significant exposure can still not be excluded. In Tier 3, extended measurements as proposed below will be required. Additionally, it should be noted that these tiers do not need to be accomplished separately. Approaching one or all tiers concurrently is possible. This concurrent approach may be driven by time constraints (only a limited opportunity to be on-site) and ability of the investigator. An experienced or expert occupational hygienist would have the capability to accomplish all three tiers in one visit.

37. Section 5.1 provides a description of the tiers and suggests measurement methods and measurement strategies for each tier. Whenever relevant, quality assurance and assessment measures are provided in more detail. Section 5.2 provides additional information on validation and experiences related to the utilization of a tiered approach. Finally, Section 5.3 gives some recommendations for the use of the harmonized tiered approach and concludes this report.

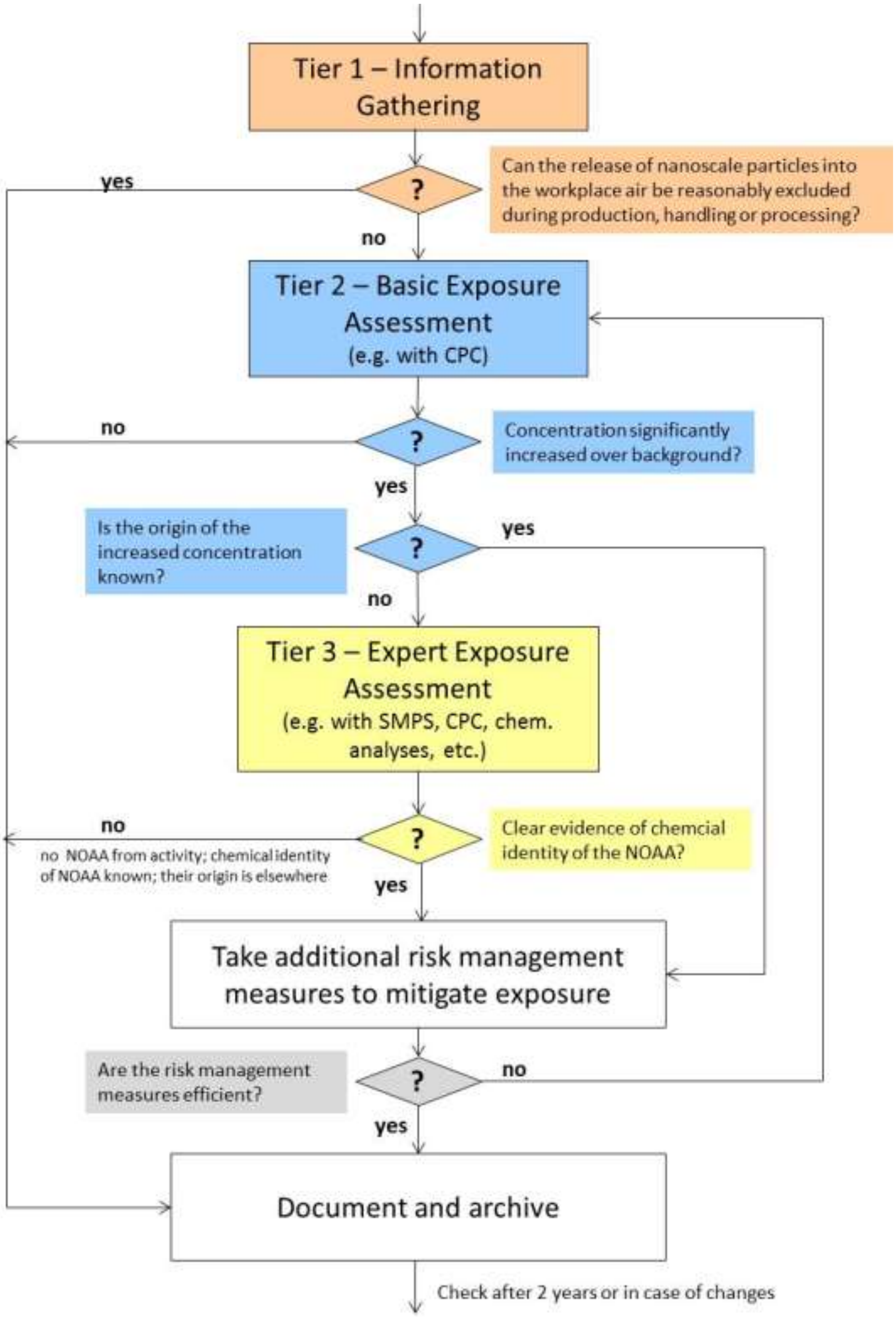

Figure 1: Flow chart of the tiered approach

5.1 The Tiered Approach-Tiers 1, 2, and 3

38. Details for each of the 3 tiers are provided in Sections 5.1.1, 5.1.2, and 5.1.3. For each tier, a brief introduction highlights the objective of the tier, followed by a clear list of criteria or data that should be collected in that tier. A flow chart of the decision tree for the tiered approach is shown in Figure 1.

5.1.1 Tier 1: Information gathering

39. The aim of Tier 1 is to gather as much information as possible according to established best practices in industrial hygiene on the occupational workplace under consideration, including workplace activities and the materials handled. Examples of risk management tools that contain information gathering guidance include the Precautionary Matrix for Synthetic Nanomaterials and risk or control banding tools, e.g. Control Banding Nanotool, NanoSafer, and Stoffenmanager Nano may also be used. All gathered information is then analyzed and used to determine if additional assessment is required. Tier 1 is generally a paper study, but it can include a visit to the workplace to inspect potential locations where nano-objects may be released into the occupational environment. Tier 1 may also include the analysis of material samples in a laboratory to verify if the material handled is a nano-object. In addition to release scenarios, all available information on the hazard potential of the materials handled should be gathered. In case of a very high hazard potential, i.e. a very low exposure could lead to health effects, it should be checked carefully whether the methodologies described in Tier 2 and Tier 3 are sufficient to detect critical exposure levels. In cases where no sufficient methodologies are available as described in the tiers, information on possible alternative approaches must be identified and added to this approach. In the worst case, a new methodology must be developed.

5.1.1.1 Minimum requirements for data gathering

40. The minimum information that should be gathered during Tier 1 is listed below. The examples provided are meant to be illustrative rather than comprehensive. Therefore, the skilled industrial hygienist should expand this list to be sufficiently comprehensive during the information gathering stage.

- Information related to the workplace, including
  - The type of workplace and its potential variability, considering e.g., the number of different nano-objects produced, their production volumes, volume of the production zone, and the volume of the facility in general, etc. such as a manufacturing environment in which larger volumes of a single (or few) and consistent nano-object are processed; versus a research environment in which smaller volumes of diverse arrays of nano-objects are processed,
  - Relevant information related to previous exposure assessment results, for example, for a given process step, information on nuisance dust exposure as part of a background assessment from other work processes, engines or welding using e.g. spatial and/or temporal information,
  - The location and type of exposure control measures,
  - Any occupational guidance already in place, such as a company's internal recommendations on exposure limits for a given workplace if such exist.
- Information related to the nano-objects in the occupational environment, including

  - The composition of nano-objects processed or handled as e.g. powders, aerosols, slurries, or as components in a nanocomposite or a product intermediate,
  - The structure of the nano-object, including if it is a fibre according to the World Health Organization (WHO) criteria or a granular bio-persistent particle; For fibrous materials which may be potential hazardous, specific detection techniques, such as EM analysis from Tiers 2 and 3 may be required,
  - Any known or suspected hazards (including health, fire, and explosion) associated with the nano-objects or chemically comparable analogue bulk material.

- Information related to the workplace activities, including
  - Processes and handling steps, such as weighing, packaging, pouring, and mixing of nano-objects in the open versus conveying or high temperature synthesis in a fully enclosed system,
  - Processing of nano-containing intermediates, including the machining or milling of nancomposite, compounding using nano-enabled intermediates; or use of nanomaterials to facilitate production,
  - The presence of other processes in the workplace that may affect measurements or the measurement strategy employed, such as a docking door that opens to allow a forklift to enter the facility periodically,
  - The presence or absence of ventilation, HVAC, or air currents that could create positive or negative pressure that could impact the measurement strategy for airborne NOAA (refer to Section 4, Behavior of Airborne NOAA for more information).

5.1.1.2 Data analysis and decision-making

41. Once the information described in 5.1.1.1 has been gathered, the data should be analyzed in order to determine if the potential for release of engineered nano-objects into the occupational environment can be excluded. Tier 2 measurements are required if the release of engineered nano-objects cannot be excluded.

5.1.1.3 Data reporting requirements

42. During Tier 1, the focus should be on descriptions and yes/no responses and not on laboratory data or numerical information. In order to provide consistency and uniformity in the gathering and documentation of information as described in 5.1.1.1, a template for data gathering should be used. Two example templates are provided in Section 7 of this document for illustrative purposes. These templates can be tailored to be more appropriate for a given occupational environment. Additionally, following the data analysis step as described in 5.1.1.2, if the determination is made that a release of nano-objects into a workplace environment can be excluded, then that decision and all findings should be documented and archived for future reference. However, if the data analysis step finds that the release of nano-objects cannot be excluded, the practitioner must proceed to Tier 2 as described below.

5.1.2 Tier 2: Basic exposure assessment

43. The aim of Tier 2 is to conduct a basic exposure or release assessment. Tier 2 focuses on a straightforward approach for determining whether an exposure to engineered nano-objects may occur by a) utilizing easy-to-use, portable equipment and b) applying up-to-date knowledge. Tier 2 is the first tier in the harmonized approach that includes laboratory and/or field measurements. Key aspects to Tier 2 include characterizing a workplace environment for airborne NOAA using instruments and strategies previously discussed in Section 4 of this document. Additionally, Tier 2 measurements include an assessment of the background, also previously described in Section 4 of this document.

5.1.2.1 Measurement methods to be utilized

44. Tier 2 focuses on conducting a basic exposure assessment using easy-to-use, portable equipment to measure airborne NOAA. In addition, review of existing data or measurement of respirable nuisance dust in the workplace is recommended. The order of magnitude of dust exposure may support the decision on an appropriate measurement strategy for NOAA. As previously discussed in Section 4, however, a single commercial instrument capable of conducting exposure characterization for airborne NOAA in occupational environments does not yet exist. For this reason, utilization of multiple instruments, including real-time (commonly CPC and OPC) and off-line analysis (commonly EM) is required unless the source of elevated concentrations and the corresponding particle characteristics are known. For the case of off-line analysis, sample collection is required as was previously described in Section 4. Additionally, as the appropriate exposure metric is also still being debated, the determination of number concentration (or possibly surface area) beside mass concentrations is generally encouraged, given the limitations noted in Section 4 of the document for these various instruments. The determination of airborne number concentration collected in conjunction with off-line EM analysis forms the basis of the basic exposure assessment.

5.1.2.2 Guidance on specific measurement strategies

45. In order to determine the airborne number concentration and to collect samples for offline analysis as described in 5.1.2.1, a suitable measurement strategy must be employed that is tailored for the measurement scenario being conducted. As previously discussed, several factors must be considered in developing and implementing a suitable measurement strategy. As such, data from Tier 1 will be critical in developing the appropriate measurement strategy. Key factors and illustrative examples include the following:

- Selecting suitable instruments and analyses
  - Consider the goal of the exposure assessment and select instruments capable of measuring the appropriate exposure metric, taking into account any limitations on the instruments as described in Section 4.
  - Consider the combined use of real-time and off-line techniques for measuring airborne characteristics as well as compositional and/or morphological characteristics of interest.
  - Before any measurement campaign, all instruments must be calibrated to assure high data quality. This may also include cleaning of the device, possibly by the vendor depending on the previous measurement campaign.

  - Before any measurement campaign, it is recommended that each instrument is verified using internal reference or benchmark aerosols for size-classification and parallel measurements using internal reference instruments.

- Determining suitable measurement durations and frequencies

  - Identifying crucial information on the emission sources provides insight for the subsequent exposure assessment.

  - For a given process, consider any temporal fluctuations that may occur as well as any characteristic times for the process (such as ramp up time, time at steady state, and time for shut down) and tailor the measurement duration and/or measurement frequency accordingly. Additionally, the instrument selected must have a sufficient time resolution to be able to complete the measurement in the time scale of the process required, particularly for very short measurement durations.

  - If the particle concentration in the workplace is to be monitored permanently, an appropriate monitor for permanent operation needs to be chosen.

- Identifying suitable measurement locations

  - Consider workplace activities or air current conditions (established through positive or negative pressure, for example) in locating the inlet of instruments and record observed timed activities for correlation with measurement results.

  - Consider spatial variations that may occur from the point of release to the instrument inlet and their potential impact on measurement data.

- Conducting background measurements

  - Consider temporal and spatial variations that may impact background measurements as discussed in Section 4.

  - Select the background measurement scenario most suitable for the situation, including simultaneous (would require a second measurement instrument, increasing cost and requiring data related to the performance of both instruments compared to each other as discussed in Section 4) or sequential (may be impacted by temporal and/or spatial variations) measurements as discussed in Section 4.

  - Consider indoor versus outdoor variations as filtered inlet air will present a lower background than outdoor (ambient) air.

5.1.2.3 Minimum requirements for measurements

46. In Tier 2, the time resolved total (number) concentration must be collected and documented for at least 45 minutes for both the assessment and the background. The time period of 45 minutes is a suggestion from the expert group of nanoGEM but maybe changed when more experience with the tiered approaches have been gathered. If a characteristic time of possible release is shorter than 45 minutes, then the time resolved concentration for the entire duration of the assessment should be collected and documented. Sampling for the length of the activity or task is important as well as a shift-based approach, which will generate an understanding of observed task or shift and peak concentrations. The online measurement of

the particle concentration may be accompanied by particle sampling for off-line analysis to obtain a more definitive proof for the presence or absence of the nanomaterial in workplace air. The sampling duration depends on the requirements for the subsequent analysis.

5.1.2.4 Data analysis requirements

47. Data analysis for Tier 2 is focused on the results of time series data from real-time instruments. Particular attention should be directed toward any obvious outliers in the time series, including for the workplace environment, a process-specific measurement, or for the background. Additionally, the time series data (workplace, process, and/or background) should be analyzed for stability and any fluctuations. When the time series data are stable, the average and standard deviation for the entire duration should be calculated and noted. If the time series data show short spikes, shorter durations (e.g. 5 minutes) could be used for determining average and standard deviations. In general, the standard deviation for the background time series should be of the same order of magnitude or smaller than the standard deviations of the process time series. In this case, subtract the average background from the process concentrations. Otherwise, investigations according to Tier 3 must be conducted. Additionally, refer to the list of background measurement guidance (e.g. Asbach, 2012) regarding the need to evaluate possible differences in indoor versus outdoor background concentrations of particles as filtered inlet air will present a lower background than outdoor (ambient) air.

5.1.2.5 Data reporting requirements

48. In the data reporting for Tier 2, the following information must be recorded and archived for each assessment:

- Instrument (make, model, serial number, or other identification) and metric used, including particle size range
- Time series of concentration data
- Average and standard deviation of workplace and background concentration including information on averaging time intervals
- Information on mission sources as available.
- Information on confounding factors, e.g. thermal emission sources, forklift traffic, electromotors, etc.
- Record of workplace activities from the "activity-based" exposure assessment that may impact measurements
- Time series of workplace and background concentration need to be carefully evaluated. At a minimum, their mean value and standard deviations need to be provided. If the time resolved particle concentration (especially in the background) shows a clear trend, e.g. a constant increase or decrease, an evaluation based only on mean and standard deviation is not sufficient and the time series needs to be provided as well.
- Determination of whether or not the workplace or process concentration is deemed to be significant compared to the background

5.1.2.6 Additional equipment and data analyses where available/applicable

49. Additional off-line analyses can be conducted to augment the Tier 2 real-time measurements for chemical and/or morphological information. Sampling techniques described in Section 4 can be used for sample collection. Section 4 also describes several off-line instruments that can be used for exposure assessments. The most commonly used instruments include EM for nano-object morphology and EDX for chemical identification.

5.1.2.7 Decision criteria for moving to Tier 3

50. Based upon the findings from the Tier 2 exposure assessment, Tier 3 measurements are recommended if

- The resulting concentration difference between workplace under investigation and the background is more than three times the standard deviation of the varying background concentration. In this case the workplace or process concentration is deemed to be significantly increased and must be further assessed for the release of airborne nano-objects. The suggestion of the factor three is based on the assumed level of significance of elevated exposure concentrations and is also proposed for granular biopersistent nanoobjects without any specific toxicity. The factor three level was agreed upon by the nanoGEM expert team in absence of actual, robust data from comparison studies and should be revised in due time (nanoGEM, 2012). It has to be noted that the general measures and rules for workplace hygiene apply.

- Off-line sampling provides clear evidence for the presence of nano-objects from the workplace

51. Should the origin of the increased concentration become apparent during Tier 2, additional risk management actions may be taken according to the assessed hazard potential. Possible measures are installation of local exhaust ventilation, instead of Tier 3 measurements. The effectiveness of these new measures should be verified in another Tier 2 measurement. In case of persistent possible exposure of unknown hazard potential personal protective equipment may have to be used.

5.1.3 Tier 3: Expert exposure assessment

52. The aim of Tier 3 is to obtain as much information as possible on airborne nano-objects in the occupational environment in order to determine whether or not exposure to engineered nano-objects can be excluded or if further risk management steps need to be implemented. In Tier 3, all appropriate equipment, including personal samplers where relevant, and all techniques available should be utilized to provide a definitive conclusion regarding the presence of airborne NOAA in the occupational environment.

5.1.3.1 Measurement methods to be utilized

53. Tier 3 measurement methods extend beyond the easy-to-use, portable instruments that were the focus of Tier 2. In many of these cases, expert users must be employed to correctly operate and maintain the instruments and to analyze the resulting data. In Tier 3, real-time instruments in addition to those used in Tier 2 could include the following:

- Electrical mobility analysis for measuring particle number size distributions of submicron nano-objects,

- Optical or aerodynamic particle sizers or ELPI to measure the particle number size distributions of particles approximately >500 nm,

- Condensation particle counters or diffusion chargers to measure total particle number concentration,

- Nanoparticle surface area monitors to measure the lung (usually alveolar) deposited surface area concentration.

54. As discussed under Tier 2, these real-time instruments must be augmented with off-line analysis. The guidance on specific measurement strategies discussed for Tier 2 remains relevant for Tier 3 and specific SOPs for the devices, defining their applicability have to be written / used.

5.1.3.2 Data reporting requirements

55. Minimum requirement as stated for tier 2 (see section 5.1.2.5).

5.1.3.3 Data analysis requirements

56. With the expanded suite of real-time instruments included in Tier 3, additional data analysis is required, with specific attention on discrete particle size ranges. The data analysis requirements include the following:

- For each real-time workplace measurement, the average, maximum and minimum readings must be calculated for the entire particle spectrum for the background, workplace and corresponding supply/ventilation air inlet measurements. The same data (except for the supply air measurements) should be collected for the particle size range lower size limit (LSL) - 100 nm, 100 - 400 nm, 400 nm - 1 µm, 1 - 10 µm (only applicable to the size ranges that have been determined by nanoGEM as an inter-stakeholder panel).

- If different measurement principles have been used based upon the instruments selected, the equivalent particle diameters determined in each case must be taken into account. In any case, representation of these data must include a clear indication as to which equivalent diameter was used.

- The time series for the particle number concentration and the geometric mean of the particle size distribution at the workplace must be presented and every relevant event interpreted. The same data must be collected for the particle range LSL - 100 nm, 100 - 400 nm, 400 nm - 1 µm, 1 - 10 µm (only applicable to the size ranges that have been determined).

- The Concentration Ratio should be calculated and evaluated for the entire size range, as well as for the ranges LSL - 100 nm, 100 - 400 nm, 400 nm - 1 µm, 1 - 10 µm.

57. Note that the data reporting requirements for Tier 3 remain consistent with those discussed in Tier 2, Section 5.1.2.5.

5.1.3.4 Additional equipment and data analyses where available/applicable

58. Off-line analyses should be conducted to augment the Tier 3 real-time measurements for chemical and/or morphological information as described in Tier 2. Additional off-line analysis can include analysis of gravimetric samples and surface dust samples.

5.1.3.5 Decision criteria for whether additional risk management measures are required

59. Based upon the findings in Tier 3, additional risk management measures will be required if the workplace concentration is significantly increased over the background and if the size distribution, morphological and/or chemical analyses clearly show that the increase is a result of nano-object release. Basically, the decision on risk management measures has to be guided by the principle on hierarchy of controls. When additional risk management measures are employed, it is advisable that the effectiveness of those risk management measures are verified by repeating Tier 2 and potentially Tier 3 analyses.

5.2 Evaluation and Experiences

60. Ideally, any given measurement strategy should be evaluated and verified against real cases. Unfortunately, there are no published reports or articles except from the NEAT strategy (Methner, 2009) that document the experiences with and possible improvements to a proposed measurement strategy. Ideally, the comparability and reproducibility of a given measurement strategy should be evaluated, for example, by concurrent measurements and evaluations by different teams at the same location. The first so-called "round-robin-test" with this regard has been conducted within the nanoGEM-project where five different laboratories concurrently measured one workplace. The first results are promising and will be published in the near future (personal information by Kuhlbusch & Asbach). To build upon the above mentioned uncertainties, further uncertainties arises from the use of different measurement devices for the same measurement strategy, altering the detectable particle size range, changing the lower sensitivity, different response times or reacting differently to cross sensitivities like particle properties.

61. With the above review of 14 published reports, reviews, and articles, it becomes evident that a broad general consensus for a tiered approach exists. However, there is still a need for more consensus building regarding the interpretation of results from the tiered approach, which will most likely come from round-robin testing. The next step to be pursued requires the testing of the comparability and reproducibility of the measurement and data treatments within and between workplace measurement and assessment teams. Additionally, in the light of precautionary approaches, it will be important to investigate the sensitivity to ensure that there is very limited risk of false negatives following each of the specific well-defined measurement procedures. Some general points for consideration are given in the sections that follow.

5.2.1 The evaluation process

62. A measurement strategy can only be evaluated since there are no primary standard for this available. Principle methodologies to define uncertainties, lower detection limits, assessment values, etc. must be developed as part of the standard measurement strategy. These methodologies must allow for the use of different measurement devices and must be able to consider the different measurement circumstances influencing the measurements, including, for example, short term working steps as cleaning and maintenance as well as the influence by background concentrations. This evaluation process must be part of the SOPs, guidelines, and standards that support the measurement strategies in the field. Non-routine work processes may not be possible to cover by the measurement strategy, but still the general work safety measures apply.

5.2.2 Guidance on conducting valid measurements

63. Several standard Quality Assurance/Quality Control (QA/QC) procedures can be applied to the measurement strategy framework as follows:

- All devices and instruments should be well maintained and, if possible, calibrated such that the instrument is traceable to a primary standard. In cases where the latter is not possible, a factory calibration is required.

- If possible and applicable, the use of nano-reference materials is recommended to ensure high quality and comparability between different measurements. Example nano-reference materials include polystyrene latex, colloidal gold, or colloidal silica for e.g. size or collection efficiency measurements. Reference materials must be used according to their intended use and may not apply for all measurements, including for determining particle number concentration.

- All general performance checks (for example, zero, flow rates, etc.) must be conducted and documented prior to and following measurements.

- In sampling, field and media blanks as well as positive and negative controls (if applicable) should be collected. Analysis should be conducted in e.g. accredited laboratories for analysis.

5.2.3 Examples of processes that can be used to evaluate the performance

64. General performance criteria must be established for the different measurement values according to the need in the corresponding tier. This can be done, for example, by co-locating two instruments of the same make and model in a field comparison prior to and after a measurement campaign. The ratio of the readings of the two instruments should be within the manufacturer stated range of accuracy for that instrument. If the results are not within the range needed for the assessment, the field values may need to be discarded and the assessment measurements must be repeated. Additional examples for evaluating the performance of instruments and measurement values include testing for drifts, cross sensitivities, etc. These tests must be defined in detail in the corresponding SOPs, with consideration given to instrument, metric, and tier.

5.2.4 Economics (Cost of equipment)

65. Equipment costs needed for conducting measurements of nano-objects, particularly in Tier 3, are quite expensive and may also require expert knowledge in their operation and interpretation. Therefore, in addition to the costs associated with instrumentation, there are also costs associated with qualified and trained personnel. In many cases, the labor costs can outweigh the instrument costs. This is one of the reasons for the development of the tiered approach. For Tier 1, no instruments are needed. However, an experienced occupational hygienist with knowledge of the possible use and release of nano-objects is required. For Tier 2, real-time, in-field instrument costs needed for measurements range from 5-15 k€ (US$ 7-20k) (as of 2013). For Tier 3, the minimum cost of real-time, infield equipment to conduct measurements is estimated to be > 100 k€ (US$ 135k) with an additional need of experienced personnel.

5.2.5 Link to respirable mass concentration

66. Workplace exposure measurements for airborne particulates are often mass based with a focus on the respirable particle size range. The sensitivity of these measurements is designed for particles with > 400 nm aerodynamic particle diameter and can certainly include agglomerates of nano-objects often present at workplaces. The measurements in Tiers 2 and 3 are complementary to that of the respirable mass in that the additional measurements allow for the assessment of possible exposure to nano-objects below 100 nm. Data obtained with mobility particle sizers, particle number counters, and particle surface area measurement devices cannot be converted to the respirable mass concentration without allowing for significant errors associated with the assumptions that must be used in such conversions. For this reason,

the current mass based methodology can be used as an indication but needs to be further adapted to higher sensitivity for the assessment of occupational environments for airborne NOAA.

5.3 Final Recommendations and Conclusions

67. This document provides an overview of 14 publications that propose strategies to assess exposure to airborne NOAA. In these publications, there is strong consensus that a pragmatic yet effective approach is needed to keep labor and cost-intensive measurement campaigns to a minimum. Therefore, the strategy proposed in this document includes a three-tiered approach. Tier 1 focuses on data gathering, and Tier 2 includes simplified measurements. Only if Tier 2 reveals a significantly increased particle concentration in the workplace should an intensive Tier 3 measurement campaign be necessary. As described in Section 5.2, the costs and labor efforts for Tier 2 measurements are significantly lower than for Tier 3, thus making this approach also feasible for small and medium enterprises.

68. The focus of the three-tiered approach is clearly on assessing the exposure to or release of NOAA into a workplace environment. It is not considered to be a risk assessment strategy, which would also require an approach to assess the toxicity of the material. However, this strategy is a risk-based approach rather than a health based strategy that would rely on toxicology data. In this risk-based approach, the objective of the three- tiered approach is to conduct an exposure or release assessment to determine whether an exposure to engineered NOAA may occur and to determine if there is a need for further risk management steps to be taken. The approach described in this document can be seen in the context of risk management and risk mitigation. It can also be utilized to assess the effectiveness of risk mitigation measures, such as local ventilation and exhaust systems. In fact, the approach requires risk management measures to be taken if a significant increase of the NOAA concentration is detected (see Figure 1).

69. Currently, none of the commercially available aerosol measuring and sampling instruments is able to fulfill all requirements of an exposure assessment. Instead, a suite of instruments must be used. This increases the complexity of each measurement. The instrumentation described in this document is intended to give an overview of the commercially available equipment at the time of developing this approach (2014). Users are encouraged to carefully familiarize themselves with the instruments, including their capabilities and limitations.

70. A further impact on effective measurement strategies and/or exposure characterization and risk management is the lack of health based OELs and clarification on an exposure metric to be employed with a high enough sensitivity to NOAA.

71. As described in Section 5, the tiered approach represents the first step towards a harmonized NOAA exposure assessment strategy. As this has not yet been validated, users of the approach are highly encouraged to publish their data and findings in international journals or to share them with other users of the approach in order to identify and overcome shortcomings and to improve the overall harmonized tiered approach to measure and assess the potential to airborne emissions of engineered nano-objects (<100nm) and their agglomerates and aggregates (≥100nm at workplaces.

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7. ANNEX

7.1 Example Template 1

72. An example template is provided below, which represents data recommendations from a 2010 Workshop report; "Harmonization of Measurement Strategies for Exposure to Manufactured Nano-objects; Report of a workshop.

73. * Data Reporting Template

74. Recommended minimum set of contextual information to be collected and reported for Tiers 1, 2 or 3.

- The institute that collects the samples
- The premise in which samples are collected
- The location (inside the premise) in which the samples are collected
- The worker who is being sampled or who is present during the stationary measurement
- The sampling equipment and situation
- An adequate description of the process and facility
- The activity that is performed during the measurement (with specific exposure modifiers)
- Exposure mitigation, e.g., exhaust ventilation, PPE and other control measures that are in place during the measurement
- Climate conditions during the measurement e.g., temperature and relative humidity
- The product (with active nano ingredient) that is handled during the activity• The measurement results that are derived from the measurement device

7.2 Example Template 2

75. An adapted example checklist is provided below, which represents recommendations from nanoGEM as part of their SOP on "Information Gathering"

76. Background Information:

- Documentation of the workplace to be evaluated
- Address of the enterprise
- Name of the area supervisor
- Industry branch (e.g. manufacturing industry)
- Magnitude of the operations involving nanomaterials (Laboratory, pilot plant, industrial scale)

77. Material Information:

- Product description / chemical description (CAS-Nr.)
- Phase of matter (solid as powder/granulate, liquid as suspension or paste)
- Particle morphology (particle, plate, wire/tube)
- Solubility (e.g. water solubility)

- Is the material toxic in terms of substance specific toxicity?
- Surface composition / modification
- Crystal structure (amorphous, crystalline)
- Utilization (raw material, as component in matrix (weight-percent)
- Used amount (e.g. over one day or over one process)
- Is there a material safety data sheet? If so, attach to documentation

78. Action Information:

- What kind of action is being performed (e.g. weighing out, decantation, blending, dispersion...)?
- Description of the workplace area (location, local dimensions, ventilation, .)
- Duration and frequency of action (per shift, per week)
- How many workers perform the specific action?
- Apart from workers, are other persons potentially exposed? If so, how many?

79. Safety Measure Information:

- Results of a substitute test, a safety test using a substitute material
- Procedural safety measures (e.g. contained process, wet processing, automated process) including applied schedule for maintenance
- Safety measures for ventilation (e.g. closed or open acquisition, exhaust hood, automatic or manual)
- Maintenance schedule for technical safety
- Organisational safety measures (e.g. limitations on the number of workers, operating instructions)
- Individual safety measures (e.g. breathing mask, protection gloves, lab coat)
- An assessment from the person, responsible for information gathering, whether the designated safety measures are already implemented in the company.

80. Checklist following Tier 2 or Tier 3:

81. Aim of the information gathering process following the SOP is the assessment, whether exposure measurements can be conducted following the Tiered Approach. These questions are therefore to be answered:

1. Are nanomaterials being used in the workplace?

2. Does an OEL exist for the identified nanomaterial?

82. If both answers are yes, then exposure measurements following the Tiered Approach should be conducted.

83. Also, it can be clarified whether the exposure measurement can directly begin with Tier 3 protocol "Measurement of the inhalation exposure to nanoscale product materials and ultrafine aerosols at workplaces including the background concentration"

1. Do the considered nanomaterials possess health relevant morphologies?

84. Toxicological studies proved that these materials can already induce health effects if the exposure concentration is in the range of the background concentration. For now, only WHO-defined fibres are considered health relevant.

85. If the answer is yes, the measurement has to be directly started following Tier 3 protocol. Morphological characterization of the nanoscale structures have to be conducted. Single nanotubes/nanofibres, identified as WHO-fibres and agglomerated in open clusters, are to be treated this way. SOP's for this case are to be developed.

86. If the answer is no, the tiered approach has to be followed starting with the screening at Tier 2.