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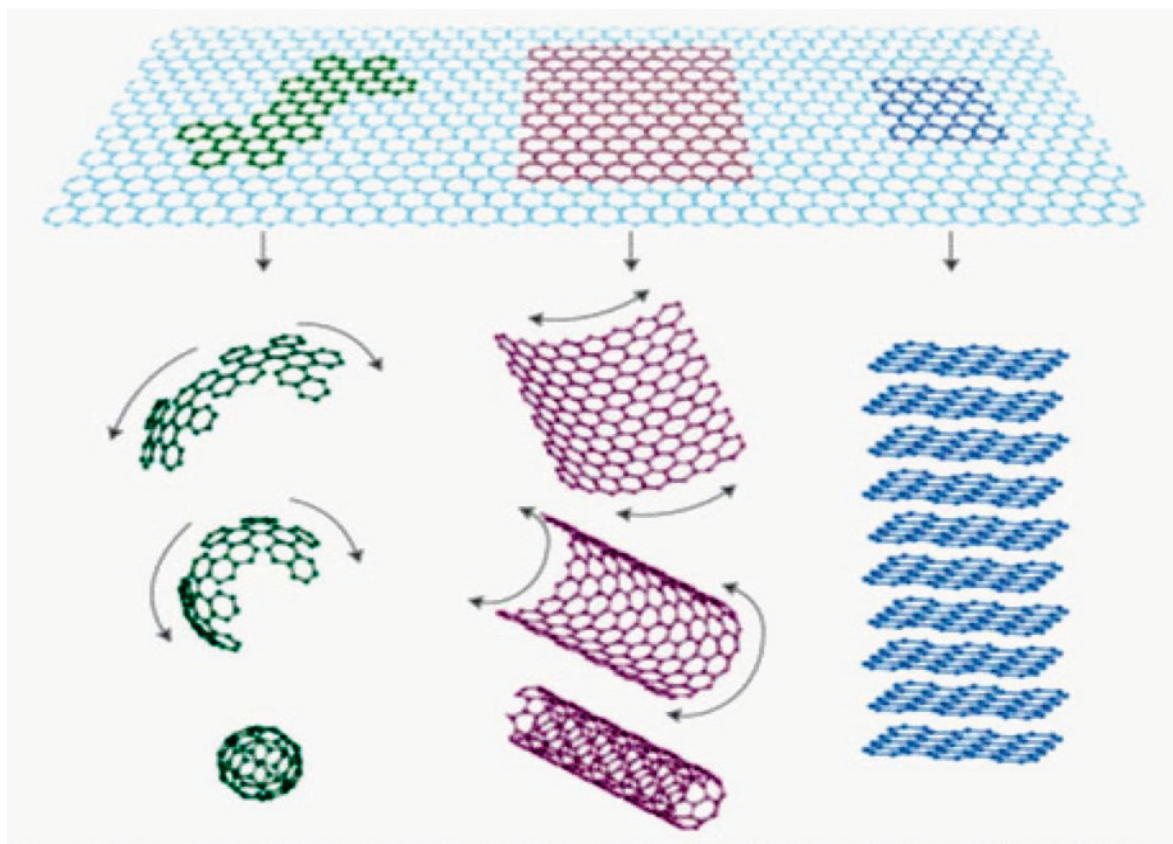
*Environmental Quality and Installations, Advanced and Additive Materials:
Sustainability for Army Acquisitions*

Methods Evaluation for Assessing Release of Manufactured Nanomaterials from Polymers, Consistent with the NanoGRID Framework

Advanced and Additive Materials: Sustainability for Army Acquisitions

Lynne T. Haber, Anthony J. Bednar, Alan J. Kennedy,
Mark L. Ballentine, and Richard A. Canady

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Methods Evaluation for Assessing Release of Manufactured Nanomaterials from Polymers, Consistent with the NanoGRID Framework

Advanced and Additive Materials: Sustainability for Army Acquisitions

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Abstract

This Technical Report (TR) extends on the ERDC NanoGRID (Nanomaterials Guidance for Risk Informed Deployment) program and considers methods needed to assess material released from composites made with manufactured nanomaterials (MN). Specifically this TR builds from the measurement literature on multi-walled carbon nanotubes released from a matrix to additional application to other MN. The TR informs product development decisions using NanoGRID by facilitating consideration of whether risk characterization is feasible for a given choice of product composition without substantial investment in analytical methods development. In many cases product use can be well characterized and the resulting methods requirements are simple, while in other cases the nature of product use may result in unmeasurable exposures to MN due to the analytical characterization constraints. Understanding these cases prior to product scale-up will enable more accurate cost projections and reduce potential harm of exposures to MN if they are later identified as posing potential health risks. Furthermore, applying the NanoGRID framework to guide evaluation of MN release measurement methods will aid in prioritizing methods evaluation and methods development work in process in ISO TC229 and ASTM E56.

The intention of this TR is to clarify risk management uncertainty for product development.

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Preface

This study was conducted for the Engineer Research and Development Center (ERDC) Environmental Laboratory (EL) under Project Number EQ/I 835, “Advanced and Additive Materials: Sustainability for Army Acquisitions.” The technical monitor was Ms. Shinita Jordan.

The work was performed by the Environmental Processes and Risk Branch (EPR) and the Environmental Chemistry Branch (EPC) of the Environmental Processes and Engineering Division (EP), ERDC-EL. At the time of publication, Dr. William M. Nelson was Branch Chief, CEERD-EPR, Mr. Warren P. Lorentz was Division Chief, CEERD-EP, and Dr. Elizabeth A. Ferguson, CEERD-EMJ was the Technical Director for the Environmental Quality and Instillation Research Program. The Director of ERDC-EL was Dr. Jack E. Davis and the Director was Dr. Ilker R. Adiguzel.

COL Ivan P. Beckman was Commander of ERDC, and Dr. David W. Pittman was the Director.

Acronyms and Abbreviations

Acronym	Meaning
AAS	Atomic Absorption Spectroscopy
EPC	Environmental Chemistry Branch
EL	Environmental Laboratory
EPE	Environmental Processes and Risk Branch
ERDC	Engineer Research and Development Center
MN	Manufactured Nanomaterial
MWCNT	Multi-Walled Carbon Nanotubes
NRC	U.S. National Research Council
OECD	Organisation for Economic Cooperation and Development
PA	Polyamide
TOR	Threshold of Regulation
TR	Technical Report
USFDA	U.S. Food and Drug Administration
UV	Ultraviolet

1 Introduction

1.1 Background

This technical report (TR) provides a methodical approach to considering methods needed to measure the first step of “release” of manufactured nanomaterial (MN) that have been added to a product. The overall goal of this approach is to inform selection of appropriate methods for measuring release in support of product use and safety decisions. Through this approach, the TR also provides a logical basis for review and evaluation of the utility of available methods, or identifies the absence of appropriate methods, to assess material released from commercial polymer composites. This TR is not focused on describing methods per se, rather the goal is to describe information that should be considered in selecting methods to support decision-making.

The TR begins with a review of how the processes resulting in release vary with the physical and chemical nature of the product as it interacts with environment or use conditions at various life cycle stages, focusing primarily on the consumer-use portions of the product life cycle. Aspects of the product that affect release are also considered, including the composite structure and the nature of the MN that is embedded in the composite (Collier et al. 2015a; Crane et al. 2008; Hansen et al. 2008, 2007). The TR then considers potential transformations of the MN during the physical or chemical changes that cause the release, based on the potential stresses on the product, and on the relative resilience of the matrix and the MN. These transformations, and their effect on the form of the released material, are again evaluated in terms of their effect on selection of methods to measure the released material. The last part of this TR addresses considerations for characterizing and quantifying the released material in support of particular decision components.

A key aspect of this TR is the use of the problem formulation and scoping through use of the NanoGRID decision support tool (<https://nano.el.erdcdren.mil/tools.html>) to determine and define the nature of the data needed, and, based on that determination, the nature of the needed analysis. As described by the U.S. National Research Council (NRC), the problem formulation and scoping (henceforth referred to as problem formulation) is a description of the purpose and context of the analysis,

and the nature of the decision that the analysis aims to support (NRC 2008). Without the need to support a decision, there would be no need for an analysis. This approach facilitates a focus on evaluation of methods that have practical utility in support of decisions being made for product development.

Another key concept is that the MN release analysis should be fit-for-purpose, as addressed in part by the intended use questions in Tier 2 of NanoGRID. The analysis should be sufficient to support the needed decision, but the depth of analysis (including characterization of uncertainty) should be consistent with the information needed to support the decision. In particular, this TR addresses methods for evaluating release in the context of informing decisions about human health risk. Issues related to ecological risk assessment are outside the scope of this TR.

This TR supplements the approach of the NanoGRID project, (Collier et al. 2015b), and (Martin et al. 2017a, 2017b, 2017c), in which a tiered guidance for risk-informed testing of nanotechnologies has been developed. A key aspect of that guidance was the development of a framework for evaluating the potential for a specific nanotechnology to release material meeting nano-specific parameters. These five tiers are: 1) screening criteria, 2) release potential, 3) environmental persistence, 4) sustainability, and 5) in depth product investigation. The framework minimizes the costs and resources needed for testing by using a tiered approach, with screening based on factors such as structure, size, surface area, relevant-use scenarios, unique behaviors, and release potential.

An additional goal is to summarize key aspects of the NanoGRID framework that can be leveraged into a TR currently under development by ISO TC229/PG29 (ISO TR) regarding the evaluation of MN release measurement methods. The ISO TR will formulate a fit for purpose approach for considering the utility and availability of methods to measure MN release from nano-enabled products. NanoGRID will be considered by the team developing the ISO TR as an organizing and scope defining framework for methods evaluation.

Tier 2 of the Collier et al. (2015) framework provides two options for consideration of exposure, either to conservatively assume 100% release and 100% persistence of the material, or to conduct a bench top release study, and then feed those results into the hazard portion of the

assessment. This TR identifies considerations that can be used to refine the exposure assessment, even at Tier II, so that additional options may be available, thus, aiding in the integration of the NanoGRID tiered approach into the ISO TR. These considerations carried through to the ISO TR may also extend the decision-support provided by NanoGRID itself. For example, with a more detailed review using the ISO TR to evaluate method utility and availability (fit for purpose to a use scenario), the assessor may be able to identify products and scenarios where evaluation of the potential for release can use simple, standardized release-measurement methods. This would allow release and persistence in those scenarios to be conservatively estimated (at less than 100%), based on scenario-specific information. Thus, this TR reflects early thinking that will be developed and enhanced in the ISO TR under TC229/PG29, in addition to similar work in progress in ASTM E56. It builds on earlier work related to release of nanomaterials, including (Kingston et al. 2014; Martin et al. 2017c; Wohlleben and Neubauer 2016).

In order to achieve an overarching synthesis of the factors affecting measurement of release across life cycle and media in support of specific levels of decision, this TR considered in detail the full body of research around one type of MN, multi-walled carbon nanotubes (MWCNT) and a limited number of polymers. Consideration of all MN and all composite materials would have resulted in a much broader range of input data that would have been intractable within the resources available. Nonetheless, MWCNT and polymers with widely-differing physical properties were chosen for the literature search and initial evaluation in this TR, so that a range of measurement methods and decision needs could be considered to inform a broader decision approach. A more complete consideration of additional MN and composite materials could be added in future editions of the TR or as addenda, as their addition informs measurement methods or decisions not addressed in this TR.

1.2 Objectives

The objectives of this work were to: (1) disseminate current knowledge on quantitation of MN release from nano-enabled products; (2) align and leverage the NanoGRID framework to risk-based, problem formulation approach and to determine the most applicable release tests on a case specific basis; and (3) clarify risk management uncertainty for product development.

1.3 Approach

This TR integrated literature knowledge and fit-for-purpose measurement methods for characterizing nanotube (and other MN) release from solid matrices, and outlined an approach to improve and to use NanoGRID as a decision tool for selecting and executing more relevant, robust and cost effective MN release methods.

1.4 Scope

The scope of this TR is to streamline measurement methods and decisions for characterizing MN release into the environment and move those methods toward standardization.

2 Understanding the Effect of Product Attributes and use on MN Release

This section is intended to aid consideration of the factors that influence the need for methods, so that the availability and utility of methods can be evaluated with respect to decision needs identified by NanoGRID. This section presents the conditions of release throughout the life cycle, the material attributes that affect release, and the effects of release conditions on the form of MN released.

2.1 Conditions of release throughout life cycle

Understanding of the potential for release of MN from a nano-enabled product begins with an understanding of the product and the potential for human exposure to release of MN from the product. Risk is a function of health hazard of the MN and the human exposure, and there is no risk if there is no exposure. Thus, key elements of the problem formulation include 1) determining the potential for human exposure to the product component that contains the MN, and 2) evaluating the potential for MN release from that component.

2.1.1 Evaluating exposure to the component that contains the MN

The first release evaluation element is consideration of where in the product the component with the MN occurs, and the potential for human contact under the conditions of normal consumer product use. Potential human exposure during manufacture of the product and at the end of the life cycle (e.g., during recycling or disposal) are not the focus of this TR, but are addressed briefly in this section. For example, if a nanoenabled product is encased within a consumer product, or is part of a machine where it is accessible only during maintenance, there are limited opportunities for human exposure as part of the release event, although there may be potential for exposure during episodic maintenance. Factors to consider at this point might include the following issues:

- A description of the component and how the MN is part of the component (e.g., is it in direct contact with human skin, on the surface of the component with infrequent skin contact but subject to mechanical wear, and/or encased and poorly accessible)?

- A description of common use scenarios, including frequency of use and relevant population (e.g., consumer, occupational, adults, or children). Consideration of the conditions of use (e.g., temperature, indoor vs. outdoor) is also important for considering potential weathering and other sources of wear.
- Impact of maintenance on the component and potential for exposures.

Consideration of these sorts of factors is a basic part of any exposure assessment, but is of particular importance for the subject of this TR, in light of the complexity of both assessing exposures to MN and tying those exposures to toxicity for evaluating risk. Specifically, consideration of the potential for human contact with the nano-enabled component, and releases from that component, are an important part of any framework related to release, such as the framework to be developed in the ISO TR under TC229/PG29. If the component is encased in a sealed container and there is no potential for human exposure, further screening is not needed for this portion of the life cycle. However, confirmatory analysis using simple MN component detection methodologies may be indicated during the prototyping and final production phases of the product development process. Other analyses may be needed to evaluate the risk potential during manufacture or disposal.

2.1.2 Evaluating potential for MN release from the product component

The second release evaluation element of problem formulation addresses the potential for MN release. Researchers (Duncan 2015; Duncan and Pillai 2015) differentiated between two general release paradigms. The first paradigm, reviewed by Duncan and Pillai (2015), involves diffusion, dissolution, or desorption of the MN from the composite matrix. These mechanisms are most relevant when the composite is in contact with a liquid matrix, such as for biomedical devices, in food packaging, or water infrastructure (e.g., residential water pipes). One might also hypothesize that desorption (together with mechanical stress) may be relevant for composites that come in contact with human skin. Duncan and Pillai (2015) reviewed studies of MN release by these mechanisms, but none of the studies reviewed considered MWCNT, the initial case evaluation of this TR. It was unclear whether such studies were not performed with MWCNT due to lack of relevant applications, lack of expectation of de-sorption, dissolution or desorption events for MWCNT, lack of readily available detection methods to differentiate MWCTs from the matrix, or some combination of these and other reasons. However, given the fibrous nature

of MWCNT, it is plausible to expect that this group of mechanisms would be less relevant to MWCNT than they would be for some other MN, such as nano-metal oxides. Duncan and Pillai (2015) discussed the use of empirical testing, theoretical approaches, and semi-empirical approaches to avoid needing to estimate 100% migration of a specific MN within a specific polymeric composite.

The second general release paradigm is degradation of the composite matrix (Duncan 2015). This is an area that has been extensively evaluated as part of the NanoRelease project (Froggett et al. 2014; Kingston et al. 2014; Wohlleben et al. 2017; Wohlleben and Neubauer 2016), particularly in the context of MWCNT embedded in composites. This earlier work has identified several key degradation mechanisms, and has included a number of studies that have specifically measured release via these various mechanisms. Key mechanisms include the following:

- Thermal stress (heat or cold)
- Mechanical stress (e.g., sanding, drilling, cutting, grinding, shredding)
- Chemical stress (e.g., hydrolysis, acid/base)
- Photodegradation (ultraviolet (UV) light, fluorescent light)
- Weathering (e.g., UV light, fluorescent light, wind, heat, rain)
- Washing scenarios
- Sweat scenarios

In order to determine which of these mechanisms may be important, one needs to go back to the problem formulation and describe the general scenario for use. Some important questions to consider include the following:

- What is the nature of the product (e.g., consumer product, construction material)?
- Is the nano-enabled component a finished product, or will it be undergoing further processing (potentially leading to additional mechanical stresses)?
- Where will the product be used (e.g., temperate climate, outside under weather extremes)?
- What are the relevant aging scenarios?
- Will the component be immersed in water (continuously or intermittently)?

Based on the responses to these questions, the assessor can structure decision steps, information needs, and analysis to determine the potential for release, the likely media into which release may occur, rates of release, and the potential likelihood of human exposure. This information can then inform the kinds of sampling and analytic methods that may be needed to support decisions about product composition or methods to measure MN release for risk management.

A number of studies have quantified release of MN from various composites under a variety of conditions (Froggett et al. 2014; Wohlleben and Neubauer 2016). In particular, release of MWCNT from epoxy and polyamide (PA) composites have been evaluated under conditions of mechanical stress (e.g, Bello et al. 2010, 2009; Cena and Peters 2011; Fleury et al. 2011; Golanski et al. 2012; Gomez et al. 2014; Heitbrink and Lo 2015; Hirth et al. 2013; Huang et al. 2012; Kang et al. 2017; Ogura et al. 2017a, 2017b; Starost et al. 2017), artificial weathering by UV light and rain (Busquets-Fité et al. 2013; Fernández-Rosas et al. 2016; Petersen et al. 2014; Vilar et al. 2013; Wohlleben et al. 2017; Wohlleben and Neubauer 2016), and thermal stress (Ribeiro et al. 2013; Schartel et al. 2005; Schlagenhauf et al. 2015). Several studies have also evaluated release of MWCNT from other composites (Kaiser et al. 2014), or release of other MN from composites (Wohlleben and Neubauer 2016). (Koivisto et al. 2017) created a release library of quantitative data on release amounts and properties of released fragments from 374 different scenarios of different composites, MN, and release scenarios. These studies are useful for bounding or initial characterization of the potential amount of release under demanding conditions, and in some cases for relating the amount released to the amount of MN in the tested composite, although additional considerations, as discussed in the remainder of this TR, are important before the results can be used in a risk assessment and decision support context.

Importantly, many of the studies evaluated the impact of multiple stressors (i.e., occurring during weathering and other aging processes). Consideration of multiple stressors is important, such combinations could result in greater MN release and exposure than either factor alone. For example, UV exposure or some chemicals may degrade a composite matrix, without degrading the MN embedded in the composite (Duncan 2015). The degradation may lead directly to the release of MN particles, or the particles may collect at the surface of the material, and thus, be more

accessible to other release mechanisms. For a fibrous MN, the degradation may leave a tangled surface network of MN fibers that are more easily sheared off under conditions of mechanical stress. The combination of composite degradation with mechanical stress may result in greater release of the MN in a nanoscale form than would occur solely with either stressor. Note that this combined effect is different from the phenomenon reported by Kingston et al. (2014), where degradation of an epoxy composite can lead to MWCNT-rich areas on the surface that may protect the epoxy from UV degradation and reduce the potential for MWCNT release from further UV exposure.

2.2 Material attributes that affect release

Attributes of the composite matrix (polymer) and the MN will affect release rates and release forms, and thereby inform the need for specific kinds of sampling and analytic methods.

2.2.1 Consideration of polymer used in the composite

After consideration of the specific use scenario, another important part of the problem formulation that informs method choice is description and identification of the polymer used in the composite. This allows for the identification of the physical properties of the polymer with regard to its effect on quantitative release rates and the nature of the released material (e.g., primarily bound in polymer fragments or free MN). This information would then inform both the qualitative and quantitative need for specific sampling and measurement technologies. This information can be gathered on a generic basis from the literature as a first cut to identifying methods needs, followed by a more specific evaluation as required.

For example, Kingston et al. (2014) reviewed composite characteristics affecting CNT release potential for epoxy, polyamide, polyurethane, polyethylene, and polycarbonate. They noted that the polymer composites are specifically formulated with materials such as plasticizers, stabilizers, UV protective additives, surfactants, and polymerization modifiers, to attain certain physical and chemical properties. These properties may include making the polymer compatible with other design elements, promoting adhesion, increasing flexibility, and reducing friction. The nature of these additives, together with inherent characteristics of the polymers, determine the release characteristics of the polymer composite, and of the MN embedded in it. For example, epoxy and polycarbonate are hard and

brittle, while polyamide, polyurethane, and polyethylene are soft and ductile. These differences affect how the composite deforms and fractures under mechanical stress, including the potential for the composite to elongate around the MWCNT at breaks, while determining whether protrusions occur. It is likely that polymer matrices that are softer and more flexible would show stronger resistance to release of MWCNT from mechanical stresses, while harder resins such as epoxies have higher release potential (Kingston et al. 2014). Kingston et al. (2014) concluded that “it is fairly unlikely that free MWCNT will be released, but that CNT embedded in or attached to small polymer fragments is the most likely form of release.”

Susceptibility to chemical stressors also differs among composites. For example, epoxy resins are highly resistant to solvents, acids, and bases (Kingston et al. 2014). Nylons (polyamides) are also stable in many solvents, but can be eroded by oxidants such as hydrogen peroxide or chlorine based decolorants. Table 5 of Kingston et al. (2014) lists the five major types of MWCNT polymer systems, their mechanical characteristics, and characterizes the susceptibility to a variety of different wearing or release mechanisms. This type of table could be used in the semi-quantitative evaluation of release potential for a specific product and in determining the type of release measurements that may be necessary (see Section 3).

This approach could be generalized for other embedded MN in addition to MWCNT. Polymer additives may also affect durability to abrasion, reaction to water, or reaction to UV radiation. The impact of these additives should be considered in light of the release point and media combinations identified in the preceding section for a given use.

2.2.2 Consideration of MN interactions with the composite

As considered for the nature of the composite, the nature of the MN also contributes to the potential for release. Key characteristics of the MN affecting interaction with the composite should be specified, including the nature of any functionalization, adducts, coatings, or other aspects of the MN composition that may affect MN release rates. This information can then inform relative MN release rates in combination with polymer uses, and in turn, inform requirements for quantitative or qualitative measurement in support of decision needs.

For example, surface functionalization of MWCNTs is often used to improve compatibility with the polymer matrix, and the release potential will be affected by any chemical bonding between the MWCNT and the polymer (Kingston et al. 2014). Data on the impact of functionalization on release are limited, however, and additional studies on the impact of functionalization are needed in order to develop a systematic approach. One area where data are available is on the increased thermal stability of amine-modified MWCNTs in epoxy. Kingston et al. (2014) states that this increased thermal stability suggests that typical consumer use at elevated temperatures would result in only limited release of the MWCNTs from epoxy. Additionally, MWCNTs functionalized with aromatic amines had better dispersion characteristics when compared to pristine MWCNTs.

The state of the dispersion of the MN in the composite matrix should also be specified. Kingston et al. (2014) identified the following critical factors for the release of MWCNTs from epoxy composites: 1) their successful dispersion and incorporation into the epoxy matrix, 2) length and orientation of the MWCNT, and 3) and surface functionalization. Kingston et al. (2014) noted that agglomeration and higher filler contents could result in improper impregnation in the epoxy matrix and lead to composite failure, suggesting that assumptions of maximal incorporation rates and release rates may be limited by product design issues. Information on the nature and degree of dispersion in the matrix may enable conceptual modeling in the future, and thus, facilitate risk management decisions with limited testing. Recent efforts to address grouping and “essential nano-specific characteristics” should be considered in the approach (e.g., Arts et al. 2014, 2015).

Tracer elements that can serve as a marker for the MN should be identified, since they can aid in identification of potential of surrogate measures for the detection or quantification of the released MN. For example, cobalt is a catalyst for the manufacture of some types of MWCNT, and has been used as a marker for MWCNT exposure (Pauluhn 2010). This information can provide a basis for feasible analysis and decision support under some product use conditions.

As discussed further below, the relationship between the MN and the matrix should also be considered in light of the relative resilience of each. A highly resilient (e.g., pliable and resistant to shear stresses) MN may be released at different rates than a stiff MN.

2.3 Effects of release conditions on the form of MN released

Consideration of the overall composite structure of the materials with respect to their potential interactions with release mechanisms and measurement methods will also inform measurement needs. As reviewed in Harper et al. (2015), the release mechanisms include physical and chemical stressors that may change the nature of the released material. Structured evaluation of this information is important because of the wide variety in matrix and filler types, and the effect that variation can have on likelihood of release, type of release (particles with filler in them, free nanoscale particles, free filler, degraded filler, etc.), and on magnitude of release (Kaiser et al. 2014). Each of these factors may influence the type of method that is needed to detect or measure the release, or to confirm a lack of release. Both the nature of the released material and the potential for transformation of the MN, either during manufacturing or release, need to be considered. The physical form of the MN and its relationship to the composite at the release point will affect the choice of sampling and measurement methods. The form of the released particles is also key for determining both the dose to immediate receptors and the ultimate fate and transport of the particle.

To aid in considering the potential for transformations at the release point, nano-enabled products and release scenarios can be grouped into those for which the MN is less resilient than the matrix (e.g., Ag-textile, Cu-wood), and those for which the MN is more resilient than the matrix (e.g., weathering of MWCNT-epoxy, of MWCNT-PA). Hirth et al. (2013) linked the potential for the development of MWCNT protrusions to the elongation-at-break percent of the host composite, and suggested that materials that elongate to form a “neck” are less likely to have MWCNT protrusions.

3 Characterizing MN Released From Products

This section addresses issues related to analysis of the released nanomaterial. A large variety of different analytical methods are available for conducting this analysis. The appropriate choice of method(s) will depend on decision needs regarding potential implications of release of MN. Use of the NanoGRID framework to identify decision needs throughout the product development process will greatly clarify where resources may be needed for research and standardization of measurement methods. In some cases, the methods needed to support a decision may be readily available and standardized. In other cases, the methods may be experimental or not calibrated for nanoscale measurements (Petersen et al. 2015). In still other cases, there may be no methods to measure a particularly critical characteristic or no standardized methods to do so. Furthermore, methods may be available but have prohibitive costs in time or resources to be useful to support a decision need.

Elaboration of these possibilities using decision frameworks such as NanoGRID will inform standards work currently in process under various standards development processes in ISO and ASTM, including a TR currently in process by ISO TC229/PG29. As an example, several methods for detection, characterization, and quantitation of metal-containing nanomaterials, such as FFF-ICP-MS and SP-ICP-MS, exist, however, no such broadly applicable method exists for carbon-based nanomaterials, other than perhaps microscopy (Bednar et al. 2015). This challenge has led to the development of decision-tree flow charts which can aid in the selection of appropriate methods for characterization of carbon-based nanomaterials, using both common and specialized research techniques (Martin et al. 2017a, 2017b, 2017c).

Some methods provide only *qualitative* information on the nature of the released material, such as its shape or topography. While not providing quantitative information that feeds directly into exposure quantification used in risk characterization, an understanding of such qualitative factors may be critical for determining the future behavior of the MN, such as its potential for further interactions with other materials, and ultimately its fate and transport. Qualitative factors such as crystal structure are also important for determining the toxicity of MN such as nanoscale silver and

nanoscale TiO₂. Information on related characteristics can also be important. For example, crystallinity can be a proxy for other properties such as surface chemistry and solubility (OECD 2016).

In other cases, *semi-quantitative* methods that focus on whether a MN can be detected may be sufficient where demonstration of a lack of release is needed to support decisions of material choices for products. Finally, statistically rigorous high volume sampling methods that would support quantitative characterization of MN in released material may be needed in situations where there are relatively high levels of release that may feed directly into exposure pathways.

Based on the problem formulation and description of the scenario, as elaborated in Section 2, the assessor can determine the nature of the analytical methods needed, including both the endpoints that need to be evaluated and the level of precision needed (e.g., detection vs. quantitative evaluation) in order to address the relevant risk assessment questions. Answering those questions, in combination with an understanding of the capabilities, strengths, and limitations of various methods, will determine what methods need to be applied.

3.1 Key information challenges for understanding the relevance of release information

In order to relate the exposure to health risk, it is important to be able to connect the exposure to relevant measures of toxicity, but there are at least three challenges to making this connection. The first is that, for most MN, it is not clear which characteristics are key determinants of toxicity. MN may differ in size of the primary particle and the nature of the aggregated state, the resulting surface area, nature and degree of functionalization, coatings and other modifications, surface charge, crystal state, and surface modification. To aid in obtaining useable toxicity data, some researchers have used standardized commercial versions of some MN, but some aspects (e.g., surface charge and degree of aggregation/agglomeration) of even standardized versions will vary with the method of preparation, even when starting with the same commercial product.

The second major challenge is that the appropriate dose units for prediction of toxicity are often not known, and exposure needs to be measured in dose units that can be related to relevant toxicity benchmarks (Hull et al. 2012). Surface area has been identified as reasonably predictive

of human health and/or aquatic toxicity for some materials, such as TiO₂ (Sager et al. 2009) and nanosilver (Kennedy et al. 2015), but is not readily measured in a screening context. Identification of the appropriate dose metric for MWCNT is more problematic, due to the lack of practical methods for fiber counting, although some recent assessments have used carbon mass as the basis (Erdely et al. 2013; Kuempel 2011). Carbon mass may be appropriate when comparing exposure to free MWCNT from those based on a single commercial product, but is more problematic in the context of release measurements.

The third significant challenge to connecting MN exposure measurement to potential health risk relates to understanding the material being measured that has been released from the MN enabled product. As noted in Section 2, the MN may undergo transformations in the context of the release process. Furthermore, as noted in Section 2, release of MWCNT embedded in composites can result in a combination of fragments of various sizes (nanoscale and non-nanoscale), including composite with or without the MWCNT embedded in or bonded to the surface, along with some fraction of free MWCNT. Further, abrasion of various matrices themselves may result in release of nanoscale particles (Brame et al. 2015). Determining the relevant dose, or even the dose-metric of the MWCNT in this situation may be complex to the point of impossibility. Furthermore, collection of the released material to use in toxicity testing seems prohibitive when the combinations of release scenarios are considered for any particular composite. However, the available data indicate that release of free MWCNTs is rare for many of the composites examined to date, although some scenarios releasing free MWCNTs were identified (Harper et al. 2015). This means that the exposure and toxicokinetics of the released material for use in decision support for product use may often be determined primarily by the composite and the released particle size, rather than the behavior of the free MWCNT. This logical conclusion, if confirmed in standardized testing for combinations of composite and MN, may greatly simplify measurement needs under some use conditions.

In light of these challenges, the state of the science suggests a reframing of problem formulation to earlier points in product development. Consideration of the challenges suggests that a key initial question is whether the MN is released in the use scenario of interest and could result in human exposure beyond *de minimis* levels. Under this formulation, a key analytical issue becomes detection methods coupled with product

development and prototyping phases. If the MN can be detected (with a sensitivity based on a widely accepted definition of *de minimis*), then a more extensive analysis is necessary, as described in the framework of Martin et al. (2017b, 2017c). If sufficient nanoscale material is released, a hazard characterization (corresponding to Tier 4 of Collier et al. (2015)) may also be necessary (Martin et al. 2017a). If the MN cannot be detected, then more detailed analytical methods are not needed. This sort of approach is consistent with the idea of making sure that the assessment is “fit for purpose,” as is the intention of selecting release studies by their relevant use and potential release scenarios in Tier 2 of NanoGRID and Collier et al. (2015). This approach to product development is similar to regulatory contexts such as the Threshold of Regulation (TOR) used by the U.S. Food and Drug Administration (USFDA) for food contact materials (Cheeseman et al. 1999). Thus, rather than needing to prove a negative (no release), which is essentially an impossible task (Alberts et al. 2018), the TOR approach could be used to identify some degree of release (and thus exposure) that can be considered *de minimis* from a toxicological basis. The goal of the targeted release testing then becomes determining whether release is below that *de minimis* level. The Engineer Research and Development Center (ERDC) is taking incremental steps toward this goal by establishing a carbon nanotube detection limit for a fast mobility particle analyzer after abrasion studies (Alberts et al. 2018).

3.2 Using NanoGRID to inform methods selection

NanoGRID decision tree approaches can be used to plan decision support needs within components of the overall measurement method choice. Martin et al. (2017b, 2017c) lay out a framework for the types of testing needed for characterizing material post-release, beginning with consideration of the nature of the sample (solid, solution/suspension, or airborne), including purification and characterization steps. It also identifies screening steps to avoid unnecessary testing, such as analyzing liquid samples to confirm the presence of NM. Working within the structure provided by NanoGRID, the ISO TC229/PG29 effort may be able to add additional characterization of analytical methods with regard to their utility for various problem formulations (e.g., screening, semi-quantitative, and quantitative dose-response evaluation), in addition to considering ease and cost of use.

Considering this application, the following four methods (choices) of the NanoGRID decision tree approach can be used: 1) identification of

parameters that need to be measured based on the problem formulation, and framing decision support needs to be addressed in 2) sampling methods, 3) sample preparation, and 4) analytical methods selected. These are addressed in the following subsections. Selections guided by NanoGRID for each component are affected by both the materials selection and release conditions described in Section 2 of this TR.

3.3 Identification of parameters that need to be measured

Problem formulation should identify the decisions that need to be made and what data are needed for risk characterization to support decision makers. The number of parameters that could be measured for MNs is extensive, and their relationship to parameters measured in toxicity studies is complex due to incomplete and inconsistent characterization across the toxicity data sets (OECD 2016). Use of NanoGRID, as elaborated in Martin et al. (2017a, 2017b, 2017c), to parse through and describe the anticipated risk characterization needs in the context of these parameter choices is a critical component of problem formulation. Use of tiered approaches, like NanoGRID, to evaluate parameter measurement needs for decision support should be taken up in standards development.

For example, NanoGRID can be used to identify scenarios within a product life cycle where a screening assessment determination is sufficient to support decisions, such as when the relevant nano-enabled component is in a sealed container at a particular life cycle stage. NanoGRID would be used to support use of either a logical test (e.g., no access is possible during the use phase) or to a screening test of prototypes to evaluate the manufacturing process for possible emissions of the MN (e.g., is release below a *de minimis* rate compared to toxic levels). In some decision contexts, a simple determination of the presence of component elements of the MN may be sufficient.

If the potential for a release cannot be eliminated in the screening evaluation, subsequent stages of evaluation in a tiered approach based on NanoGRID could be used to determine the type of information needed to support the decision and the level of precision needed. This consideration would include the nature of the finished product, the uses and potential conditions of release, and the specific composite and MN embedded in the composite. Consideration of the specific MN, and the factors determining exposure and toxicity for that MN, should also be incorporated in problem formulation (Martin et al. 2017a). For example, stiffness and aspect ratio

may be critical for nanotubes, while crystal structure may be important for certain metal MNs (e.g., TiO₂).

3.3.1 Framing decision support needs addressed in sample collection

Determining validity of sampling collection with respect to decision needs may present particular challenges for NM release characterization. Therefore, integration of decision needs evaluation with the limitations of sample collection methods should be considered in application of NanoGRID to measurement methods needs evaluation. For example, the sample collection needs will depend on the analytical technique to be employed and the goals of qualitative or quantitative characterization of the MN. Issues such as heterogeneity (particle size and type) and interaction of surface charge with sampling media may affect sampling frequency. In some cases the needed sampling frequency may be prohibitively expensive.

If evaluation through NanoGRID approaches indicates that a quantitative risk assessment is needed to support decisions, it is important that the sample collection process would not affect characteristics that may related to toxicity, such as the aspect ratio, defect rate, and stiffness for MWCNT. Similarly, the sampling process would need to not affect the particle size and crystal form for TiO₂.

Scenario-specific considerations within a NanoGRID framework can be used to further clarify the sampling needs for decision support. For example, breathing zone measurements during machining provide information on potential occupational exposures, while continuous area samples may be appropriate for evaluating exposures to consumer products under conditions of actual use.

3.3.2 Framing decision support needs in sample preparation

Additional challenges in generating data to inform risk characterization are introduced when preparing the sampled material for analysis. The purposes of the sample preparation step may be to remove contaminants, concentrate the MN for analytic procedures, or to obtain the MN in a form appropriate for the application of the chosen measurement method(s). The issues can be complex because simple dilution or extraction steps can change the toxicity characteristics of the material. Here again, a structured approach to understanding decision support needs based on NanoGRID can be used to identify where such issues may arise. If sampling and

analytic needs require a concentrate or extract of the MN, then further validation of the resulting data with respect to the decision need may be required. For example, agglomeration/aggregation state is affected by concentration in predictable ways, so a back-calculation to an unagglomerated state for particle size distribution may be indicated by decision needs. Alternatively, a more sensitive method may be required to evaluate a dilute sample as a study validation step.

As with collection, it may in some cases be necessary to preserve the properties of the MN in the same state as in the matrix into which they were released. Whether such preservation is needed is determined by, for example, whether a screening or surrogate measure will support the decision need, or whether a more detailed quantitative analysis of an “as potentially exposed” MN characteristic is required.

3.3.3 Framing decision support needs addressed in analytic methods

A wide variety of instruments and analytic measurement methods are available to characterize MNs, including multiple methods for key MN characterization endpoints such as particle size. The structured evaluation approach of NanoGRID can be used, or adapted through additional standards work, as in ISO TC229/PG29, to inform the selection of the methods to support identified decision needs. The choice of analytical methods will depend on the problem formulation, including factors such as the time and cost for conducting the measurement, method sensitivity, and potential biases in the measurement. For example, methods to support a qualitative decision about whether the material can be detected may be simpler than those needed for a quantitative characterization of a set of parameters for the same MN in support of dose estimation (OECD 2016). Thus, for example, atomic absorption spectroscopy (AAS) can be useful for screening for detection of the components of the MN, such as cobalt or other catalyst used in manufacture as a trace component of a particular MWCNT. The choice of analytic method is further complicated by the fact that data for key characteristics, such as particle size, can vary depending on the analytic method so that different studies of the same material report it as containing different particle sizes. To aid in determining the appropriate measurement method, it would be useful to have a compilation of methods, organized according to the utility for various problem formulations (e.g., screening, semi-quantitative, and quantitative dose-response evaluation), and should include ease and cost of use. Such a compilation could build on the information compiled by Martin et al. (2017b).

4 Conclusion

The review and evaluation provided in this TR is intended to aid in identifying “fit for purpose” measurement approaches and methods for the initial release or emission of MN from products using them. This expands the approach of NanoGRID by identifying how its tiered decision support framework can be used to focus selection or development of MN measurement methods, and thereby, more completely inform risk management decisions. A specific outcome of this evaluation may be, for example, to provide intermediate options between doing a benchtop release test and making a conservative assumption of 100% release. The evaluation may also support selection of appropriate methods to use in the benchtop release test or identify near-term methods-research needs to support introduction of new materials into products. Potential enhancements to NanoGRID suggested by this evaluation to further support risk-informed testing of nanotechnologies are proposed (Table 1).

Table 1. Recommendations for extending NanoGRID.

Need	Recommendation
Provide additional context to problem formulation.	Add a decision point to Tier 2 to consider the finished product and scenarios to determine whether logical consideration of potential release points and evaluation of the potential for release can avoid the need for a benchtop release study or additionally target the benchtop study. Some suggested framing questions are provided in Section 2.1.
Consideration of how the nature of the matrix affects the nature of released materials.	Based on user input on the composition of the matrix, provide information on the potential for release of free NM. This would likely involve interplay between basic information in Tier 1 and consideration of product stresses in Tier 2 .

This work provides input to standards development in process at ISO and ASTM by framing the need for measurement methods standards for MN in terms of risk management decision support for product development that can exploit novel capabilities of emerging nanoscale materials. In particular, application of NanoGRID as a framework for guiding evaluation of the need for measurement methods may be useful in guiding development of the current nanomaterial release measurement effort being undertaken by ISO TC229/PG29 (Table 2).

Table 2. Recommendations for using NanoGRID to inform ISO TC229/PG29.

Need	Recommendation
Select the most relevant release tests based on intended use. Select a targeted path of high impact combinational tests to generate the worst case condition.	Integrate the test ranking questions and multi-criteria decision analysis components of Tier 2 into the ISO TR to the extent practicable within the confines of a written document. The ISO TR may also refer to use of the NanoGRID electronic executable to make this ranking of decision analysis less abstract.
Clarify the simple vs. difficult paths to product development considering sample collection, sample preparation, and analytic method selection for characterizing health risk of MN use.	Integrate problem formulation structure of NanoGRID into the ISO TR evaluation of utility of MN measurement methods. Present and adapt the presentation of NanoGRID and other risk management tools within the ISO TR document so that evaluations of methods-utility elements (material characteristics, sampling methods, analytic methods choices) refer to and are bounded by realistic decision needs.
Plan resource needs for methods development and standardization in terms of mission critical product development.	Include case studies in the ISO TR that can be used as a demonstration for how frameworks such as NanoGRID can be used to aid in test/measurement selection.
Predict and manage product development dead ends where safety issues may arise for use of emerging nanomaterials.	Address in the ISO TR the use of decision frameworks such as NanoGRID to identify critical “no-go” gaps in current ability to measure MN release rates in a form useful for evaluating toxicity and risk.

Furthermore, there is a need to consider the impact of product design on the kinds of releases that may enter into potential exposure pathways leading to populations. Framing questions are provided to aid in the determination of relevant release mechanisms, based on the exposure and use scenario, and could be incorporated into the ISO TC229/PG29 project.

The release potential is affected by the specific chemical and physical properties of the polymer composite in which the MN is embedded, and the properties of the added MN. Evaluation of specific combinations (e.g., this polymer, this additive, this MN, this surface modification on the MN) and the physical and chemical forces that cause release can aid in understanding the resulting potential for release, and thus, the measurement needs. For example, soft, deformable polyamide polymers may form a neck around MWCNTs, limiting the potential for release of free MWCNT fibers in arid environments, but these polymers have a higher release rate in aqueous environments. UV sensitive epoxy polymers are more suited to aqueous environments during use phases, but they may degrade and release free MN in open air weathering environments at

disposal phases. The detailed consideration of composite combinations and the forces affecting release will require more evaluation of current information and standardization needs, as is currently planned within ASTM E56 and ISO TC229.

Consideration of approaches to sampling, extraction, and analytic needs and capabilities in the framework of NanoGRID and extensions as in Martin et al. (2017a, 2017b, 2017c) support consideration of possible roadblocks for characterizing and quantifying released material. A key part of this analysis that can be aided by the structured approach of NanoGRID is linking the measurement approaches that are available back to the problem formulation that defines the overall risk management decision needs. In some cases, the methods needed to support a particular decision may be readily available and standardized. In other cases, the methods may be experimental or not calibrated for nanoscale measurements. In still other cases, there may be no methods to measure a particularly critical characteristic or no standardized methods to do so. In still other cases, the methods may be available but the costs in time or resources may be prohibitive, rendering the methods not useful to support a decision need.

A final note regarding issues affecting the development of this TR and evaluations of MN measurement needs is that standard definitions or agreement is needed on the use of key terms used. This need affects evaluation of the literature, and focused development of useful measurement methods. Even terms such as release and transformation can be confusing in discussion of measurement of MN-composites in support of risk management. While it may seem that these are simple terms, they in fact can take on new meaning by different users of this TR. For example, the “released material” from an MN enabled composite may or may not include, in some reader’s frame of reference, transformations of the polymer caused by the MN (e.g., changes to particle size or changes to polymer characteristics). In some readers’ interpretations, the “released material” may not include embedded MN that is unavailable for occupational evaluations, but that is available for secondary transformation in environmental transport pathways. Transformation events or definitions may also need to be defined or considered in terms of the particular characteristics of the MN that affect toxicity or the propensity for inclusion of particular MN characteristics in particular exposure pathways.

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14. ABSTRACT This Technical Report (TR) extends on the ERDC NanoGRID (Nanomaterials Guidance for Risk Informed Deployment) program and considers methods needed to assess material released from composites made with manufactured nanomaterials (MN). Specifically this TR builds from the measurement literature on multi-walled carbon nanotubes released from a matrix to additional application to other MN. The TR informs product development decisions using NanoGRID by facilitating consideration of whether risk characterization is feasible for a given choice of product composition without substantial investment in analytical methods development. In many cases product use can be well characterized and the resulting methods requirements are simple, while in other cases the nature of product use may result in unmeasurable exposures to MN due to the analytical characterization constraints. Understanding these cases prior to product scale-up will enable more accurate cost projections and reduce potential harm of exposures to MN if they are later identified as posing potential health risks. Furthermore, applying the NanoGRID framework to guide evaluation of MN release measurement methods will aid in prioritizing methods evaluation and methods development work in process in ISO TC229 and ASTM E56. The intention of this TR is to clarify risk management uncertainty for product development.				
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