Comparative assessment of nanomaterial definitions and considerations for implementation

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American Chemistry Council | Nanotechnology Panel

Abstract

The use of nanomaterials is bringing promising new advances to science and technology. In concert have come calls for increased regulatory oversight to ensure their appropriate identification and control. If nanomaterial-specific regulations are implemented, it will be critical that they are accompanied by definitions that are clear, consistent and practical to apply. Numerous definitions for nanomaterials have been proposed by various government, industry, and standards organizations; however, these definitions differ in their core elements and scope. A comprehensive comparative assessment was conducted on existing nanomaterial definitions with the goal of identifying elements essential for a sound regulatory definition. Common elements across definitions included size and dimensions; however, size limits were inconsistent, and several important elements were not captured consistently, including: consideration of agglomerates and aggregates, distributional thresholds, novel properties and solubility. Other important differences included number size distributions versus weight distributions and natural versus intentionally-manufactured materials. Accordingly, this analysis was extended to identify the critical elements to clearly define the materials subject to a nanomaterial regulation. The analysis also evaluated the extent of characterization required to determine whether a material falls within current nanomaterial definitions and found that some are not aligned with available analytical capabilities. Overall, this analysis highlights the similarities and differences in currently proposed nanomaterial definitions as well as the technical constraints that will need to be addressed for the successful implementation of a regulatory nanomaterial definition.

Background

Many regulatory bodies have developed formal or advisory definitions of "nanomaterial" to identify materials of potential interest. Interest may differ based on agency mission and authority, resulting in a multitude of definitions with varying degrees of consistency. Inconsistency among definitions may impede information sharing and increase compliance costs. Also, the implementation of some definitions may be hampered by current analytical capabilities.[1] Our analysis shows the inconsistencies among the key material properties in existing definitions and can assist regulators by identifying core elements of regulatory definitions without dictating a single definition for all situations.

Although not regulatory definitions, many of the definitions included in our analysis build upon definitions of "nanoscale," "nano-object" and "nanomaterial" developed by the International Organization for Standards (ISO):

- *Nanoscale: size range from approximately 1 nm to 100 nm.*[2]
- *Nano-object: material with one, two or three external dimensions in the nanoscale.*[3]
- *Nanomaterial: material with any external dimension in the nanoscale or having internal structure or surface structure in the nanoscale.*[4]

A regulatory definition of "nanomaterial" should identify clearly materials that may possess properties of interest. Drawing on previous work[5] and our analysis, we suggest the following core elements in a regulatory definition of "nanomaterial":

- Solid, particulate substances;
- Intentionally manufactured at the nanoscale;
- Consisting of "nano-objects" as defined by ISO, but, to avoid ambiguity, without the word "approximately" to describe the size range;
- A weight-based cutoff for ISO-defined nanomaterial content;
- Consideration of aggregates and agglomerates of nanomaterials; and
- Exclusion of aggregates/agglomerates if they cannot be readily broken down into nano-objects.

The elements listed above can be used as a first step to identify "nanomaterials" that may be of regulatory interest. Further evaluation of materials identified by this definition will involve consideration of hazard, use patterns, and potential human and environmental exposures on a case-by-case basis.

[1]Linsinger et al. 2012. Report EUR 25404 EN; [2]ISO/TS 12805:2011; [3]ISO/TS 27687:2008; [4]ISO/TS 80004-1:2010; [5]International Council of Chemical Associations. 2010. http://www.icca-chem.org/ICCADocs/Oct-2010_ICCA-Core-Elements-of-a-Regulatory-Definition-of-Manufactured-Nanomaterials.pdf.

Existing Nanomaterial Definitions

Organization	Definition	Product Category	Status
European Commission Cosmetics Directive (2009)	"Nanomaterial" means an insoluble or biopersistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.	Cosmetics	Regulatory Definition
Australian Government Department of Health and Ageing (2010)	Nanomaterials are industrial materials intentionally produced, manufactured or engineered to have unique properties or specific composition at the nanoscale, that is a size range typically between 1 nm and 100 nm, and is either a nano-object (i.e. that is confined in one, two, or three dimensions at the nanoscale) or is nanostructured (i.e. having an internal or surface structure at the nanoscale). Aggregates and agglomerates are included and applies to materials where 10% or more of the particles by number count meet the above definition.	All non-food	Advisory Definition
Health Canada (2011)	Health Canada considers any manufactured substance or product and any component material, ingredient, device, or structure to be nanomaterial if it is at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale, or if it is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena.	All	Advisory Definition
United States Food and Drug Administration (2011)	There is no formal agency definition. However, when considering whether an FDA-regulated product contains nanomaterials, or otherwise involves the application of nanotechnology, FDA will ask: Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.	Cosmetics, Pharmaceuticals and Food	Advisory Definition
United States Environmental Protection Agency (2011)	There is no formal agency definition. However, the agency has outlined key criteria across several documents[1] including: particle size between 1 and 100 nm in at least 1 dimension; the material exhibits unique properties compared to larger sized particles; the material is engineered at the nanoscale; inclusion of aggregates and agglomerates; and a distribution of particles with greater than 10% by weight less than 100 nm.	All except: Cosmetics, Pharmaceuticals and Food	Advisory Definition
European Commission (recommendation for a definition; 2011)	"Nanomaterial" means a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.	All	Advisory Definition
European Commission Biocides Directive (2012)	"Nanomaterial" means a natural or manufactured active substance or non-active substance containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm.	Biocides	Regulatory Definition
French Ministry of Ecology, Sustainable Development and Energy (2012)	"Substance at nanoscale": a substance intentionally produced at nanometric scale, containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for a minimum of 50% of particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm. Fullerenes, graphene flakes and single-wall carbon nanotubes with one or more external dimensions below 1 nm are considered as "substances at nanoscale".	All	Regulatory Definition
Taiwan Council of Labor Affairs (Chemical Substance Nomination & Notification; 2012)	A nanomaterial is one which is intentionally manufactured or designed and meets any of the following conditions: A) Material with one or more external dimensions or an internal or surface structure on the scale from 1-100 nm; B) It is smaller or larger than the nanoscale above in all spatial dimensions and exhibits one or more nanoscale phenomena/property (for example, increased intensity and chemical reactivity).	All	Advisory Definition

[1] See for example U.S. EPA. 2007. Nanotechnology White Paper, EPA 100/B-07/001; Federal Register. 2011. FR Doc. 2011–33255. 76(249):81441.

Elements of Existing Definitions

Organization	Size	Solubility	Aggregates and Agglomerates	Distribution Threshold	Intentionally manufactured/ engineered	Novel properties
European Commission Cosmetics Directive	1-100 nm	Yes	Yes	No specific mention	Yes	No
Australian Government Department of Health and Ageing	1-100 nm	No	Yes	10% by number	Yes	Yes
Health Canada	1-100 nm and larger[a]	No	Yes	No specific mention	Yes	Yes
United States Food and Drug Administration	1-100 nm and larger[b]	No	No specific mention	No specific mention	Yes	Yes
United States Environmental Protection Agency	1-100 nm	No	Yes	10% by weight	Yes	Yes
European Commission (recommendation for a definition)	1-100 nm	No	Yes	50% by number	No	No
European Commission Biocides Directive	1-100 nm	No	Yes	50% by number	No	No
French Ministry of Ecology, Sustainable Development, Transport and Housing	1-100 nm	No	Yes	50% by number	Yes	No
Taiwan Council of Labor Affairs	1-100 nm and larger[a]	No	No specific mention	No specific mention	Yes	Yes

[a] **Health Canada and the Taiwan Council of Labor Affairs have indicated the inclusion of materials larger than the nanoscale in all dimensions if they exhibit one or more nanoscale properties/phenomena.**
[b] **The USFDA indicates the inclusion of materials up to one micron if material it exhibits properties or phenomena that are attributable to its dimension(s)**

Core Elements and Considerations for Implementation

SIZE

- Most definitions use a size range of 1-100 nm.
- While 100 nm is arbitrary, data support that most unique phenomena occur < 100 nm.[1,2]
- Some guidance documents recommend expanding the definition to include particles >100 nm with "nanoscale properties" (see Novel Properties); however, there are very few examples of "nanoscale" phenomena at >100 nm.
- Most size-related effects can be predicted.
- The lower limit can only distinguish particles from molecules, although carbon nanotubes are typically <1 nm in diameter.
- It is important to note that particle populations are not monodisperse (see Distributional Threshold).

Recommendation: The range 1-100 nm should be used, but if larger sizes are to be included on the basis of unique properties, the definition of "nanoscale property" needs clarification as to whether it relates to biological effect, chemical property, or other parameters.

SOLUBILITY

- Most current definitions do not consider solubility, but solubility is an important determinant for particle assessment.
- For those particles that dissociate to molecular form in a solvent, the rate of dissolution distinguishes the definitions of "soluble" and "persistent."[3]
- Surface architecture, coatings, agglomeration, and other factors influence dissolution.

Recommendation: For biological relevance, a regulatory definition should consider the element of solubility (i.e., does the rate of dissolution predict biologically relevant exposure to the particle or to the dissolved molecule?).

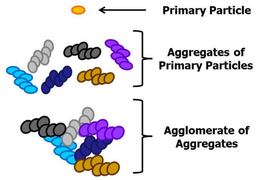
AGGREGATES AND AGGLOMERATES

Nanomaterials exist in different forms: isolated primary particle; aggregates; and/or, agglomerates. High temperature manufacturing processes (e.g. carbon black, metal oxides) will form "aggregates," as individual particles (e.g. "primary particles" or "nodules") collide and adhere/fuse to other individual particles of similar size, forming a robust aggregated structure. Key properties of an aggregate:

- The constituent primary particles/nodules which formed an aggregate are historic artifacts. The aggregate is the permanent entity.
- An aggregate's size is determined by the frequency of primary particle collisions. The higher the frequency of collisions, the larger the aggregate's size.
- Aggregates range in size and may measure > 100 nanometers.
- An aggregate's size and shape have a fundamental influence on a nanomaterial's properties.
- Aggregates of primary particles have inherently larger surface areas than their bulk counterparts.
- Aggregates are held together by stronger forces, such as covalent bonds.
- Aggregates are robust, indivisible structures that may be broken apart in very high energy processes, if at all.[4,5,6]

As a manufacturing process continues, agglomerates may form. Key properties of an agglomerate:

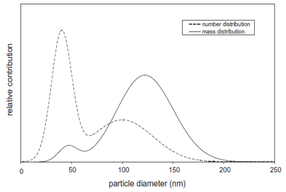
- Agglomerates are a collection of weakly bound individual particles or aggregates, or they may be a mixture of the two.
- Agglomerates are held together by weaker forces, such as van der Waals forces or physical entanglement.
- Agglomerates range in size and will likely measure >100 nanometers.
- Agglomerates will break apart in high energy processes. [4,5,6]



Recommendation: A definition should differentiate between aggregates and agglomerates and consider the potential for these structures to break down into smaller, potentially nanoscale particles.

DISTRIBUTIONAL THRESHOLD

- Defining a material by its mean particle diameter may be inappropriate as a sample with a mean particle size >100 nm may have a significant portion of the particulate population in the nanoscale range. However, without a distributional cut-off, any particulate substance could be defined as a nanomaterial as it contained some small fraction of particulates in the nanoscale range.
- Many definitions recognize this as an important component but differ in their consideration of how to define the particle size distribution (i.e. **weight percentage distribution vs. number count distribution**).
- While the number count distribution has been proposed by several groups, weight distribution has the sensitivity necessary to ensure regulatory evaluation and compliance and is more consistent with available analytical methodologies, detection capabilities, and safety assessments.



Example of a particle distribution presented as number and mass distributions (Reprinted from Reg Tox Pharm Vol 65, Bleeker et al., Considerations on the EU definition of a nanomaterial: Science to support policy making, pages 119-125 © 2012, with permission from Elsevier.)

Recommendation: As with the 100 nm cut-off used for defining size limits, a weight percent cut-off of 10% is considered a reasonable distributional threshold to effectively capture materials that have been the subject of regulatory interest.

INTENTIONALLY MANUFACTURED/ENGINEERED

- Nanoscale particles are not new to nature. They can be found in sea spray, volcanic dust, and baked goods.[7,8]
- Nanomaterials may be incidentally present in many solid materials and produced incidentally in combustion products.[7]
- ISO defines a **manufactured nanomaterial** as **intentionally produced for commercial purposes** to have specific properties or specific composition (e.g., transparency).[9]
- ISO defines an **engineered** nanomaterial as a **designed for specific purpose** or function (e.g., quantum dots).

Recommendation: Definitions should focus on intentionally manufactured and/or engineered nanomaterials, not naturally occurring and incidentally produced nanomaterials.

NOVEL PROPERTIES

Key drivers for the development of nanoparticles are the novel properties that larger forms of the same material do not have. For example:

- The melting point of tin is 232°C when particle size >100 nm but is reduced to 14°C at 6 nm.
- Cadmium selenide is normally a semiconductor, but, when formed into a quantum dots, the movement of electrons changes, resulting in size-dependent visible light emissions when excited.
- Gold becomes catalytic at the nanoscale.

These examples demonstrate that some nanomaterials have novel properties making them different from their non-nano forms.[1]

Recommendation: Definitions of nanomaterials should include only those materials with novel properties not observed in non-nano forms.

References

[1] Auffian et al. 2009. Nature Nanotech. 4:634-641; [2] Stoeger et al. 2009. Environ Health Perspect 114:328-333; [3] Borm et al. 2006. Part Fibre Toxicol 3:11; [4] Donnet et al. 1993. Carbon Black: Science and Technology. Dekker, New York; [5] ISO/TS 80004-1:2010; [6] Gray, C.A. and Muranko, H. 2006. J Occup Environ Med 48:1279-1290; [7] National Nanotechnology Initiative. www.nano.gov/nanotech-101/nanotechnology-facts; [8] Sk et al. 2012. Sci Rep 2:383; [9] ISO/TS 80004-1:2010.

Conclusions

Regulatory definitions of nanomaterials should be globally consistent in the consideration of the following:

- **Solid, particulate substances**
- **Continued use of 1-100 nm to define nanoscale**
- **Describe the characteristics of solubility that make it biologically relevant**
- **Differentiate between aggregates and agglomerates, and consider the potential for these structures to break down into nanoscale particles**
- **Distributional threshold of 10% by weight**
- **Exclude naturally occurring and incidentally produced nanomaterials**
- **Focus on materials with novel properties not present in non-nano forms**