



Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

Scientific Basis for the Definition of the Term "Nanomaterial"

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ABSTRACT

With the expected increase in the applications of nanotechnology, more and more products will be manufactured containing components which will fit the commonly used definition of the nanoscale, as having a size between approximately 1 and 100 nanometre. There is no scientific evidence in favour of a single upper limit. Moreover, there is no scientific evidence to qualify the appropriateness of the 100 nm value. Notably, defining the nanoscale as having a size between approximately 1 and 100 nanometre would not be without problems within a regulatory setting. There is a need for a more elaborate description to identify unequivocally a nanomaterial or a product containing a nanomaterial for various EU regulatory bodies. In any regulatory setting, the most important terms that have to be described clearly to avoid misunderstanding and/or misuse are "size" (what is meant by "nanoscale") and "nanomaterial" (what is meant by "nanomaterial").

This opinion provides advice on the essential scientific elements of a working definition for the term "nanomaterial" for regulatory purposes. Existing definitions formulated by various bodies are reviewed and discussed. Specific issues are addressed which need to be considered when a definition for nanomaterials has to be used in a regulatory setting. By discussing various issues, several questions may be answered:

- When is a material a nanomaterial?
- Should there be a distinction based on the origin or application of the material?
- Is there a specific size (threshold) when a material changes its properties?

In order to define an enforceable definition of "nanomaterial" for regulatory use it is proposed to set an upper limit for nanomaterial size and to add to the proposed limit additional guidance (requirements) specific for the intended regulation. Crucial in the guidance that needs to be provided is the extended description of the nanoscale. Merely defining single upper and lower cut-off limits is not sufficient in view of the size distributions occurring in manufactured nanomaterials. Although many nanomaterials are produced for specific properties at the nanoscale, at the moment it is not possible to identify a specific size or a specific generic property that is suddenly introduced or changed with size. Alternatively, a tiered approach may be required depending on the amount of information known for any specifically engineered nanomaterial and its proposed use.

Keywords: nanomaterial, definition, scientific basis, SCENIHR

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EXECUTIVE SUMMARY

With the expected increase in the applications of nanotechnology, there is an urgent need to identify by clear unequivocal descriptions what can be considered as a nanomaterial and what should not be. This need to identify a nanomaterial comes from the uncertainty regarding the risk assessment and safety evaluation of nanomaterials.

It should be stressed that "nanomaterial" is a categorisation of a material by the size of its constituent parts. It does not imply a specific risk, nor does it necessarily mean that this material actually has new hazard properties compared to its constituents. However, size will influence biodistribution (and distribution kinetics) in an organism or in an ecosystem.

There is sufficient evidence that there is a change in some properties of the material at nanoscale size which is, for instance, due to the increased surface-to-volume ratio. These nano-specific properties raise concerns over their potential to cause harm to humans and the environment. The chemical reactivity of nanoparticles often relates to the surface area. Consequently, the chemical reactivity increases per mass dose for smaller particles of the same type, while this effect may or may not be associated with an increase in biological activity or toxicity. It is this uncertainty that warrants the careful evaluation of possible risks associated with nanotechnology products. However, at the moment it is not possible to identify a specific size at which a specific property would change or appear, or a specific property that is introduced or changed with size.

Several international and national organisations have proposed definitions for the nanoscale and for nanomaterials (summarised in Annex I). In most of the definitions proposed, the size refers to one or more external dimensions or an internal structure within a specified size range. There is no scientific evidence in favour of a single upper limit. However, an upper limit of 100 nm or approximately 100 nm is commonly used. There is no scientific evidence to qualify the appropriateness of this value. Some definitions have also included a reference to specific properties or nano-specific properties.

This opinion provides advice on the essential scientific elements of a working definition for the term "nanomaterial" for regulatory purposes. The major question for both regulators and manufacturers is to identify when a material or product can be considered a nanomaterial. It should be noted that, in the metric system, the "nanoscale" is the range below 1 micrometre (μm) and above 999 picometre (pm). Criteria relevant for the discrimination between nano and non-nano are discussed using a working definition for the nanoscale of approximately 1 to 100 nm. Any material with one or more internal or external dimensions in the nanoscale is then considered a nanomaterial. The feasibility of including specific properties as elements of a definition was assessed.

When considering any definition for nanoscale and nanomaterial, size is the predominant feature. This requires that adequate validated methodologies are available for carrying out measurements at the nanoscale (i.e. below 1 μm). Any nanomaterial should be described by its size and number size distribution, including the methodologies used for the measurement.

Solely referring to size as "one or more external dimensions" will NOT capture aggregates and agglomerates of primary particles or, importantly, more complex multi-component nanomaterials that are widely used in medical and cosmetic applications as their external dimension is likely to be larger than a specified upper size limit. The inclusion of a reference to "internal structure" with the same specified range as the external dimensions will include materials that consist of aggregates, agglomerates and multi-component assemblies within the scope of the definition. This would also include nanoporous and nanocomposite materials.

To distinguish a dry, solid, nanostructured material from a non-nanostructured material, the volume specific surface area (VSSA) can be a complementary criterion, based on its

integral material surface area per unit volume. A limitation of the determination of the VSSA using the BET-method is that it is only applicable to powders and/or dry solid materials and it is not directly applicable to suspensions. Expressing the surface area related to the volume instead of mass allows for an additional criterion independent of the density and size, or size distribution of the nanomaterial. A VSSA above $60\text{m}^2/\text{cm}^3$ would indicate an average size below 100 nm, thus indicating a high nanomaterial content. Therefore, a VSSA above $60\text{m}^2/\text{cm}^3$ would indicate a nanomaterial.

Data on the size distribution should be taken into account when describing a nanomaterial. When only a part of the material has a size within the size range of the definition or description it should be clear whether and when such a material will be considered a nanomaterial. This may be by allowing a part (certain %) of the number size distribution to be below a certain threshold or by using the information on the size distribution itself. Based on the mean or median and its standard deviation, a material might be considered as a nanomaterial when $>0.15\%$ of the material, as indicated by the number concentration, has a size below the designated upper size limit.

As size is a key element in any definition of a nanomaterial, there seems to be a need for the development of validated standardised methods to determine size and its corresponding distribution to ensure comparability of results.

There is a multitude of possibilities for the application of coatings and surface modifications to nanomaterials. Purposely applied and environmentally acquired coatings can have a major impact on nanomaterial interaction with biological systems. The coating and core together control the properties of a given nanomaterial and it is not useful to look at either the properties of the core or of the coating in isolation as they may not be representative of how the nanomaterial will behave in a given environment. The variability in coatings on nanomaterials prohibits the feasibility of including criteria based on surface properties within a definition as these properties may vary with coatings.

Several physico-chemical properties from the OECD Working Party on Manufactured nanomaterials (WPMN) list of 16 characteristics were evaluated as possible discriminators for the identification of a nanomaterial. They were crystalline phase, photocatalytic activity, zeta potential, redox potential, radical formation potential, water solubility and the octanol-water partition coefficient. It was concluded that while all of these properties are very useful for the purpose of risk assessment, none of them appears to be universally applicable as a criterion within a definition for all nanomaterials.

Like any other material, nanomaterials can be degraded either chemically or by solubilisation; in fluids, they can form agglomerates or stable dispersions depending on solvent chemistry and surface coating. Features associated with solubility (and degradability) of nanomaterials are very important for risk assessment in view of the possibility for persistence and accumulation both in man and the environment. These features include size and shape, water solubility, surface charge and surface reactivity. However, these features cannot be translated into a definition as they are part of the characterisation of a nanomaterial and can change for each individual nanomaterial depending on chemical composition, surface modification and the immediate environment of the nanomaterial.

Certain nanomaterials and composite materials may have incorporated internal or external structures at the nanoscale to confer nanospecific characteristics to that composite. As the external dimensions of nanocomposites would be typically larger than 100 nm, most nanocomposites would not be considered to be nanomaterials with a definition based solely on external size. The internal structure with a size at the nanoscale would be an element to include in a definition, as then nanocomposites will be included in the definition of a nanomaterial. There are also nanocomposites where one phase is a bulk one. Exclusion criteria would have to be developed to avoid considering macroscopic composite objects as nanomaterials.

In order to designate more specifically purposely made nanomaterials within the regulations, the terms "engineered" or "manufactured" may be used. When considering

purposely made nanomaterials, the meaning of “engineered” or “manufactured” also needs to include the processing (e.g. grinding or milling resulting in size reduction, or chemical processing) of materials to obtain materials at the nanoscale.

In conclusion, size is universally applicable to all nanomaterials and is the most suitable measurand. A defined size range would facilitate a uniform interpretation. For regulatory purposes the number size distribution should also be considered using both the mean size and its standard deviation for further refinement of the definition. Alternatively, a specific fraction of the number size distribution might be allowed to be within the specified size ranges of the definition. For dry powders, the volume specific surface area (VSSA) may be added to the size as a discriminator to identify nanomaterials. In addition, the definition should include both external and internal nanostructures.

For the lower limit of the definition of nanomaterials, the size of 1 nm is proposed. However, around 1 nm, there is ambivalence between molecules, nanoclusters and nanoparticles.

At the moment, no scientific data are available to indicate that a specific size associated with special properties due to the nanoscale can be identified for nanomaterials in general. There is no scientific evidence in favour of a single upper limit. However, there is by general consensus an upper limit of 100 nm which is commonly used. There is no scientific evidence to qualify the appropriateness of this value. Notably, the use of a single upper limit value might be too limiting for the classification of nanomaterials and a differentiated approach might be more appropriate. This approach could be based on a relatively high upper threshold for which it is assumed that the size distribution at the lower end will always be above the lower, more critical threshold. The lower threshold would be the critical threshold for which extensive nano-specific information has to be provided in order to perform case-by-case risk assessment.

In addition to size, any regulatory definition should be limited to purposely-designed nanomaterials (e.g. engineered or manufactured nanomaterials) including the processing of nanomaterials.

Based on specific requirements regarding risk assessment for regulatory purposes, for specific areas and applications, modifications of any overarching definition may be needed.

1. BACKGROUND

The services of the European Commission urgently need to elaborate a working definition for the term "nanomaterial" to ensure the consistency of forthcoming regulatory developments to guide, as appropriate, the effective implementation of the existing regulation, and to contribute to international work and dialogue on nanotechnology definitions.

The SCENIHR adopted a scientific opinion on "The scientific aspects of the existing and proposed definitions relating to products of nanoscience and nanotechnologies" at the 21st plenary meeting on 29 November 2007¹. Moreover, both SCENIHR² and the predecessor to the Scientific Committee on Consumer Safety (SCCS)³ have provided further advice on the definitions of the term nanomaterial and other related terms in their opinions. Moreover, the European Food Safety Authority (EFSA) used the terms and definitions suggested by the SCENIHR in the opinion on "The potential risks arising from nanoscience and nanotechnologies on food and feed safety" on 10 February 2009⁴.

In order to prepare a science-based definition of nanomaterials, the services of the European Commission need clarification on the size ranges and other relevant characteristics and corresponding metrics reported in the scientific literature, the types of physical and chemical properties particular to nanomaterials, the relevant thresholds, as well as the most appropriate metrics to express such thresholds.

The development of the policy and regulatory activities on nanotechnologies requires the establishment of a working definition of nanomaterials as a matter of urgency. Therefore, SCENIHR is requested to provide a scientific opinion on the issues mentioned below in accordance with the accelerated procedure referred to in Article 9.13 of the Rules of Procedure, in co-operation with other Scientific Committees of the European Community and, as appropriate, with external experts.

2. TERMS OF REFERENCE

Advice on the essential elements of a science-based working definition: Based on current knowledge, the Committee was invited to provide advice on the essential elements of a science-based working definition of "nanomaterials" and, specifically, to identify the most appropriate metrics to define materials at the nanoscale, taking into account:

- (i) Reported size ranges and other relevant characteristics and corresponding metrics: The size ranges and other relevant characteristics (e.g. specific surface area, shape, density, spatial arrangements, aggregation, agglomeration, etc.) and corresponding metrics of materials reported as "nanomaterials" in the scientific literature;
- (ii) Characteristics: A first indication of possible characteristics and associated mechanisms that alone or in various combinations may lead to different properties;
- (iii) Physico-chemical properties: The physical and chemical properties that materials may show as a result of being at the nanoscale or having a nanoscale structure;
- (iv) Threshold(s): The threshold(s) at which properties identified in (iii) above may be expected to occur (the threshold(s) may be "below" or "above" depending on the relevant characteristic(s) and associated metric(s)).

¹ http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_012.pdf

² http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_023.pdf

³ http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_099.pdf

⁴ <http://www.efsa.europa.eu/en/scdocs/scdoc/958.htm>

3. SCIENTIFIC RATIONALE

3.1. Introduction

The rapid development, increased production and use of nanomaterials have raised concerns that such materials may introduce new hazards during occupational exposure, consumer exposure and/or on environmental exposure. Nanomaterials are being engineered for their specific physico-chemical and biological characteristics thus providing novel materials with promising technological advances.

Reduction of size can result in materials with specific physico-chemical properties that distinguish them from the bulk⁵ (larger size) of the same material (Auffan et al. 2009, Gleiter 2000, Jiang et al. 2008, SCENIHR 2006). The properties of a material generally depend on its chemical composition and on the environment at the interface (such as the surrounding medium (air, liquid, solid), temperature, and pressure). With decreasing particle or structure size there is an increase in surface area in relation to the volume resulting in an increase of molecules/atoms on the surface with potentially a change in surface reactivity.

With the progress in nanoscience, nanomaterials are typically engineered to have specific properties. Bottom-up methods such as chemical synthesis and self-assembly yield nanomaterials that are often not directly comparable to any “bulk” counterpart. Such bottom-up methods typically yield nanomaterials that are composed of multiple components. Many nanomaterials are engineered and manufactured for their specific properties, often with well known chemical composition. Although the toxicological profile of its chemical components may be well known, there may be cases where nanomaterial specific properties raise concerns over their specific potential to cause harm to humans and the environment. This raises the question as to whether the current risk assessment methodology, as used for “classic” substances (chemicals) in the EU, can be used for nanomaterials or whether there is a need to perform another kind of risk assessment (Kreyling et al. 2006, Oberdörster et al. 2007, Oberdörster 2010).

Part of the concern can be attributed to the fact that it is currently not known whether the current assays used for hazard identification and risk assessment of substances (chemicals) can also be applied to risk assessment of nanomaterials or whether they need to be modified. Obviously, a sufficiently precise assessment of the constituent chemical ingredients is a prerequisite for such an analysis. Currently, the OECD is running a sponsorship programme aiming at investigating whether the assays described in the various OECD guidelines for the testing of chemicals (OECD 2009a) can be applied to nanomaterials. These guidelines comprise five sections: 1, Physical chemical properties; 2, Effects on biotic systems; 3, Degradation and accumulation; 4, Health effects; and 5, Other test guidelines. An “OECD series on principles of good laboratory practice and compliance monitoring” and an “OECD series on testing and assessment” complement these guidelines. A major issue is that so far the testing guidelines were developed for chemicals with only limited attention given to the testing of particles (powders) for risk assessment.

In the pharmaceutical area, since 1990, a growing number of nano-sized products have been approved for routine human use as nanopharmaceuticals and nano-sized imaging agents. In this context, the methodology used to assess preclinical safety of both specific nanomaterials and first generation nanomedicine products has already been documented (Gaspar and Duncan 2009). Moreover, for such products there has been considerable post-market patient surveillance documenting both safety and efficacy.

⁵ In particle toxicology, the term “bulk” is often used to distinguish nanoparticles from larger particles of the same chemical substance. Equally relevant is the comparison of the nanoparticulate form of a chemical with the free (atomic, ionic, molecular) gaseous or dissolved species. All possible species (gaseous/dissolved, nanoform, aggregates/agglomerates and conglomerates with other materials) may play a role in the way nanomaterials affect organisms. In this text, the term “bulk” is used to refer to all non-nano species of a nanomaterial.

Previously, use of a case-by-case approach for safety evaluation and risk assessment of nanomaterials has been recommended (EFSA 2009, FDA 2007, SCENIHR 2009) as extrapolation from one nanomaterial to another is not considered feasible even when the basic chemical composition is the same. For example, a nanomaterial with a particle size of 20 nm must be considered differently from a nanomaterial of 80 nm. There is growing pressure to set a definition that will allow identification of those "nanomaterials" for which a separate or alternative safety evaluation and/or risk assessment is needed rather than the standard methodology applied to "classic" materials/chemicals.

It should be stressed that "nanomaterial" is a categorisation of a material by the size of its constituent parts. It does not imply a specific risk, nor does it necessarily mean that this material actually has new hazard properties compared to any smaller constituent parts of the nanomaterial or the bulk (or larger sized powder form), if such exist. Engineering of "nano" size can, but not necessarily does, result in a change of physico-chemical properties. However, size will always result in a corresponding change in biodistribution (and distribution kinetics) in an organism or in an ecosystem. There is an analogy with the toxicological assessment of chemical compounds (with some new issues however) in that regardless of whether a compound is synthesised to be nature identical, or extracted from natural substances, it does not provide any clue about its toxicity profile. Moreover, it is well known that due to differences in distribution and/or metabolism, even different isomeric forms of the same compound can have different toxicity and efficacy.

Standard chemistry and physics define atoms, molecules, polymers, supra-molecular aggregates, colloids, particles and (nano)clusters, and how they are discriminated or characterised. In the context of material properties it is important to note that the size of individual large molecules reaches well into the nanometre range, and here, like in any other case, the property of such molecules can be designed by chemical synthesis. Similarly, the size of nanoparticles and nanoclusters reach into the sub-nanometre range.

The key question to be answered is what elements or characteristics should be included in a definition of nanomaterials for regulatory purposes. However, one should not confuse the definition of a subject with the necessary characterisation of that subject. While it is very useful to know some parameters, they may be actually part of the characterisation/description of the nanomaterial. Also, it is important to note that a parameter or characteristic would have to be applicable to all nanomaterials if it were to be included in a universal definition for "nanomaterial". In this opinion, several scientific and practical considerations are discussed that may have an effect on the description of a nanomaterial.

3.2. Existing/proposed definitions

Several definitions for nanomaterials have been formulated by various national and international bodies including BSI, FDA, Health Canada, ISO 2008, OECD 2008, SCENIHR 2007 (see Annex I) and considerations on a definition for regulatory purposes has been recently provided by the Joint Research Centre of the European Commission (Lövestam et al. 2010). A common feature of many definitions has been to specify an upper size limit for nanomaterials of 100 nm for one or more external dimensions. Others have argued that it is difficult to ascribe the specific upper threshold to this value. An upper limit of 1,000 nm has been proposed for pharmaceuticals (Brouwer et al. 2010, FDA 2010). It is argued that a single upper threshold of 100 nm (or a 1 nm–100 nm range for nanomaterial size) cannot be considered to properly distinguish nanomaterials from their bulk counterparts as it does not take into account issues like size range, size distribution and specific properties (electrical, mechanical, optical) at the nanoscale. Thus a more elaborate description of a nanomaterial may be needed that can be used as a working definition for regulatory purposes. Equally, it must be noted that other elements included in a definition must be applicable to all possible nanomaterials.

In the definitions proposed so far, the lower size varies from approximately 1 nm, 0.1 nm, and 0.2 nm to no lower limit for one or more external dimensions. It seems necessary to include a lower limit in a definition for nanomaterials because at the sizes mentioned, we enter the area of molecules and atoms which should not be included in a definition of a nanomaterial. The size of some individual large molecules may reach well into the nanometre range. While this will result in some molecules being considered nanomaterials (e.g. fullerenes), others may just be large molecules without any indication of being a nanomaterial.

Most definitions also include reference to the internal structure with the same specified size range. The latter includes aggregates and agglomerates of particles within the scope of a nanomaterial. Aggregates and agglomerates would not be captured by a definition solely based on external dimensions. This internal structure seems to be a logical criterion that could be included. However, including this criterion would also include nanoporous materials such as membranes within the definition and this may seem counterintuitive to those who are more familiar with the concept of nanomaterials as nanoparticles. In addition, the change in physicochemical characteristics is included in some definitions/descriptions. In some definitions, this criterion is in addition to the size specification while in others it supersedes the size requirement. The latter would allow materials that are larger than 100 nm that show specific properties to be included in the definition/description of a nanomaterial. This criterion implicitly assumes that there is a corresponding bulk counterpart for the nanomaterial to compare properties with. If there is no bulk phase, this criterion does not have any meaning as the frame of reference is not defined.

In addition, some regulatory definitions are already present in the legislation (e.g. EU Cosmetics Directive) or presented by governmental institutions as a basis for general discussion (e.g. Health Canada 2010).

A hierarchical approach to the terminology within nanotechnology and nanosciences has been described by ISO where a nanomaterial can be either a nanoobject (one or more external dimensions in the nanoscale) or a nanostructured material (internal structure or surface structure in the nanoscale) (ISO/TS 27687:2008, ISO/DTS 80004-1 in press). In this context, a nanomaterial is solely defined by its size which can refer to either internal or external dimensions. The SCENIHR 2007 opinion describes a framework that follows mainly existing terminology with additions only for specific keywords within nanotechnology and nanosciences (SCENIHR 2007).

In conclusion, the definitions/descriptions of nanomaterials formulated so far have: i) given a general size frame for nanomaterials in both external and internal dimensions; and ii) some have referred to the unique physico-chemical characteristics of the specific material under discussion. Whilst such broad definitions can be scientifically justified, they are not easy to apply within the context of a regulatory framework.

3.3. Parameters to be considered

A “nanomaterial” may consist of a single element or numerous different elements. The term may apply to both simple and complex inorganic and organic substances as well as derivatives thereof and mixtures, including nanocomposite materials. All nanomaterials may be chemically and/or physically modified. They may be coated (covalently or non-covalently) or otherwise functionalised to obtain their specific technologically required performance.

Typically “nanomaterials” are manufactured using “top-down” (e.g. mechanical methods/milling, thermal methods, high energy methods, top-down chemical fabrication methods (e.g., anodizing), lithographic methods,, etc.) or “bottom-up” methodology (e.g. chemical synthesis, supramolecular assembly, covalent conjugation involving multiple components, colloid chemistry). Complex multi-component nano-sized materials

have been engineered using a combination of both of these routes, and indeed many emerging nanomaterials are prepared by sequential application of several different manufacturing steps.

The nature of the manufacturing process, and any integral purification steps, will ultimately govern the purity of the final product, particle size distribution and heterogeneity of other parameters. In addition to the specific physico-chemical properties of a material, these factors, together with storage conditions and degree of aggregation, play a major role in determining ultimate biological behaviour.

Here we discuss key criteria that should be considered when using a definition for the nanoscale and/or nanomaterials in a regulatory context. These criteria are a non-exhaustive list but are considered the most important ones for which guidance might be needed when applying any regulatory definition for nanotechnology.

3.3.1. Size

Size is the universal element that is included in all proposed definitions thus far. The use of size is indicated by the prefix "nano-", which specifically means a measure of 10^{-9} units, the nature of this unit being determined by the word that follows.

Upper Size Limit

As mentioned in section 3.2., most previous reports specify an upper limit for a nanomaterial of approximately 100 nm (and a lower limit of approximately 1 nm for one or more external dimensions).

The upper physical size-range for nanomaterials may also be considered depending on the intended application of the cut-off (i.e. material properties or risk). While the upper size limit of 100 nm would catch the most obvious nanomaterials, such as primary particles (e.g. carbon nanotubes, metal based nanoparticles of various shapes etc.), hierarchical assemblies of primary particles such as agglomerates and/or aggregates would typically have external dimensions greater than this. Additionally, formation of aggregates and agglomeration can occur due to a number of deliberate and accidental mechanisms (see, for example, the review by Schneider and Jensen 2009). When hierarchical assemblies, aggregates and agglomerates are included in the determination of size, their presence induces a shift to larger sizes.

Particulate nanomaterials may also be reported with larger sizes due to coatings or functionalisation by long-chain organic compounds. Hence, for risk assessment purposes, it may be necessary to define a threshold size based on the size of the core of the individual particulate nanomaterial and not the complete functionalised particle.

In particular, more complex nanomaterials such as liposomes, e.g. loaded with drug particles or metal particles that are widely used in medicinal and cosmetic applications would typically have external dimensions greater than 100 nm for one or more external dimensions. The inclusion of "internal structure" with the same specified upper limit would however define such structures as nanomaterials provided the components are within the specified upper limit. The next-generation hybrid nanomaterials are already under development and are typically based on the concept of a hierarchical assembly of many components (e.g. quantum dot superlattices, dendrimers and polymers) (Schmidt and Bodmeier 1999). Therefore, a reference to the internal structure should be included within the definition as this would then also capture complex assemblies provided the internal structure was within the specified range. Any definition should aim to be overarching to also include next-generation nanomaterials in order to avoid quickly becoming obsolete (Roco 2004).

Lower size limit

Focusing on the external dimensions, the lower cut-off size for nanomaterials presents another challenge as 1 nm or less also includes the size of atoms, molecules and clusters. Depending on the specific compounds, there will be a transition from atoms to nanoclusters, or molecules to particles, at different sizes which makes the definition of a specific lower size limit challenging. A lower limit is needed, but will not definitively avoid all the problems stated. Indeed, molecules are defined by the covalent links between atoms. They range from sub-nanometre dimensions (CO, O₂ etc.) up to the size of some globular proteins (~5 nm) and to macroscopic dimensions in the case of interlinked structural proteins (collagen, ...) and many technical polymers. It should be noted that around 1 nm in size there is ambivalence between molecules, nanoclusters, and nanoparticles.

Methods for characterisation of size

The specific method(s) used to determine nanomaterial size is very important. There are currently very few standard methods for determining size. There is also an apparent lack of awareness that different techniques may not measure the same thing, e.g. the size determined by transmission electron microscopy (TEM) does not include any organic coatings while that measured by dynamic light scattering (DLS) does, and in addition includes the ionic double layer. Domingos et al. (2009) reported that size could deviate considerably from that indicated by the manufacturer depending on the methodology used for characterisation. For example, differences in the order of two to three magnitudes were reported, with the methods coming closest to the manufacturer's information being TEM and atomic force microscopy (AFM). Sizing a particulate material needs to be done using different techniques depending on whether the nanoparticles occur as a powder, are dispersed in a liquid, are coated or are embedded in a solid material. Not all methods measure the same size, e.g. TEM and AFM measure the size without any organic coatings while the size determined by DLS includes the organic coating in the measurement.

In conclusion, it should be realised that, at the lower nanoscale, there are atoms, molecules and clusters with sizes well above the proposed 1 nm lower limit for the nanoscale that should be taken into consideration when designating a material as nanomaterial based on the lower limit of size. For the upper limit the presence of complex structures, agglomerates and/or aggregates should be taken into consideration. To overcome problems in a definition associated with complex structures a reference to the size determination of possible internal structures might be included. In addition, the methodology with which the size was determined should be indicated as this affects the outcome of the measurement. More reliable information is obtained when the determined size is reported using a few different complementary standardised methods. As size is a key element in any definition, it can be concluded that there is a need for the development of validated standardised methods to determine size.

3.3.2. Size distribution

One cannot consider size without addressing the issue of size distribution. It is important to note that most nanomaterials produced will have a size distribution although it has been demonstrated that it is possible to produce monodisperse nanoparticles (Park et al. 2005). Thus for every threshold proposed there remains the question of whether a product should be defined as a nanomaterial (or not) when there is a fraction of the size distribution that falls below and/or above the chosen threshold(s). The following text on size distribution refers to the distribution in the size of one or more external dimensions, specifically primary particle size. The external size of aggregates/agglomerates of primary particles is not considered as these may not be at the nanoscale although the same considerations would apply to the constituent internal primary particles.

Clearly it is important that any figure given for the size of a particular product (i.e. nanomaterial formulation or production) must be qualified with a specific descriptor of the size distribution. If the size distribution follows a normal distribution the size can be described by its mean and the distribution by \pm the standard deviation (SD). However, most nanomaterials do not show a normal distribution, and many can be described by a log-normal distribution. This can be described by the median diameter and the geometric standard deviation. For all nanomaterials it is essential that the appropriate statistical measure of both average size and size distribution is presented.

It should be stressed that data on size and number size distribution should be complemented by information describing the number concentration of the particles as well as the mass concentration. Clearly, a low mass concentration of nanoparticles in a product may still represent a high number of particles and a mass based distribution can be skewed by the presence of relatively few large and thus heavy particles. A specification would be required that indicates whether the size distribution is provided for the mass, volume concentration, or number concentration.

The standard deviation of the size distribution may be used for fine tuning of the definition of a nanomaterial. For example, materials might be defined as being NOT a nanomaterial as the mean size plus/minus three times SD (meaning 99.7% of the data set or measured nanoparticles) indicating that 99.85% of the sizes is above a certain upper size limit. Or the other way around: any material is a nanomaterial when $>0.15\%$ of the material, based on number concentration, has a size below the upper limit.

In conclusion, the size distribution cannot be ignored and should be taken into account when defining/describing a nanomaterial. When only a part of the material has a size within the size range of the definition/description it should be clearly described whether and when such a material will be considered a nanomaterial or not. This may be by allowing a part (certain %) of the size distribution to be below a certain threshold or by using the information on the size distribution itself. The size distribution of a material should be presented as size distribution based on the number concentration and not on the mass concentration of a nanomaterial product as a small mass concentration may contain the largest number fraction.

3.3.3. Specific surface area

Since some nanoparticulate materials may have a wide range in size distribution it is difficult to draft a suitable definition based on a single parameter such as the median or mean diameter of such a distribution. Indeed this definition may be extended to provide additional parameter(s) such as the standard deviation of a normal distribution or the geometric standard deviation of a lognormal distribution.

Even with the addition of a second size-related parameter, this size-based definition falls short in the case of highly agglomerated and/or aggregated particles. For this reason, most definitions include a reference to the internal structure which would capture such structures, provided the primary particle size of the aggregate is within the specified size range. However, there are difficulties associated with the measurement of primary particle size in aggregates that should not be overlooked. For agglomerates, aggregates, and porous materials, measurement of the surface area may be more meaningful. Such materials may exhibit a large surface area even when a sizeable fraction of the external size distribution (e.g. the aggregates and agglomerates) is much larger than 100 nm.

To overcome this problem the specific surface area of a particulate powder material is an important complementary parameter. Kreyling et al. (2010) have suggested using the volume specific surface area (VSSA) as an additional parameter. This VSSA is an integral parameter determined from the entire particulate powder material including the whole size range distribution, with all external and/or internal surfaces. It characterises the entire particulate surface area per volume of a solid and/or powder material.

A threshold for the distinction of nano- versus micro-sized material can be derived based on a proposed threshold of the minimal surface area of the particulate material. For example, based on the upper size limit of 100 nm spherical particles of unit-density for a nanomaterial, such a threshold of the volume specific surface area (VSSA) would be set at:

$$VSSA \geq 60 \text{ [m}^2/\text{cm}^3\text{]}$$

This means that any material with a $VSSA \geq 60 \text{ m}^2 / \text{cm}^3$ will fall in the category of nanostructured material, even though it may consist of a broad size distribution and be aggregated and/or agglomerated.

This VSSA threshold limit can be generalised to other values of VSSA when it is derived from other diameters (D):

$$VSSA(D) \geq 6000 / D \text{ [m}^2/\text{cm}^3\text{]} \quad (D \text{ given in units of nanometre})$$

A practical advantage of the VSSA parameter is its simple calculation from two parameters usually available for each commercial nano- or micro-structured powder material (e.g. in CAS specifications). The two parameters are the bulk density (ρ) given in g/cm^3 and the mass specific surface area (SSA) given in m^2/g of nanostructured material; the latter is usually determined by nitrogen absorption methodology called the BET-method after Brunauer, Emmett and Teller (Brunauer et al. 1938).

$$VSSA = SSA * \rho$$

The BET-method allows surface area or porosity measurements within pores or other nanostructures as small as about 1 nm. Hence, the density of only the material without the empty spaces in between is required. Thus, the use of the bulk density (ρ) provides an integrated reasonable first estimate of the atomic or molecular structural alignments at the smallest material units. A limitation of the BET-method is that it is only applicable to powders and/or dry solid materials and not to nanomaterials embedded in solids and suspensions.

Note, the estimated VSSA of a material is valid for the entire material as analysed; if a fraction/subset of the material (e.g. fractionated by size) is analysed this subset will have a different $VSSA_{fr}$ which may be above or below the VSSA of the initial entire material.

In conclusion, the volume specific surface area (VSSA) is a complementary qualifier (criterion) to distinguish dry solid nanostructured material from non-nanostructured material based on its integral material surface area per material volume. The proposed threshold limit is $VSSA \geq 60 \text{ m}^2/\text{cm}^3$ beyond which the material is considered to be nanostructured.

The volume specific surface area could be considered as an additional criterion that could be used to identify dry solid powders as nanomaterials. However, for materials with a VSSA below $60 \text{ m}^2/\text{cm}^3$ there is still the possibility that a fraction may have a VSSA above $60 \text{ m}^2/\text{cm}^3$ in view of the size distribution within the preparation. In addition, it should be noted that not all nanomaterials are amenable to VSSA determination (e.g. dispersions, nanocarriers etc.) and this may limit its applicability. Also for complex assemblies that have an external size greater than 100 nm (e.g. nanocarriers in drug delivery) the specific surface area of the internal components is intrinsically not measurable.

3.3.4. Surface modification

Surface modification of a nanomaterial can either be done by coating, functionalisation or other means, which may be chemical (organic, inorganic or both) or physical (e.g. irradiation, surface attrition) (Burda et al. 2005, Daniel and Astruc 2004, Love et al. 2005). These can be composed of a single external interface or more sophisticated multilayered shells. For example, a TiO_2 nanoparticle can be coated with a thin layer of

SiO₂ (inorganic surface treatment) and the SiO₂ layer can be further treated with an alkylsilane (organic surface treatment). These form so-called “core-shell” type nanomaterials where the coating is the shell and a given core can have multiple shells (Chen et al. 2007, Selvan et al. 2007, Yu et al. 2005). Coating may also refer to the charged groups on the surface of a nanomaterial, e.g. the hydroxyl groups on the surface of a silica particle. The type of coating on the outer surface of a given nanomaterial determines its stability to degradation or aggregation in a given medium. The choice of coating is usually application driven and has a direct influence on the binding of the nanomaterial with biomolecules, lipids proteins etc. and thus can affect the interaction of the nanomaterial with biological systems (Chen et al. 2007, Selvan et al. 2007).

It is important to realise the enormous variety of surface modifications that are possible. Nanomaterials can have identical surface coatings but completely different cores or vice versa. There can be multiple coatings on a given surface (Chen et al. 2007). Moreover, a nanomaterial may acquire coating materials (proteins, lipids etc.) from the environment by natural processes. The stability of the coating (it may degrade or dissociate with time or it may leave remnants of covalent anchoring chemistry attached to the nanomaterial etc.) is also a key factor. The properties of a given nanomaterial are determined by both the core and coating, i.e. the coating is an intrinsic part of the nanomaterial and cannot be considered separately.

In conclusion, there are a multitude of possibilities for the application of coatings on nanomaterials. Purposely applied and environmentally acquired coatings can have a major impact on nanomaterial interaction with biological systems. The coating and core together control the properties of a given nanomaterial and it is not useful to look at either the properties of the core or coating in isolation as they may not be representative of how the nanomaterial will behave in a given environment. Thus, each combination of a nanomaterial and a coating has to be considered as an individual case when safety evaluation of a specific nanomaterial is considered.

The variability in coatings on nanomaterials challenge the feasibility of including elements based on properties within a definition as these properties may vary with coatings as highlighted above.

3.3.5. Other physico-chemical characteristics

There are other physico-chemical characteristics that may be of relevance when considering which elements should be included within a definition.

Nanoparticles and nanostructured materials may be characterised by a number of physico-chemical characteristics. The OECD WPMN has specified 16 parameters for describing the primary nanomaterial, of which seven, plus voluntary information, are related to the material properties and not to the physical appearance and state of the material (OECD 2008b).

Some of these parameters and their relevance are discussed as potential criteria to be included in a definition.

Crystalline phase, crystallinity and small structures

Specific inorganic compounds show changes in crystalline structure and morphology as a function of particle size/specific surface area (e.g. Navrotsky 2008). For example, TiO₂ occurs in at least four different natural polymorphs (amorphous, anatase, brookite and rutile) changing with decreasing specific surface area (e.g. Ranade et al. 2002, Zhang and Banfield 1998;). Based on determined crystalline sizes, Ranade et al. (2002) showed that all transitions occurred within the 1 to 100 nm range where the stability field between the X-ray amorphous state and crystalline anatase was observed between 150 and 433 m³/g.

Auffan et al. 2009 have looked into the definition for nanomaterials, reviewed the effects of size on physicochemical properties of several semiconducting nanomaterials, and suggested that the evidence for novel size-dependent properties alone, rather than particle size should be the primary criterion in any definition (Auffan et al. 2009). For the evaluated nanoparticles unique properties were generally identified to occur when the diameter of nanoparticles was below 30 nm due to changes in crystalline structure or surface-to-volume ratio that enhanced their interfacial reactivity. However, the analysis appears not to be based on defined requirements for percent change. Another older review including other compounds indicates that changes in i.e. conduction bands and redox activity could occur at larger particle sizes (Gilbert and Banfield, 2005). However, it is still unknown whether these properties are associated with a change in toxicological risk.

When the solid compounds are very small in size, a complete translational symmetry disappears. Such atomic structures that can no longer be adequately described in the same terms as the bulk material are called "clusters" or "nanoclusters". Typically, nanoclusters consist of only a few to a few thousand atoms, so their size may range from far below 1 nm to approximately 10 nm (Aiken and Finke 1999). The smallest full-shell metal particle clusters contain 13 metal atoms and the number increases by $10 \cdot n^2 + 2$, where n is the number of filled atom shells in the icosahedral symmetry.

However, it is clear that not all nanomaterials are crystalline or consist of clusters so while crystalline phase and structures are very important properties for specific nanomaterials, they are not applicable to all. Thus, it is unclear how it could be included as an element in a definition.

Redox potential

The redox potential is a measure of the tendency of an entity to lose or acquire electrons. Species that readily acquire electrons (reduction) have a high relative redox potential (e.g. Au^{3+}) while those that lose electrons have a low redox potential (e.g. Na). By definition, the redox potential of a species is measured against a reference potential or reference electrode (e.g. hydrogen, calomel or Ag/AgCl, KCl). Measurement of the redox potential is meaningful for nanomaterials which can participate in electron transfer or uptake. Coating of nanomaterials may also participate or inhibit the redox activity of the nanoparticle.

While the redox potential may be useful in determining how active a given nanomaterial would be in human and environmental oxidation-reduction processes, it is unclear how this could be included as an element in a definition.

(Photo)catalysis

Photocatalytically active materials are semiconductors in which electron-hole pairs are formed upon exposure to light that generate highly reactive free radicals on the material surface. Titanium dioxide is a semiconductor of this kind.

By definition, photocatalytic activity is highly material dependent and within materials is size dependent. Activity can also be enhanced or completely switched off by surface treating the material or introducing dopants. Thus, while photocatalytic activity is very relevant for risk assessment, it is not a property that all nanomaterials will have. Due to this, it is unclear how it could be included as an element in a definition.

Radical formation potential

The photocatalytic decomposition of water on the surface of a TiO_2 nanoparticle results in the generation of free radicals on the surface of the nanoparticle surface which in turn react with other organic matter. This is an example of the potential of a given nanomaterial to generate free radicals. However while extremely valuable for the purpose of risk assessment, it is currently unclear how this measurand could be standardised such that it would be meaningful to consider it as an element in a definition.

Zeta potential (surface charge)

Particles suspended in a solution may be charged and surrounded by an ionic cloud. This cloud is called the electrical (or interfacial) double layer. The double layer consists of the inner charged layer at the particle surface and a polarized stationary layer with opposite charge around the surface. Simplified, it can be said that the zeta potential is the potential between the dispersion medium and the stationary layer of fluid attached to the dispersed particle. The zeta potential varies with the pH and salinity of the liquid.

The apparent zeta potential of a given nanomaterial is controlled by the coating and nanomaterials with different cores and shells that have the same outer shell exposed to solution will have the same zeta potential. While the zeta potential is useful for the purposes of risk assessment, it is unclear how it could be included as an element in a definition.

Radical formation potential

The photocatalytic decomposition of water on the surface of a TiO₂ nanoparticle results in the generation of free radicals on the surface of the surface which in turn react with other organic matter. This is an example of the potential of a given nanomaterial to generate free radicals. However while extremely valuable for the purpose of risk assessment, it is currently unclear how this measurand could be standardised so that it would be meaningful to consider it as an element in a definition.

Water solubility

Solubility has already been included on one definition—that of Directive 76/768/EEC on cosmetic products — in which it is associated with bio-persistence.

It is evidently important to know the aqueous solubility and (bio)degradability of nanomaterials to assess their potential for accumulation. Insoluble, non-degradable nanomaterials would have a high priority for risk assessment as (bio)persistence/accumulation may be associated with chronic hazardous effects.

The words “solubility” and “persistence” are often used to discuss rate of “degradation”. Complex multi-component systems often degrade to their constituent macromolecular/nanosized components. In principle, the stability of a nanomaterial drops with decreasing size.

There are IUPAC definitions for solubility, dissolution, solution, colloidal dispersion and colloidal. However, these definitions pre-date more recent advances in nanomaterial engineering and manufacturing. It is apparent from the current scientific literature that there is ambiguity in terms of what is implied when dissolution is used to describe what occurs when a nanomaterial is added to solvent (IUPAC Gold Book, <http://goldbook.iupac.org>).

In some literature, nanomaterial solubility implies that the nanomaterial degrades to its molecular units in solution (e.g. Ag releasing Ag⁺ ions in solution) (Auffan et al. 2009). In other literature this would be termed degradation (Doty et al. 2005, Prasad et al. 2005). Dissolution has also been used to refer to individual nanomaterial units (nanoparticle, nanotube, aggregate etc.) dispersed in solution when the dispersion is indefinitely stable (Banerjee et al. 2005, Lin et al. 2004, Selvan et al. 2007). In the recent physics and chemistry literature in particular, the terms solubility and dispersion are used interchangeably to refer to the latter situation.

This ambiguity is recognised in the current OECD Guidance manual for the testing of manufactured nanomaterials; OECD's Sponsorship Programme where it is stated that “It must be recognised that solubility and dispersibility are not identical though the distinction can be difficult to recognise with [manufactured nanomaterials]” (OECD 2009b).

The ambiguity with regard to solubility creates potential interpretation problems when including solubility as an element in a definition. In addition, if water insolubility was added as an element, the final surface coating on a nanomaterial could determine

whether it is considered to be a nanomaterial or not; e.g. soluble nano-ZnO would not be considered to be a nanomaterial whereas insoluble coated nano-ZnO would be.

Octanol-water partition coefficient.

The water-octanol partition coefficient is only meaningful for nanomaterials that are considered to be water-soluble. As can be seen in the preceding section, there is ambiguity in terms of what is implied when a nanomaterial is described as being soluble.

While the partition coefficient is a useful parameter for risk assessment, it is of limited use as an element of a definition as it is not applicable to a wide variety of nanomaterials.

In general, the properties that can be said to change with size are those which physicists call "cooperative" such as electronic conductivity, light scattering (and its relation to absorbance), magnetism, and superconductivity. All these properties exhibit a characteristic "dimension" which may be microns (for semiconductor "quantum effects") or a few nm (for similar effects in metals). For these effects on metals and semiconductors (catalytic) reactivity depends on size, shape and atomic structure.

In conclusion, various properties may change with decreasing size depending on chemical composition. For various characteristics these changes may occur at different sizes. Although no specific characteristic can be attributed to a specific size the fact that such changes occur is evident. For risk assessment purposes it may be important to know most of the physico-chemical parameters mentioned above. However, whether they each show sufficient discrimination individually to have universal applicability to all nanomaterials appears doubtful.

3.3.6. Organic and inorganic nanomaterials

Nanomaterials have also been described in terms of "soft" and "hard" in recent literature (Nalwa 2009). There is no reported strict definition or explanation for the terms. The terms attempt to broadly differentiate nanomaterials on the basis of their chemical nature and likely behaviour in the body.

Nanomaterials regarded as "soft" are often biodegradable and non-biopersistent⁶. Those produced from natural organic materials in the form of self-assembled, processed, or encapsulated nanostructures are termed "soft". Examples of "soft" nanomaterials are liposomes, nanoemulsions, and biopolymer based nanoencapsulates.

Engineered nanomaterials that are largely inorganic and insoluble are termed "hard". Those regarded as "hard" are non-biodegradable and potentially biopersistent. Examples of "hard" nanomaterials are metals, metal oxides, and carbon materials (e.g. fullerenes, nanotubes, fibres).

It should be realised that exceptions to these categories exist especially when we consider the more complex nanomaterials including a multitude of coatings. In many cases the terms "hard" and "soft" are oversimplifications for complex hybrid materials. The terms are mainly used for applications where nanomaterials are meant (or likely) to be in intimate contact with a living organism, such as food, medicine and cosmetic products. However, these terms should not be confused with the terms "soft metal" and "hard metal" that are already used in chemistry to refer to the mechanical strength of different metals.

⁶ The term biopersistence may have different meanings. In relation to food, it will mean persistence in the body, whereas in other applications it may also mean environmental persistence. However, the main tenet is that biological systems can not deal with a biopersistent material through normal processes, e.g. digestion, metabolism, excretion, elimination etc.

In conclusion, although various descriptions are used for "hard" and "soft" nanomaterials, the most common use is a distinction between "hard" and "soft" based on the origin of the nanomaterials being organic or inorganic compounds, respectively. In general the inorganic (hard) nanomaterials such as metals and metal oxides are non-biodegradable and potentially biopersistent. In this respect the distinction between hard and soft nanomaterials is not an absolute one as certain persistent nanomaterials may be organic (carbon nanomaterials), and certain oxides may be (bio)degradable.

Thus, based on the above rationale, terms like hard or soft as markers for potential biopersistence would not be useful elements to include in the definition.

3.3.7. Nanocomposites

According to Alemán et al (2007; IUPAC Recommendations 2007; IUPAC Gold Book, <http://goldbook.iupac.org/NT07243.html>), a nanocomposite is a composite in which at least one of the phase domains has at least one dimension of the order of nanometres. A composite is in turn defined as a multi-component material comprising multiple, different (non-gaseous) phase domains in which at least one type of phase domain is a continuous phase.

Usually, a nanocomposite is understood to refer to the combination of a bulk matrix and nanophase(s) (Ajayan et al. 2003). Examples include ceramic/metal nanoparticle composites, metal intercalated graphite, nanoparticle polymer composites, carbon nanotube/polymer composites etc. Certain properties of the nanocomposite are usually designed to be superior to that of the bulk matrix. For example, small amounts of carbon nanotubes can dramatically improve the conductivity and tensile strength of rubber. Thus, composite materials may have incorporated internal or external structures at the nanoscale to convert nanospecific characteristics to that composite. This has to be considered when describing a "nano"- material, structure and/or composite, even when the ultimate size of the material/structure/composite is much larger.

It should be noted that such nanocomposites e.g. car tires with incorporated carbon black would never normally be considered to be nanomaterials. However, as nanocomposites have an internal structure on the nanoscale, they would be considered to be nanomaterials according to many of the proposed definitions included in Annex I. For many of the examples given above (e.g. nanotubes reinforced polymers), the REACH regulation would consider them as articles with typically no registration obligation, although the various components themselves may be. Composites in biomedical material are growing in popularity (e.g. dental, orthopaedic applications). These can be high volume applications.

The properties of nanocomposite materials depend not only on the properties of their individual parents, but also on their morphology and interfacial characteristics. In general, no more than a few percent of nanomaterials by weight are necessary to optimise the mechanical behaviour of nanocomposites.

Certain nanomaterials and composite materials may have incorporated internal or external structures at the nanoscale to confer nanospecific characteristics to that composite. An example of these more complex nanomaterials are liposomes, which may be loaded with drug particles or metal particles. Liposomes are widely used in medicinal and cosmetic applications, and can also be considered as nanocomposites. The next-generation hybrid nanomaterials are already in development and are typically based on the concept of a hierarchical assembly of many components (e.g. quantum dot superlattices, dendrimers and polymers) (Schmidt and Bodmeier 1999). These could also be considered to be nanocomposites. Any definition should be over-arching to ensure that it does not quickly become obsolete. Therefore, a reference to the internal structure should be included within the definition as this would then also capture complex assemblies provided the internal structure was within the specified range.

The manufacturing of nanocomposites has been foreseen by the definition of SCENIHR (2007) that defines a nanomaterial as "*being composed of discrete functional parts, many of which have one or more dimensions of the order of 100 nm or less*" (SCENIHR 2007). The definition of nanostructure mentions specifically the possible presence of internal and/or external functional parts (SCENIHR 2007). Therefore, the definition of a nanomaterial includes any material/structure/composite containing external or internal structures at the nanoscale.

In conclusion, when the internal structure at the nanoscale is an element to be included in a definition, nanocomposites will be included provided the internal structure is within the specified size range. As the external dimensions of nanocomposites would be typically larger than 100 nm, most nanocomposites would not be considered to be nanomaterials with a definition based solely on external dimension size.

This interpretation of nanocomposite for example includes car tyres that have incorporated carbon black. The inclusion of "internal structure" as an element of the definition would also mean that such nanocomposites would be defined as nanomaterials. However, nanocomposites such as car tyres incorporating carbon black or tennis rackets incorporating carbon nanotubes should not be considered as nanomaterials. This should be addressed in the definition and exclusions for such types of nanocomposites should be considered.

3.3.8. Persistence

Persistence can be defined as the property of continuation of the existence of a chemical/material. Persistence or accumulation is considered a risk factor for hazardous effects in the long-term. Persistence is used primarily in a risk assessment context to define chemicals or materials that are retained in the body or in the environment, although it could also be applied to durable products. Insoluble, non-degradable nanomaterials would have a high priority for risk assessment as (bio)persistence/accumulation may be associated with chronic hazardous effects. In this respect persistence can be considered as the opposite of soluble or (bio)degradable (see 3.3.5).

With respect to the persistence of nanomaterials, a distinction needs to be made between:

- Nanomaterial characteristics that remain constant during the life cycle.
- A nanomaterial that changes during its life cycle but remains a nanomaterial.
- A nanomaterial that is changed to a form that is no longer considered to be a nanomaterial, but nonetheless one or more of its components is able to persist. This would include metals and persistent organic pollutants (POPs). It should be noted that the classical criteria used to define POPs is lipid solubility (or a high octanol-water partition coefficient) and steric hindrance of metabolism. Neither of these criteria is particularly relevant if the material is in the solid phase.

At present there is very limited information to identify the most critical properties that are likely to lead to bioaccumulation or biomagnification. However, ready uptake, bio-stability and poor clearance are likely to be the driving factors.

In conclusion, features associated with solubility (and degradability) of nanomaterials are very important for the risk assessment of nanomaterials in view of the possibility for persistence and accumulation both in man and the environment. These features include size and shape, water solubility, surface charge and surface reactivity. However, these features cannot be translated into an element of a definition as they are part of the characterisation of a nanomaterial and can change for each individual nanomaterial depending on chemical composition, surface modification and environment of the nanomaterial. Also, if persistence was to be included as an element of a definition, it

would presume that information on which to base a decision on whether a given material was persistent or not was available. This will not be the case. In addition, it would link any defined nanomaterial with hazard and not all nanomaterials will have an associated (specific) hazard.

3.3.9. Manufactured versus natural

Three main categories of nanomaterials (nano-sized particles) can be distinguished, i.e. naturally occurring nanomaterials (e.g. gas-phase condensation products, ash, minerals, colloids), man-induced nanomaterials (by-products of human activities like ultrafine particles from high-temperature processes such as combustion and industrial processes) and engineered or manufactured nanomaterials.

Many natural or synthesised materials may be used to produce nano-sized particles by size reduction (grinding, milling). In contrast there are carbon black and silica that are also extremely high production volume chemicals (millions of tonnes per year) that have been chemically synthesised using bottom-up methods for more than 60 years. All these materials will eventually gain access to the environment, resulting in exposure of plants, animals and humans beyond the usual context of their normal presence.

Assessing the risks of all newly designed top-down and bottom-up nanosized materials is an exercise that needs to be performed carefully on a case-by-case basis. It is then, and only then, possible to conclude, in the context of each proposed use, whether there are specific risk assessment needs. Within this context both the words "manufactured" and "engineered" are used to indicate the production of newly developed nanomaterials. Although differences are defined between engineered and manufactured nanomaterials (ISO/TS 80004-1 in press), the word "engineered" nanomaterials generally includes "manufactured" nanomaterials.

In order to designate specifically purposely made nanomaterials the term "manufactured" may be used. However, this term may not be sufficient to identify all produced nanomaterials. The meaning of "manufactured" must also include the processing of materials with the purpose of obtaining materials at the nanoscale.

In conclusion, based on their origin, three types (natural, man-induced, manufactured) of nanoscale materials can be distinguished. As a result, a general definition should cover all these three types of nanoscale materials, the distinction being provided by the use of the terms natural, man-induced, and/or manufactured.

3.4. Conclusions

The various definitions for nanoscale and nanomaterial proposed so far have mainly sought to identify an inclusive size range that could be used to bring an increased understanding of the terminology that uses the prefix "nano". Although recently, ISO has taken a more elaborate approach using a general material hierarchy to define a series of core terms such as "nanoscale", "nano-object" and "nanostructured material", in past discussions SCENIHR preferred to use a more general framework based on existing terminology linked to an understanding of "nanoscale" with the aim of avoidance of the proliferation of unnecessary terms. While both have their merits, it is clear however, that neither approach actually addresses the uncertainties that are associated when "nanomaterial" definitions are requested for use as "enforceable terms" in a specific Regulatory Agency setting.

In addition to defining "nanoscale" in the context of "nanomaterial" it is important to also consider the key issues relating to both interpretation and the uncertainties associated with any inclusive size range proposed as indicative of "nanoscale".

This opinion considers several criteria in terms of their possible implications relating to interpretation of the definitions of nanoscale and nanomaterial. It should be noted that in the metric system the “nanoscale” is the range below 1 micrometre (μm) and above 999.99(9) picometre (pm). Many previous reports (see Annex 1) have recommended an upper limit for a nanomaterial of approximately 100 nm and a lower limit of ~ 1 nm. Therefore, for one or more external dimensions a working range for the nanoscale of 1 to 100 nm was used here to illustrate some of the important considerations relating to the definition of a nanomaterial and its measurands.

The key factors discussed were as follows.

Size

When considering any definition for nanoscale and nanomaterial it is evident that size is the predominant factor. It was considered what size refers to and the possible specification of an upper and lower cut-off. However, within a regulatory context size alone as a measurand might not be sufficient as any size mentioned should be controllable and enforceable. This assumes that adequate methodologies are available. Several techniques are available for measuring at the nanoscale (i.e. below 1 μm). However, the measurements made using these techniques are not always comparable. Therefore, not only is the size itself important but also the methodology used. For any accurate determination of size and size distribution at least two complementary methodologies should be used. Any nanomaterial should be described by its size and size distribution including the methodologies used for the measurement.

Size is the universal parameter that applies to all nanomaterials. It is also evident that the size distribution is an element that should also be considered. Size was taken to refer to one or more external dimensions as this will capture most nano-objects such as plates or sheets, fibres and nanoparticles. However, solely referring to size as “one or more external dimensions” will NOT capture aggregates and agglomerates of primary particles and also critically, more complex multi-component nanomaterials that are widely used in medicinal and cosmetic applications, as their external dimension is likely to be larger than a specified upper size limit. Thus a reference to the internal structure is also usually added to capture aggregates, agglomerates and complex assemblies. Based on the discussions, it seems that validated standard methods to determine size and its corresponding distribution are required.

In terms of the size limit, upper and lower cut-offs were considered. A lower size limit of 1 nm for one or more external dimensions is complicated by the fact that many molecules would then also be included and some nanoparticles may be excluded. Thus, in any definition of a nanomaterial, molecules need to be excluded. However, it should be noted that around 1 nm there is ambivalence between molecules, nanoclusters and nanoparticles.

The upper size limit for one or more external dimensions of 100 nm is complicated by the potential exclusion of aggregates, agglomerates and multi-component assemblies that would have external sizes greater than this. The inclusion of a reference to “internal structure” with the same specified range as the external dimensions will include such materials within the scope of definition. However, this would also include nanoporous materials that are not usually considered to be nanomaterials. Therefore, some additional criterion is needed to exclude such materials.

Within a regulatory context, it seems useful to specify an upper and lower limit to facilitate a uniform interpretation. Equally, there seems to be a need for validated standardised methods to determine size and its corresponding distribution as these would ensure comparability of results. Also the definition should aim to be over-arching to also include next-generation nanomaterials to avoid quickly becoming obsolete.

Size distribution

The size distribution should not be ignored and should be taken into account when defining and describing a nanomaterial. When only a part of the material has a size

within the size range of the definition/description it should be clearly described whether and when such a material will be considered a nanomaterial or not. This may be by allowing a part (certain %) of the number size distribution to be below a certain threshold or by using the information on the size distribution itself.

Using the number size distribution materials might be defined as NOT being a nanomaterial as the mean size plus or minus three times the standard deviation (SD) (meaning 99.7% of the data set or measured nanoparticles) indicates that 99.85% of the sizes are above a certain upper size limit. Or the other way around: any material is a nanomaterial when >0.15% of the material, based on number concentration, has a size below the upper limit.

The size distribution of a material should be presented as size distribution based on the number concentration (i.e. the particle number) and not on the mass concentration of a nanomaterial product as a small mass concentration may contain the largest number fraction.

To ensure comparability of results validated standard methods are needed to determine both size and its distribution.

Volume Specific Surface Area

The volume specific surface area (VSSA) is a complementary qualifier (criterion) to distinguish dry solid nanostructured material from non-nanostructured material based on its integral material surface area per material volume. For dry, solid materials, including agglomerates and aggregates, the VSSA can be estimated from the specific surface area as determined by the BET-method and the bulk density, a well known parameter. However, it should be noted that not all nanomaterials are amenable to VSSA determination (e.g. dispersions, nanocarriers etc.) and this may limit its applicability. Expressing the surface area related to the volume instead of mass allows for an additional criterion independent of the density and size or number size distribution of the engineered nanomaterial. A VSSA above $60\text{m}^2/\text{cm}^3$ would indicate an average size below 100 nm and thus a high nanomaterial content.

The volume specific surface area can be considered as an additional criterion that could be used to identify dry solid powders as nanomaterial. However, for inclusion in a general definition a limitation is that not all nanomaterials are amenable to VSSA determination. Also for materials with a VSSA below $60\text{m}^2/\text{cm}^3$ there is still the possibility that a fraction may have a VSSA above $60\text{m}^2/\text{cm}^3$ in view of the size distribution within the preparation.

Surface modifications

Surface modifications were considered in the context of including specific properties as elements of the definition. There is a multitude of possibilities for the application of coatings and surface modifications of nanomaterials. Both deliberately applied and environmentally acquired coatings can have a major impact on nanomaterial interaction with biological systems. The coating and core together control the properties of a given nanomaterial and it is not useful to look at either the properties of the core or coating in isolation as they may not be representative of how the nanomaterial will behave in a given environment. Thus, each combination of a nanomaterial with a coating has to be considered as an individual case for safety evaluation. The variability in coatings on nanomaterials prohibit the feasibility of including elements based on specific surface properties within a definition as these properties may vary with coatings.

Other physico-chemical characteristics

Several properties from the OECD WPMN list of 16 physico-chemical characteristics that are considered to be relevant for the characterisation of nanomaterials for toxicological testing were evaluated as possible discriminators for the identification of a nanomaterial. These were crystalline phase, photocatalytic activity, zeta potential, redox potential, radical formation potential, water solubility and the octanol-water partition coefficient.

It was concluded that while all of these properties are very useful for risk assessment, none of them appears to meet the criterion of universal applicability required for a definition.

Solubility and degradability are highly relevant for the risk assessment of nanomaterials. Like any other material, nanomaterials can be degraded either chemically or by solubilisation; in fluids, they can form agglomerates or stable dispersions depending on solvent chemistry and surface coating. As for the other properties listed here, they crucially affect the behaviour of a nanomaterial of concern, but they are not sufficiently over-arching to be included in a definition or to serve as a criterion for the definition of a nanomaterial. They may however be valid criteria to assess the effect or the lifetime of a certain nanomaterial in different environments and its potential to release free nanoparticles.

It was also considered whether nanomaterials could be differentiated based on persistence or whether they are organic or inorganic. It was concluded that persistence is important for risk assessment but if it were included as an element of a definition, the definition would rely on information that may not be available. In addition, it would link any defined nanomaterial with the potential for a chronic hazardous effect while this would not be valid for all nanomaterials. Defining nanomaterials as either organic or inorganic was also considered to be relevant for risk assessment but this criterion would fail to capture hybrid nanomaterials.

In general, some of the properties that can be said to change with size are those which physicists call "cooperative" such as electronic conductivity, light scattering (and its relation to absorbance), magnetism, and superconductivity. All these properties exhibit a characteristic "dimension" which may be micrometres (for semiconductor "quantum effects") or a few nm (for similar effects in metals). For these effects on metals and semiconductors (catalytic) reactivity depends on size, shape and atomic structure.

Various physico-chemical properties may change with decreasing size depending on chemical composition. For the various characteristics discussed, these changes may occur at different sizes. Although no specific characteristic can be attributed to a specific size the fact that such changes occur is evident.

For risk assessment purposes it may be important to know most of the physico-chemical parameters mentioned in this opinion. However, whether they each show sufficient discrimination to generally identify the wide variety of nanomaterials is doubtful.

Composite nanomaterials

A nanocomposite is a composite material in which at least one of the phase domains has at least one dimension of the order of nanometres. The inclusion of "internal structure" as an element of the definition is needed to include nanocomposites into the definition of nanomaterials.

However, nanocomposite also refers to a multi-phase material where at least one phase has dimensions of the order of nanometres (e.g. nanoparticles) and one phase is a continuous phase (bulk phase e.g. polymer matrix). This interpretation of nanocomposite is specific for materials that include a bulk phase material (e.g. car tyres that have incorporated carbon black). It was noted that the inclusion of "internal structure" as an element of the definition would also mean that those nanocomposites would be defined as nanomaterials.

Manufactured, natural, by-product of human activity

Based on their origin three main types of nanoscale materials (natural, by-products of human activity, and engineered/manufactured) can be distinguished. As a result, a general definition should include all three types of nanoscale materials, the distinction being provided by the use of the words natural, man-induced, and/or engineered/manufactured.

In order to designate more specifically purposely made nanomaterials within the regulations, the term “engineered/manufactured” may be used. However, the term manufactured may not be sufficient to identify all produced nanomaterials with a specific nano-risk for man and environment. The modification (processing) of materials (substances, minerals) by decreasing the size from bulk material into nanoscale materials may also pose an additional risk. As a result, the meaning of “engineered” or “manufactured” has to include the processing (grinding or milling resulting in size reduction) of materials with the purpose to obtain materials at the nanoscale.

In conclusion, a working definition based on size referring to one or more external dimensions or an internal structure with a specified upper and lower limit (100 and 1 nm respectively) seems credible. Size is universally applicable to all nanomaterials and is the most suitable measurand. For regulatory purposes, the number size distribution should also be considered using the mean size and its standard deviation to refine the definition. Alternatively, a specific fraction of the number size distribution might be allowed to be within the specified size ranges of the definition.

For dry solid powders the volume specific surface area (above $60\text{m}^2/\text{cm}^3$) can be used as an additional criterion to identify a nanomaterial.

The size range specified should capture most nanomaterials although some challenges remain in terms of inclusions and exclusions. Such challenges can be posed by molecules around the specified lower limit, as well as by nanoporous materials and nanocomposites with respect to the internal structure.

Validated standardised methods for measuring size and its distribution would be needed to ensure comparability of results.

At the moment, no scientific data are available to indicate that a specific size associated with special properties due to the nanoscale can be identified for nanomaterials in general. There is no scientific evidence in favour of a single upper limit. An upper limit of 100 nm is commonly used by general consensus but there is no scientific evidence to qualify the appropriateness of this value. The use of a single upper limit value might be too limiting for the classification of nanomaterials and a differentiated approach might be more appropriate. This approach could be based on a relatively high upper threshold for materials for which further information is missing. In this case it is assumed that the size distribution at the lower end will always be above the lower, more critical upper threshold. The low upper threshold would be the critical threshold for which extensive nano-specific information has to be provided in order to perform case-by-case risk assessment.

An example is presented below using 500 nm as high upper threshold and 100 nm as low upper threshold (see figure 1).

Category 1 median size >500 nm for materials for which further information is missing

If the median size of the material is above 500 nm it is assumed that the size distribution at the lower end will always be above the designated lower threshold of 100 nm. Thus, no further information regarding possible nanospecific properties may be needed and classical risk assessment can be performed taking into consideration the particulate nature of the material.

Category 2 median size <500 nm

When the median size is <500 nm a material is considered to be a nanomaterial and a more detailed nanospecific risk assessment is necessary taking into consideration possible nanospecific characteristics of the material.

When the size is <500 nm but >100 nm the nanospecific risk assessment may be waived when additional information is provided that the number size distribution demonstrates that the material has <0.15% (or any specified percentage) of the number size distribution <100 nm. For dry materials, the VSSA (< $60\text{ m}^2/\text{cm}^3$)

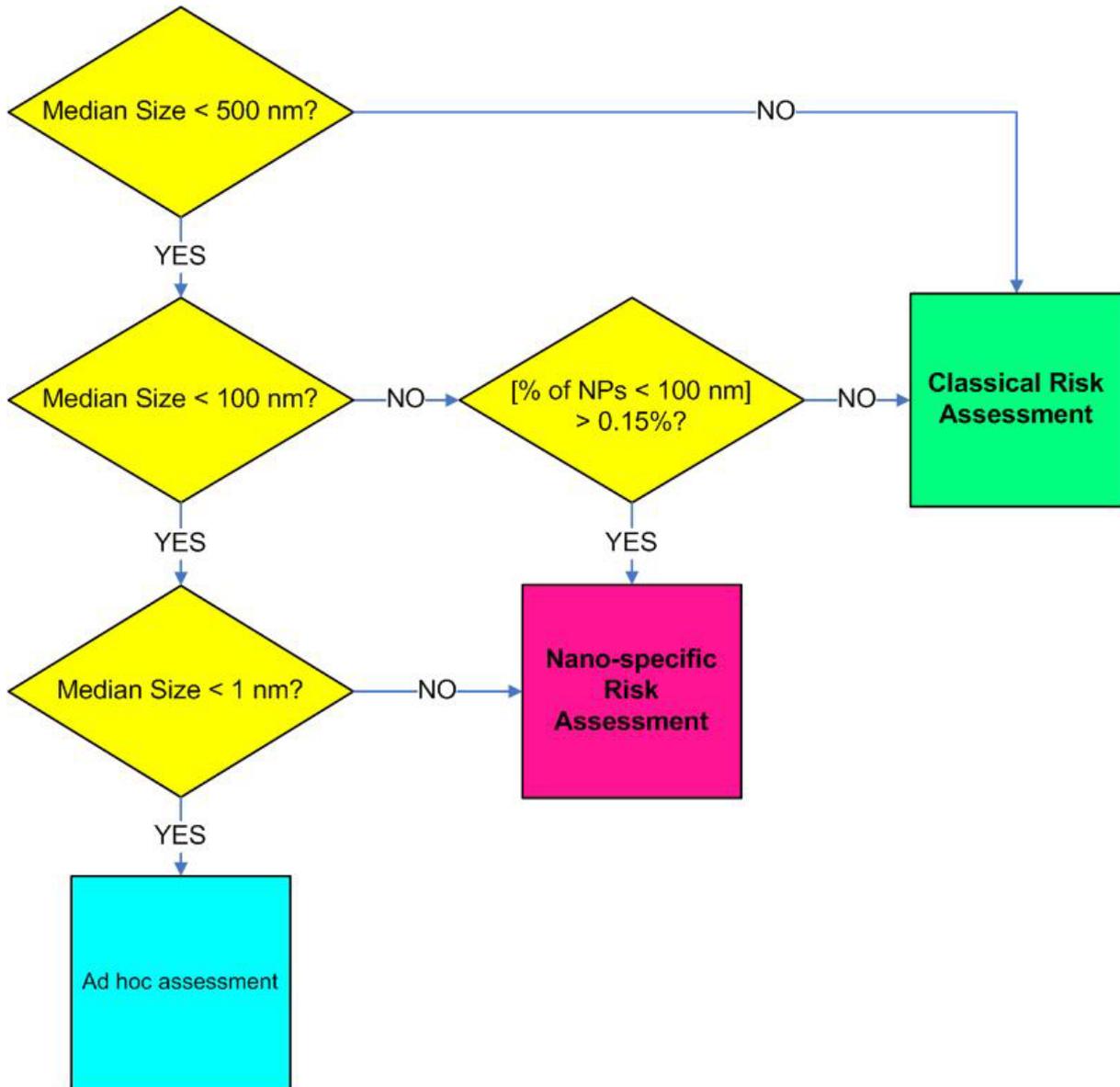
Scientific basis for the definition of the term “nanomaterial”

may be used as an additional qualifier. In these cases a classical risk assessment can be performed taking into consideration the particulate nature of the material.

Category 3 median size <100 nm and >1 nm

The material is considered to be a nanomaterial and nanospecific risk assessment has to be performed when >0.15% (or a specified percentage) of the number size distribution is <100 nm. For dry materials, the VSSA (>60 m²/cm³) may be used as an additional qualifier.

Figure 1: Risk Assessment on nanomaterials, tiered approach



4. OPINION

With the expected increase in the applications of nanotechnology there is an urgent need to identify by clear unequivocal descriptions what can be considered as a nanomaterial and what should not be. This need to identify a nanomaterial and nanotechnology product comes from the uncertainty regarding the risk assessment and safety evaluation of nanotechnology products or more specifically the nanomaterials themselves.

It should be stressed that “nanomaterial” is a categorisation of a material by the size of its constituent parts. It does not imply a specific risk, nor does it necessarily mean that this material actually has new hazard properties compared to its constituents. However, size will influence biodistribution (and distribution kinetics) in an organism or in an ecosystem. One should also consider whether the definition should aim to be overarching so as to include next-generation nanomaterials and avoid quickly becoming obsolete. Although the toxicological profile of the chemical components of a given nanomaterial may be well known, there may be cases where its specific properties raise concerns over their specific potential to cause harm to humans and the environment. This raises the question as to whether the current risk assessment methodology used for “classic” substances (chemicals) in the EU can be used for nanomaterials or whether there is a need to perform another kind of risk assessment.

Based on current knowledge, the Committee was invited to provide advice on the essential elements of a science-based working definition of “nanomaterials” and, specifically, to identify the most appropriate metrics to define materials at the nanoscale, taking into account:

- Reported size ranges and other relevant characteristics and corresponding metrics: The size ranges and other relevant characteristics (e.g. specific surface area, shape, density, spatial arrangements, aggregation, agglomeration, etc.) and corresponding metrics of materials reported as “nanomaterials” in the scientific literature;
- Characteristics: A first indication of possible characteristics and associated mechanisms that alone or in various combinations may lead to different properties;
- Physico-chemical properties: The physical and chemical properties that materials may show as a result of being at nanoscale or having a nanoscale structure;
- Threshold(s): The threshold(s) at which properties identified above may be expected to occur (the threshold(s) may be “below” or “above” depending on the relevant characteristic(s) and associated metric(s)).

There is sufficient evidence that reducing size to within the nanoscale changes some properties of the material that, for instance, have to do with the increase in surface-to-volume ratio. These nanospecific properties raise concerns over their potential to cause harm to humans and the environment. The chemical reactivity of nanoparticles often relates to the surface area. Consequently, the chemical reactivity increases per mass dose for smaller particles of the same type while this effect may or may not be associated with an increase in biological activity or toxicity. It is this uncertainty that warrants the careful evaluation of possible risks associated with nanotechnology products. However, although a change in properties may occur at the nanoscale, and indeed many nanomaterials are specifically produced for such properties, it is at the moment not possible to identify a specific size at which a specific property would change or appear, nor a specific property that is introduced with size.

Several international and national organisations have proposed definitions for the nanoscale and nanomaterials. In most of the definitions proposed, the size refers to one or more external dimensions or an internal structure within a specified size range. The typical upper limit for the nanoscale is 100 nm, while the lower limit is either 1 nm, around 1 nm, or not indicated. The definition of the nanoscale as having a size between

approximately 1 and 100 nanometre is commonly accepted, although: (i) there is no scientific evidence in favour of a single upper limit; (ii) there is no scientific evidence to qualify the appropriateness of the 100 nm value; (iii) the term "approximately" or "of the order of" cannot be used in a regulatory context; (iv) it does not take into account that a nanomaterial will comprise a range of sizes; and (v) the methodology needs to be adequate to support the applications of the definition. Some definitions have also included a reference to specific properties or nano-specific properties.

This opinion provides advice on the essential scientific elements of a working definition for the term "nanomaterial" for regulatory purposes. The major question for both regulators and manufacturers is to identify when a material or product can be considered a nanomaterial. It should be noted that, in the metric system, the "nanoscale" is the range below 1 micrometre (μm) and above 999 picometre (pm). Criteria relevant for the discrimination between nano and non-nano are discussed using a working definition for nanoscale being approximately 1 to 100 nm. Any material with one or more internal or external dimensions in the nanoscale is then considered a nanomaterial. The feasibility of including specific properties as criteria was assessed.

A definition using the range of approximately 1 nm to 100 nm, even with the addition of "engineered" or "manufactured", would include biological materials that are commonly used and processed and thus can be considered to be "engineered" in the food industry.

When considering any definition for nanoscale and nanomaterial it is obvious that size is the predominant feature. Size, when used to refer to one or more external dimension will capture most nano-objects such as plates or sheets, fibres and equidimensional nanoparticles. However, within a regulatory context, any size mentioned should be controllable and enforceable. This requires that adequate validated methodologies are available. Several techniques are available for measuring at the nanoscale (i.e. below 1 μm). Several techniques are available for measuring at the nanoscale (i.e. below 1 μm). However, the measurements obtained using these techniques are not always comparable. Any nanomaterial should be described by its size and number size distribution including the methodologies used for the measurement.

Solely referring to size as "one or more external dimensions" will NOT capture aggregates and agglomerates of primary particles nor, importantly, more complex multi-component nanomaterials that are widely used in medical and cosmetic applications, as their external dimension is likely to be larger than a specified upper size limit. In terms of the size limit, the lower and upper cut-offs of 1 and 100 nm, respectively were considered. However, a lower size limit of 1 nm for one or more external dimensions is complicated by the fact that many molecules would then also be included and some nanoparticles may be excluded. The upper size limit for one or more external dimensions of 100 nm is also complicated by the potential exclusion of aggregates, agglomerates and multi-component assemblies that would have external sizes greater than this. The inclusion of a reference to "internal structure" with the same specified range as the external dimensions will include such materials within the scope of definition. This would also include nanoporous and nanocomposite materials.

To distinguish a nanostructured material from a non-nanostructured material, the volume specific surface area (VSSA) can be a complementary criterion, based on its integral material surface area per unit volume. For dry, solid materials, including agglomerates and aggregates, the VSSA can be estimated from the specific surface area as determined by the BET-method and the bulk density, a well known parameter. A limitation of the BET-method is that it is only applicable to powders and/or dry solid materials and is not directly applicable to suspensions. Expressing the surface area related to the volume instead of mass allows for an additional criterion independent of the density of the nanomaterial. A VSSA above $60\text{m}^2/\text{cm}^3$ would indicate a nanomaterial. Similar to size, the VSSA is not an absolute discriminator for the "nano" size of materials as, even with a VSSA below $60\text{m}^2/\text{cm}^3$, a fraction of the material may have a VSSA above $60\text{m}^2/\text{cm}^3$ in view of the size distribution within it.

Data on the size distribution should be taken into account when describing a nanomaterial. When only a part of the material has a size within the size range of the definition or description it should be clear whether and when such a material will be considered a nanomaterial. This may be by allowing a part (certain %) of the number size distribution to be below a certain threshold or by using the information on the size distribution itself. For example, a material might be considered as a nanomaterial when >0.15% of the material, based on number concentration, has a size below the designated upper size limit. So, materials might be defined as NOT being a nanomaterial when the mean size minus three times the Standard Deviation (SD) of the number concentration shows that 99.85% of the sizes are above the designated upper size limit. However, different distribution thresholds might be required for specific areas of application.

As size is a key element to a definition, there is a need for the development of validated standardised methods to determine size and its corresponding distribution to ensure comparability in results.

There is a multitude of possibilities for the application of coatings and surface modifications to nanomaterials. Purposely applied and environmentally acquired coatings can have a major impact on nanomaterial interaction with biological systems. The coating and core together control the properties of a given nanomaterial and it is not useful to look at either the properties of the core or of the coating in isolation as they may not be representative of how the nanomaterial will behave in a given environment. Thus, each combination of a nanomaterial with a coating has to be considered as an individual case for safety evaluation. The variability in coatings on nanomaterials prohibits the feasibility of including criteria based on surface properties within a definition as these properties may vary with coatings.

Several properties from the OECD Working Party on Manufactured Nanomaterials (WPMN) list of 16 physico-chemical characteristics that are considered to be relevant for the characterisation of nanomaterials for toxicological testing were evaluated as possible discriminators for the identification of a nanomaterial. These were crystalline phase, photocatalytic activity, zeta potential, redox potential, radical formation potential, water solubility and the octanol-water partition coefficient. It was concluded that while all of these properties are very useful for risk assessment, none of them appears to meet the universal applicability criterion required for a definition.

Solubility and degradability are highly relevant for the risk assessment of nanomaterials. Like any other material, nanomaterials can be degraded either chemically or by solubilisation; in fluids, they can form agglomerates or stable dispersions depending on solvent chemistry and their surface coating. As for the other properties listed here, they crucially affect the behaviour of a nanomaterial of concern but they are not sufficiently over-arching to be included in a definition or to serve as a criterion for the definition of nanomaterial. They may however be valid criteria to assess the effect or the lifetime of a certain nanomaterial in one or the other environment and its potential to release free nanoparticles.

Features associated with solubility (and degradability) of nanomaterials are very important for risk assessment in view of the possibility for persistence and accumulation both in man and the environment. These features include size and shape, water solubility, surface charge and surface reactivity. However, these features cannot be translated into a definition as they are part of the characterisation of a nanomaterial and can change for each individual nanomaterial depending on chemical composition, surface modification and the immediate environment of the nanomaterial.

For risk assessment purposes it may be important to know most of the physico-chemical parameters mentioned in this opinion. However, whether they each show sufficient discrimination to generally identify the wide variety of nanomaterials is doubtful.

It was also considered if nanomaterials could be differentiated based on whether they are inorganic or organic. Certain persistent nanomaterials may be organic (carbon

nanomaterials) and certain oxides may be (bio)degradable. It would also not capture hybrid nanomaterials with inorganic and organic components. Thus, terms like inorganic nanomaterial as marker for potential biopersistence would not be a useful criterion to include in a definition.

Certain nanomaterials and composite materials may have incorporated internal or external structures at the nanoscale to confer nanospecific characteristics to that composite. The internal structure with a size at the nanoscale would be an element to include in a definition, as then nanocomposites will be included in the definition of a nanomaterial. As the external dimensions of nanocomposites would be typically larger than 100 nm, most nanocomposites would not be considered to be nanomaterials with a definition based solely on external size.

There are nanocomposites where one phase is a bulk one. It was noted that the inclusion of “internal structure” as an element of the definition would also mean that those nanocomposites would be defined as nanomaterials. Exclusion criteria would have to be developed to avoid considering macroscopic composite objects as nanomaterials.

Based on their origin, three types of nanoscale materials (natural, by-products of human activity, engineered) can be distinguished. As a result, a general definition should include all these three types of nanoscale materials, the distinction being provided by the use of the words natural, by-products of human activity or engineered (or manufactured).

In order to designate more specifically purposely made nanomaterials within regulations, the term “engineered” or “manufactured” may be used. When considering the purposely made nanomaterials, the meaning of “engineered” or “manufactured” also needs to include the processing (e.g. grinding or milling resulting in size reduction, chemical processing) of materials to obtain materials at the nanoscale.

In conclusion, size is universally applicable to all nanomaterials and is the most suitable measurand. A defined size range would facilitate a uniform interpretation. For regulatory purposes the number size distribution should also be considered using both the mean size and its standard deviation for further refinement of the definition. Alternatively, a specific fraction of the number size distribution might be allowed to be within the specified size ranges of the definition. For dry powders, the volume specific surface area (VSSA) may be added to the size as a discriminator to identify nanomaterials. In addition, the definition should include both external and internal nanostructures.

For the lower limit of the definition of nanomaterials, the size of 1 nm is proposed. However, around 1 nm, there is ambivalence between molecules, nanoclusters and nanoparticles.

At the moment, no scientific data are available to indicate that a specific size associated with special properties due to the nanoscale can be identified for nanomaterials in general. There is no scientific evidence in favour of a single upper limit. However, there is by general consensus an upper limit of 100 nm which is commonly used. There is no scientific evidence to qualify the appropriateness of this value. The use of a single upper value might be too limiting for the classification of nanomaterials and a differentiated approach might be more appropriate. This approach could be based on a relatively high upper threshold for which it is assumed that the size distribution at the lower end will always be above the lower, more critical threshold. The lower threshold would be the critical threshold for which extensive nano-specific information has to be provided in order to perform case-by-case risk assessment.

An example is presented below using 500 nm as high upper threshold and 100 nm as low upper threshold.

Category 1 median size >500 nm for materials for which further information is missing

If the median size of the material is above 500 nm it is assumed that the size distribution at the lower end will always be above the designated lower threshold of 100 nm. Thus, no further information regarding possible nanospecific properties

may be needed and classical risk assessment can be performed taking into consideration the particulate nature of the material.

Category 2 median size <500 nm

When the median size is <500 nm a material is considered to be a nanomaterial and a more detailed nanospecific risk assessment is necessary taking into consideration possible nanospecific characteristics of the material.

When the size is <500 nm but >100 nm the nanospecific risk assessment may be waived when additional information is provided that the number size distribution demonstrates that the material has <0.15% (or any specified percentage) of the number size distribution <100 nm. For dry materials, the VSSA (<60 m²/cm³) may be used as an additional qualifier. In these cases a classical risk assessment can be performed taking into consideration the particulate nature of the material.

Category 3 median size <100 nm and >1 nm

The material is considered to be a nanomaterial and nanospecific risk assessment has to be performed when >0.15% (or a specified percentage) of the number size distribution is <100 nm. For dry materials, the VSSA (>60 m²/cm³) may be used as an additional qualifier.

In addition to size, any regulatory definition should be limited to purposely-designed nanomaterials (e.g. engineered or manufactured nanomaterials) including the processing of nanomaterials.

Based on specific requirements regarding risk assessment for regulatory purposes, for specific areas and applications, modifications of any overarching definition may be needed.

5. MINORITY OPINION

None

AFM	Atomic force microscopy
BET-Method	Brunauer, Emmett and Teller
BSI	British Standards Institute
CAS	Chemical Abstracts Service
CMC	Chemistry, manufacturing and controls
CNRS	French National Center for Scientific Research
D	Diameter
DLS	Dynamic light scattering
ECDC	European Centre for Disease prevention and Control
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
FDA	(United States) Food and Drug Administration
FDA-CDER	FDA Center for Drug Evaluation and Research
FERA	The Food and Environmental Research Agency

IUPAC	International Union of Pure and Applied Chemistry
ISO	International Organization for Standardization
MAPP	Manual of Policies and Procedures
µm	Micrometre
nm	Nanometre
NP(s)	Nanoparticle(s)
NRCWE	National Research Centre for the Working Environment
OECD	Organisation for Economic Co-operation and Development
OECD WPMN	OECD Working party on Manufactured Nanoparticles
pm	Picometre
POP(s)	Persistent organic pollutant(s)
ρ	Bulk density
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RIVM	National Institute for Public Health and the Environment
SCCS	Scientific Committee on Consumer Safety
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHER	Scientific Committee on Health and Environmental Risks
SD	Standard deviation
SSA	Specific surface area
TEM	Transmission electron microscopy
VSSA	Volume specific surface area
VSSA_{fr}	VSSA fractionated by size

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ANNEX I

Selected existing definitions relevant for nanomaterials

ISO TC 229 Nanotechnologies

ISO ISO/TS 27687:2008 Nanotechnologies- Terminology and definitions for nano objects—nanoparticle, nanofibre and nanoplate.

The document lists various terms and definitions related to particles in the area of nanotechnologies. The definition described in the document for the nanoscale is:

Nanoscale: Size range from approximately from 1 nm to 100 nm.

This definition is accompanied by two notes:

Note 1: Properties that are not extrapolations from a larger size will typically, but not exclusively, be exhibited in this size range. For such properties the size limits are considered approximate.

Note 2: The lower limit in this definition (approximately 1 nm) is introduced to avoid single and small groups of atoms from being designated as nano-objects or elements of nanostructures, which might be implied by the absence of a lower limit.

Currently a new series of technical specifications is being prepared dealing with the various subjects within nanotechnology such as: core terms, nano-object, nanomaterial, carbon nano-object, nanostructured material, bio/nano interface, nanoscale measurement and instrumentation, medical health and personal care applications, and nanomanufacturing processes. These subjects will be described in the ISO/TS 8004 series dealing with the vocabulary of nanotechnologies.

OECD

Although not formally published in an OECD document, the OECD Working party on Manufactured Nanomaterials (WPMN) has published a description of a nanomaterial on its website.

The OECD states “A *nanomaterial or a nanoparticle is usually considered to be a structure between 0.1 and 100 nm (1/1,000,000 mm)*”⁷. At the nanoscale, the physical, chemical, and biological properties of materials may differ in fundamental and often valuable ways from the properties of individual atoms and molecules or bulk matter.

In a working document a more elaborate definition is published. OECD Working Party on Manufactured Nanomaterials Guidance for the use of the OECD Database on Research into the Safety of Manufactured Nanomaterials, Ver.1 October 2008.

“Manufactured nanomaterials: *Nanomaterials intentionally produced to have specific properties or specific composition, a size range typically between 1 nm and 100 nm and material which 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).*”

This definition is based solely on size.

SCENIHR

⁷ http://www.oecd.org/about/0,3347,en_2649_37015404_1_1_1_1_1,00.htm

In its "Opinion on the scientific aspects of the existing and proposed definitions relating to products of nanoscience and nanotechnologies" (SCENIHR 2007) the SCENIHR describes some basic principles relating to the nanotechnologies and the nanoscale.

"(1) ... taking into account the need to avoid the promulgation of unnecessary terms and the requirements that it should be based on sound principles of lexicology. In view of the mandate of SCENIHR, this framework has been developed in the context of risk assessment procedures. Most of the concepts and behaviour patterns seen at the very small dimensions associated with nanotechnology are not new, and can be described by the existing terminology used at larger scales. It is recognised that it is impossible to stop individuals producing new words and definitions, but it is crucial that a new language is not adopted unnecessarily by the scientific community, and that on those occasions where it is required, it is consistent with established terminology.

(2) ... Secondly, many of the terms used in nanoscience are based on commonly used words such as 'substance', 'matter' and 'material' and terms in nanoscience should not conflict with the general meaning of such words.

(3) The majority of terms that need to be considered in the context of nanoscience and nanotechnology are those that start with the prefix 'nano-', which specifically means a measure of 10^{-9} units, the nature of this unit being determined by the word that follows. There is absolutely no need to change the meaning of any scientific term, such as metre or material just because it is pre-fixed by 'nano-'.

(4) The majority of terms used in nanotechnology are broadly self-explanatory. There are, however, some situations in which explanations are required in the development of a suitable framework for this terminology, especially for risk assessment purposes. "

A clear statement was made that according to the metric system nanoscale actually means a size between 1 and 999 nm, being the size above picometre (10^{-12}) and below micrometre (10^{-6}). For the purpose of risk assessment of nanotechnology products, however, the nanoscale was limited to sizes of the order of 100 nm or less.

Nanoscale: A feature characterised by dimensions of the order of 100 nm or less.

In the opinion a framework was described involving a hierarchy of terms, the principal one of which is "nanoscale", which is considered here to be characterised by dimensions of the order of 100 nm or less. The framework builds on this concept of the nanoscale and develops series of definitions, appropriate for risk assessment purposes, based on considerations of size, shape and properties. Key words defined in this framework include nanomaterial and nanoparticle, with particular emphasis on the limits to the nanoscale, the features that characterise a nanomaterial, the distinction between different geometric shapes at the nanoscale, and the potential for harm of released discrete free particles and/or their decomposition products. Within this scheme an engineered nanomaterial is defined as:

Engineered nanomaterial: Any material that is deliberately created such that it is composed of discrete functional parts, either internally or at the surface, many of which will have one or more dimensions of the order of 100 nm or less.

EU Legislation containing a definition of "nano"

There is currently one EU regulation (Regulation EC/1223/2009 on Cosmetic Products) that includes a definition of nanomaterials. This text has foreseen a specific article (Article 2.3) to make a change in the definition possible depending on scientific and/or international developments.

Article 2.1.k of Regulation EC/1223/2009 on Cosmetic Products

(k) 'nanomaterial' means an insoluble or biopersistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.

Article 2.3 of Regulation EC/1223/2009 on Cosmetic Products

In view of the various definitions of nanomaterials published by different bodies and the constant technical and scientific developments in the field of nanotechnologies, the Commission shall adjust and adapt point (k) of paragraph 1 to technical and scientific progress and to definitions subsequently agreed at international level. That measure, designed to amend non-essential elements of this Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 32(3).

EU legislation referring to size

In addition to a specific reference for nanomaterials legislation also exists in which (non nanospecific) sizes of solid substances are included. The determination of size is specifically mentioned for solid substances/preparations when used as feed additives for animal nutrition. Such is the case for Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives:

Annex II Section II: IDENTITY, CHARACTERISATION AND CONDITIONS OF USE OF THE ADDITIVE; METHODS OF ANALYSIS

2.1.5. Physical state of each form of the product

For solid preparations data on particle size distribution, particle shape, density, bulk density, dusting potential and the use of processes which affect physical properties shall be provided. For liquid preparations, data for viscosity and surface tension shall be given. Where additive is intended to be used in water, the solubility or extent of dispersion shall be demonstrated.

The statement is built upon scientific terms which are defined elsewhere.

EU Legislation under discussion

Currently legislation for the regulation of novel foods is being prepared and has already been through a first reading of the European Parliament.

The European Parliament adopted the first reading of the legislation by a resolution on the 25th of March 2009, where Council agreement was obtained in June 2009.

European Parliament legislative resolution of 25 March 2009 on the proposal for a regulation of the European Parliament and of the Council on novel foods and amending Regulation (EC) No XXX/XXXX [common procedure] (COM(2007)0872 – C6-0027/2008-2008/0002(COD)).

Article 3.2.f

(f) "engineered nanomaterial" means any intentionally produced material that has one or more dimensions of the order of 100 nm or less or is composed of discrete functional parts, either internally or at the surface, many of which have one or more dimensions of the order of 100 nm or less, including structures, agglomerates or aggregates, which may have a size above the order of 100 nm but retain properties that are characteristic to the nanoscale."

This text is partly adapted from the SCENIHR definition, but the adaptation may create some ambiguities as within this one definition several aspects dealing with size have been included (e.g. both nanomaterials below ("below" is included in the text above with the phrase 'or less') and above 100 nm). As in the existing legislation for cosmetic products also within the proposed legislation on novel foods the possibility is included for a revision of the definition of "nano" based on scientific and/or international developments.

Article 3.3

"In view of the various definitions of nanomaterials published by different bodies at international level and the constant technical and scientific developments in the field of nanotechnologies, the Commission shall adjust and adapt point (c) of paragraph 2 to technical and scientific progress and with definitions subsequently agreed at international level. That measure, designed to amend non-essential elements of this Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 14(3)."

This definition combines size and non-specified properties that are characteristic to the nanoscale.

Miscellaneous

- FDA Nanotechnology. A report of the U.S. Food and Drug Administration Nanotechnology Task Force. July 25, 2007.

In a report of 2007 the FDA did not provide a clear definition on nanotechnology but opted for a broader approach into the subject.

"The Task Force has not adopted a precise definition for "nanoscale materials, "nanotechnology" or related terms to define the scope of its work. The Task Force concluded that it would be most productive to take a broadly inclusive approach in identifying potentially relevant studies, data and other information.

The Task Force believes FDA should continue to pursue regulatory approaches that take into account the potential importance of material size and the evolving state of the science. Moreover, while one definition for "nanotechnology," "nanoscale material," or a related term or concept may offer meaningful guidance in one context, that definition may be too narrow or too broad to be of use in another. Accordingly, the Task Force does not recommend attempting to adopt formal, fixed definitions for such terms for regulatory purposes at this time. As FDA learns more about the interaction of nanoscale materials with biological systems and about general concepts that can inform the agency's judgement, it may become productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in FDA-regulated products."

- FDA Center for Drug Evaluation and Research (CDER) June 2010 MAPP 50159

Recently FDA-CDER has published a manual for chemistry, manufacturing and controls (CMC) reviewers within the Office of Pharmaceutical Science of the FDA. In this manual designated Manual of Policies and Procedures (MAPP) 50159 a definition of a nanomaterial is included as describing a nanomaterial/nanoscale material as any material with at least one dimension smaller than 1,000 nm. The aim is to identify nanotechnology products and to enter the information obtained on the various nanomaterials into a nanotechnology database that may ultimately be used to develop

policy regarding nanotechnology products. The use of the definition is limited to this Manual only dealing with reviews of pharmaceutical products.

- Reflection paper on nanotechnology-based medicinal products for human use EMEA/CHMP/79769/2006

In the EMEA (now EMA) reflection paper, nanomedicine has been defined as follows:

"Nanomedicine is defined as the application of nanotechnology in view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale.

Nanotechnology is a broad term, which covers a wide range of methods, tools and possible applications. There are a variety of definitions reported in literature each generated for different purposes. For the purpose of this document, the definitions are based on those provided in the UK Royal Society and Royal Academy of Engineering report, the European Science Foundation foresight study on nanotechnology and the Vision paper and Basis for a strategic research agenda for Nanomedicine by the European Technology Platform on Nanomedicine:

Nanotechnology is defined as the production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale. The nanometre scale ranges from the atomic level at around 0.2 nm (2 Å) up to around 100 nm."

This definition is solely based on size.

- Health Canada Interim Policy Statement on Health Canada's Working Definition for Nanomaterials

Health Canada considers any manufactured product, material, substance, ingredient, device, system or structure to be nanomaterial if:

- a. It is at or within the nanoscale in at least one spatial dimension, or;*
- b. It is smaller or larger than the nanoscale in all spatial dimensions and exhibits one or more nanoscale phenomena.*

"For the purposes of this definition:

The term "nanoscale" means 1 to 100 nanometres, inclusive; The term "nanoscale phenomena" means properties of the product, material, substance, ingredient, device, system or structure which are attributable to its size and distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material; and,

The term "manufactured" includes engineering processes and control of matter and processes at the nanoscale."

This definition is based on size but the size range can be exceeded if there is evidence of non-specified "nano-scale phenomena".