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Nanomaterials: Classification and Properties

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1.1 Nanomaterial Classifications

The word “nano” derives from the latin word “*nanus*” and Greek word “*vávç*,” both indicating a person of very low height, i.e. a dwarf. The International System (SI) of units considers nano as a prefix to indicate 10^{-9} part of a unit; thus, for instance, a billion of a meter, a billion of a liter, a billion of a kilogram, etc. Not always the term nano is referred to a very small object. For instance, in astronomy, a nanostar is a star having a mass comparable to our Sun or even less. A first, easy, and practical criterion to define nanomaterials is based on the dimensions “tout court”: Nanomaterials are conventionally defined as materials having at least a dimension between 1 and 100 nm. As a consequence, nanoparticles have all the three dimensions in the nanometer range, nanoplates present only one dimension below 100 nm, whereas nanofibers have two dimensions in the range of nano being the remaining remarkably longer. Some common terminologies of the nanorange world are listed in Table 1.1.

Nevertheless, 100 nm as an upper limit for a nanomaterial is not always accepted. Many organizations in the world fixed different thresholds for the nanoscale, although 100 nm still remains the most common shared limit. Table 1.2 presents some recommendations suggested by different organizations.

It is immediately clear that adequate techniques to determine the dimensions of the nano-objects are required. Table 1.3 reports the methods till now available to measure the size of the objects in the nanometric range. To avoid incorrect results and classification, particular care and attention should be devoted to (i) prepare a representative sample for analysis, (ii) follow a correct sample preparation, (iii) use the most appropriate mathematical analysis to get size distribution, and (iv) consider the comparability among different laboratories. Detailed guidelines for sample preparation in GMO analysis were reported in the Joint Research Centre (JRC) technical report in 2014 [3].

A sketch of nano-objects is reported in Figure 1.1.

Table 1.1 Current definitions of terms with the “nano” suffix.

Type	Description
Nanoscale	Size range from approximately 1–100 nm
Nano-object	Material with one, two, or three external dimensions in the nanoscale
Nanoparticle	Nano-object with all three external dimensions in the nanoscale
Nanotemplate	Nano-object with one external dimension in the nanoscale and the other two external dimensions significantly larger (at least three times)
Nanofiber	Nano-object (flexible or rigid) with two external dimensions in the nanoscale and the third dimension significantly larger
Nanotube	Hollow nanofiber
Nanorod	Solid nanofiber
Nanowire	Electrically conducting or semiconducting nanofiber

Source: Adapted from ISO/TS 27687.

Table 1.2 List of the recommended upper limits suggested by different organizations.

Upper limit (nm)	Source
100	ISO
100	ASTM
100	Royal Society – SCENIHR
100	ETC group
100	Swiss Re
200	Soil Association
200	Defra
300	Chatham House
300	Friends of Earth
500	Swiss federal Office of Public Health
1000	House of Lords Science Committee

Source: Adapted from Klaessig et al. [1].

Nanosponges, the subject of this book, can be considered as porous materials having all of the three external dimensions in the micro- or macrorange and the internal cavities, pores, or voids in the nanometer range. Actually, nanosponges can be either of organic or inorganic origin, natural or synthetic [5]. A simple sketch of a type of nanosponges based on cyclodextrins is reported in Figure 1.2.

In other words, nanosponges can be counterintuitively classified as nanomaterials because of the presence of a network of nanometer-sized cavities in the bulk, despite the fact that the dimensions of a given specimen along the x -, y -, and z -axes can be larger than 100 nm. From this viewpoint, nanosponges are characterized by nanometric structural features, but they are generally not nanoparticles. A hierarchical classification of nanomaterials has been proposed based on the particular feature falling in the nanometer size domain. A graphical

Table 1.3 Techniques to measure particle sizes in the nanometer dimension range.

Method name (abbreviation)	Measurement range and medium (limiting factors)	Types of size distribution of raw data
Electron microscopy (EM)	1 nm or higher; dry (dynamic range)	Number based
Dynamic light scattering (DLS)	5–500 nm; suspension (sedimentation and scattering intensity)	(No distribution, or scattering intensity based)
Centrifugal liquid sedimentation (CLS)	20 nm and higher; suspension (particle density)	Extinction intensity based
Small-angle X-ray scattering (SAXS)	5 nm and higher; suspension (dynamic range)	Scattering intensity based
Field flow fractionation (FFF)	1–200 nm; suspension (dynamic range)	(Depends on detector)
Particle tracking analysis (PTA)	25 nm and higher; suspension (dynamic range)	Number based
Atomic force microscopy (AFM)	1 nm and higher; dry (dynamic range)	Number based
X-ray diffraction	1 nm and higher; dry (only for crystalline materials)	(No distribution measured)

Source: Adapted from Lisinger et al. [2].

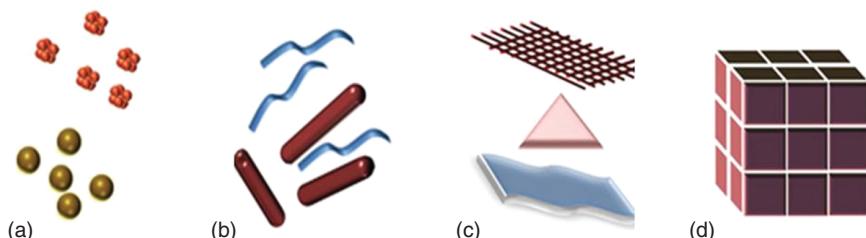
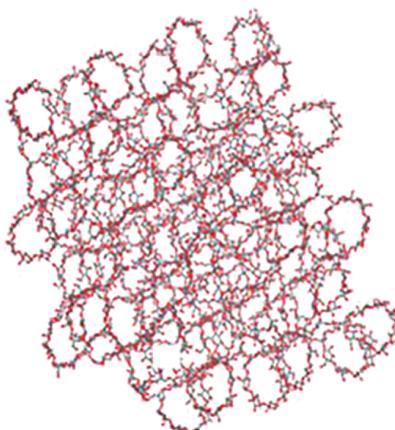


Figure 1.1 Classification of nanomaterials (a) 0D spheres and clusters; (b) 1D nanofibers, wires, and rods; (c) 2D films, plates, and networks; and (d) 3D nanomaterials. Source: Adapted from Alagarasi [4].

Figure 1.2 Possible structure of cyclodextrin nanosponge. Source: Reproduced under CC license from Singh et al. 6. Published by The Royal Society of Chemistry.



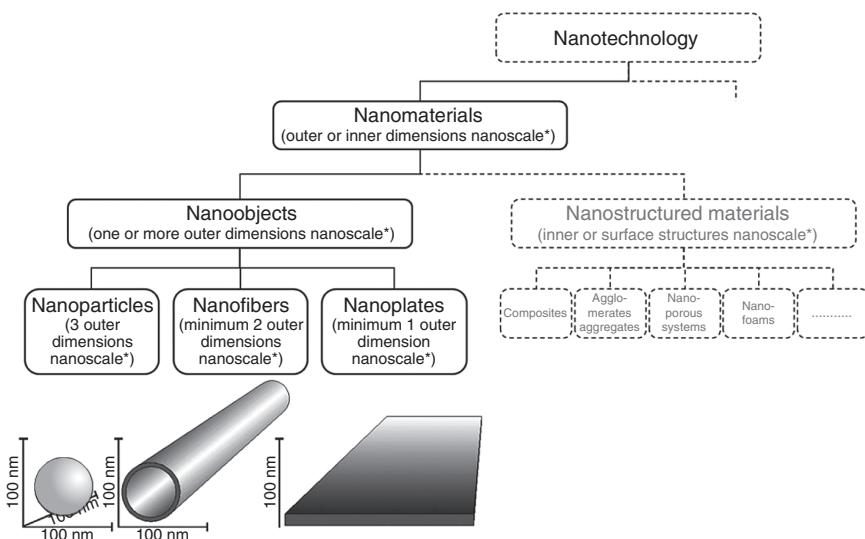


Figure 1.3 The ISO definition of nano-objects. Included as nano-objects are nanoparticles (nanoscale in all the three dimensions), nanofibers (nanoscale in two dimensions), and nanoplates or nanolayers (nanoscale only in one dimension). Source: Krug and Wick 2011 [7]. Reprinted with permission from John Wiley & Sons.

summary, along with the relevant normation (*vide ultra*), is shown in Figure 1.3. The identification of the characteristic of a given material belonging to the nanometric range is particularly relevant for safety and health. IUPAC Glossary of Terms used in Toxicology indeed gave the following definition of “nanoparticle” [8]: “Microscopic particle whose size is measured in nanometers, often restricted to the so-called nanosized particles (NSPs; <100 nm in aerodynamic diameter), also called ultrafine particles,” whereas no listed definition of nanomaterial has been proposed yet.

Several times, nanomaterials can also be included in other bulk materials to form nanocomposites with external dimensions larger than 100 nm, but entrapping nanoparticles in the bulk. Although under discussion, even these materials should be seen as nanomaterials. This is the case of materials with antibacterial properties and made of nanoparticles dispersed in several environments such as fabrics, plastics, chitosans, etc. In a similar way, nanoparticles of reducing agents dispersed in a hydrogel provided superior performances in the reduction of organic dyes in comparison with molecular systems [9]. Polymers are particularly a suitable matrix to disperse nanoparticles. PVDF can host TiO₂ nanoparticles showing an improved surface hydrophilicity and permeability of PVDF membranes and the decreasing adsorption capacity of protein, indicating an antifouling ability of such modified PVDF membranes [10].

On the other hand, it is important to note that even more ambiguity arises in the definition of the lower limit of the dimension of nanomaterials, generally set at 1 nm. Accordingly, also molecules, clusters, supramolecular assemblies – sometimes referred to as supermolecules – and not only nanoparticles

can fall in this limit. In fact, a supramolecular assembly can be considered like the formation of a well-defined complex of several molecules held together exclusively by noncovalent bonds. The main characteristic of such aggregates is that they possess an intrinsic mobility that leads to ordered nanostructures upon equilibration between aggregated and nonaggregated states, thus providing a number of interesting properties in biomedical applications, in therapy and delivery, information technologies, environmental sciences, chemical storage, separation and/or purification and transport, and catalysis among the other [11]. Nevertheless, the accepted 100 nm cutoff value is not based on a clear-cut scientific basis, but it is much more related to political decisions. It should be stressed that changes in the physicochemical properties of nanomaterials related to the particle size take place as a continuum and that no switch of physical and chemical properties can be realistically expected at the exact value of 100 nm. In 2010, a complementary definition of nanomaterial was proposed by Kreyling et al. [12] on the basis of the volume-specific surface area (VSSA). VSSA is easily determined by dividing the external surface area of particle S by its solid volume V . Alternatively, VSSA is obtainable by multiplying the specific surface area by the material density. This ratio is conventionally expressed as m^2/cm^3 units. Thus, a particulate material having a $\text{VSSA} \geq 60 \text{ m}^2/\text{cm}^3$ should be considered as a nanomaterial. This limit corresponds to monodispersed spherical particle with a diameter of 100 nm. As a consequence, a value higher than $60 \text{ m}^2/\text{cm}^3$ inevitably indicates the existence of spherical particles smaller than 100 nm, in accordance with the former classification. The main strength of such a definition is in the possibility to use parameters easily achievable for virtually any material. For example, surface area and density can either be retrieved from handbooks and databases or measured by BET and density measurements, respectively. The VSSA-based definition overcomes the limitations of the definition of nanomaterials according to a single-size parameter, as in the case of nanomaterials where a broad size distribution is present. In such a case, a fraction of the particle population may fulfill the 1–100 nm criterion, whereas a significant part may fall outside the nanorange, thus making difficult any decision on the classification of the material, especially for the legislator or for regulatory agencies. Similar cases are those where aggregation or clustering of nanoparticles are likely to occur, thus making a single-size parameter insufficient for a clear-cut discrimination of nanomaterials. From a practical point of view, the VSSA approach has the main advantage of providing legislators with a simple and clear cut-off in order to approve or not a nanomaterial. Additionally, the VSSA criterion may also be useful in the regulatory field and helps correct political decisions. Nevertheless, it should be pointed out that the VSSA approach often leads to the false-positive classification of nanomaterials, and to this regards, it appears excessively protective in consideration of health and safety concerns. Moreover, despite this criterion sounds simple and of practical uses without the necessity of sophisticated analyses, VSSA values highly depend on the shape of the nanoparticle: for example, the threshold value drops down to $40 \text{ m}^2/\text{cm}^3$ for fiber or rodlike nanoparticles and to $20 \text{ m}^2/\text{cm}^3$ for sheetlike nanoparticles.

1.2 Nanomaterial Peculiarities

Despite the recent explosion of the term nanomaterials in the common language, it is important to point out that a lot of nanomaterials are of natural origin and largely diffused in the environment. For instance, dust volatized, ocean spray, soot from forest fires, and volcanic eruptions are typical examples. Nevertheless, most of them are intentionally engineered and manufactured to proper applications. A constantly growing number of applications of engineered nanomaterials are reported in cosmetics, sporting wear and goods, tires, electronics, and medicine. In this latter case, nanomaterials can be used as an aid to make diagnosis easier and/or to improve the drug pharmacokinetics and bioavailability. Although the lexicon containing the nano- suffix is quite recent, some nanomaterials are on the market since longtime. This is the case of “carbon black” used from 1915 to reinforce car tires. It is estimated that today the annual production of carbon black exceeds 10 million tons, being about 85% used in rubbery industries. Other well-known nanomaterials commercially available are fumed silica, titanium dioxide, zinc oxide, and, more recently, silver nanoparticles. In addition, nanoparticles are a component of smoke. However, the great interest toward nanomaterials arises from the observation that the basic properties of the matter change at the nanoscale level. Reduction of size, in fact, has many relevant effects on the properties of the nanoparticles. A nonexhaustive list of them includes the enhancement of hardness, strength, and fracture ductility; the decrease of the melting point; the increase of heat capacity; the decrease of Debye temperature; the increase of conductivity for nanometals; the decrease of Curie temperature; the onset of nonlinear optical properties; the enhancement of the catalytic activity; the swap of solubility; and even the color variation as a function of the particle size.

A key concept when dealing with nanomaterials is the dramatic enhancement of the surface area with decreasing object dimensions. This fact is clearly shown in Figure 1.4.

Actually, a relevant part of the unique properties of nanomaterials can be explained by the incredible increase in the surface area available.

The paradigmatic example depicted in Figure 1.4 illustrates this concept. In a virtual experiment, a cube of 1 cm on a side is progressively reduced in a collection of smaller cubic particles, keeping the total mass constant. The starting cube has a total surface area of 6 cm^2 . In the second step, the initial cube is decomposed into cubes of 1 mm on a side. The overall number of such cubes is 10^3 . The overall surface can be calculated as $(6 \text{ mm}^2/\text{object} \times 10^3 \text{ objects}) = 60 \text{ cm}^2$. In a third step of the virtual experiment, the cube of 1 cm on a side is decomposed into cubes of 1 μm on a side. As $1 \text{ cm} = 10^4 \mu\text{m}$, the total number of little cubes is now $(10^4)^3 = 10^{12}$ cubes. The overall surface area is now $6 \times 10^{12} \mu\text{m}^2$, corresponding to 6 m^2 . The final step is getting to the nanodimension. As $1 \text{ nm} = 10^{-9} \text{ m} = 10^{-7} \text{ cm}$, the calculation shown above leads to the astonishing numbers of 10^{21} little cubes, each accounting for a surface of 6 nm^2 . The sum of surface areas is $6 \times 10^{21} \text{ nm}^2$, i.e. 6 km^2 !

One of the most dramatic effects of dimension on the physical properties is their influence on the melting point of metals. Changes in melting point are due

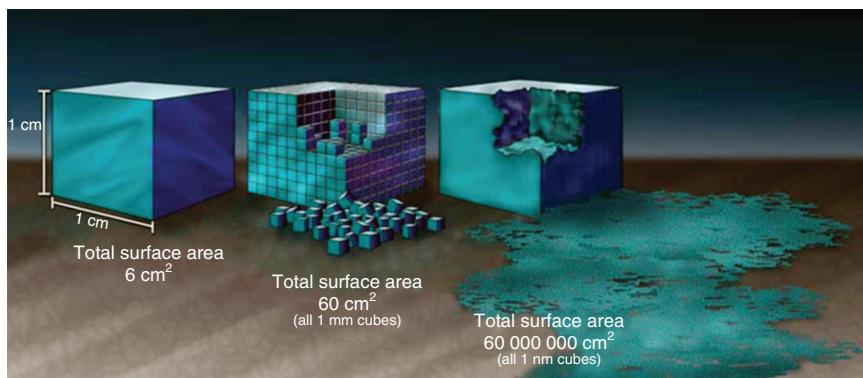


Figure 1.4 From macro- to nanomaterials: the effect on the surface. Source: Image from www.nano.gov/nanotech-101/special.

to the much larger surface-to-volume ratio than bulk materials, at nanoscale level, thus drastically altering their thermodynamic and thermal properties. This phenomenon was first theoretically predicted by Pawlow in 1909 on a thermodynamic model [13], experimentally proved by himself in 1910 [14].

For example, a decrease of almost 600 °C in the melting point of gold is observed on passing from 11 nm particles to 1 nm particles size, as shown in Figure 1.5. This effect may be estimated from the dimensionality of related physical values using the simple Gibbs–Thompson relationship [16]:

$$\Delta T_m(x) = T_{mB} - T_m(x) = T_{mB} \frac{4\sigma_{sl}}{H_f x \rho_s}$$

where T_{mB} is the bulk melting temperature, σ_{sl} is the solid–liquid interface energy (per unit area), H_f is the bulk enthalpy of fusion (per gram of material), and ρ_s is the density of solid considered of spherical shape having a diameter.

Very similar behavior can be observed with other elements such as aluminum as depicted in Figure 1.6.

Beside a great number of evidence for metallic nanoparticles, the linear dependence of T_m on $1/x$ was validated for other compounds such as oxide nanoparticles with covalent/ionic bonds, namely, Bi_2O_3 nanoparticles as reported in Figure 1.7. This effect appears to be even more accentuated than metallic melting point depression. This indicates that the effect is independent of bond nature and is purely caused by the geometry-dependent surface/volume ratio. In addition, the melting point decrease is much more higher for 10 nm Bi_2O_3 nanoparticles than 10 nm gold nanoparticles.

Another peculiar effect of nanomaterials much more related to the topics of this book is the melting behavior of organic materials once confined or entrapped in porous solid. This situation is quite common in nature and in biological systems like cell membrane, ion channels, etc. In these cases, the confined material has a great interaction with the surface wall. As one of the consequence, the melting point of the pore solid $T(d)$ decreased with a decreasing pore diameter. According to the theories of solidification in a capillary, the decrease of the melting point

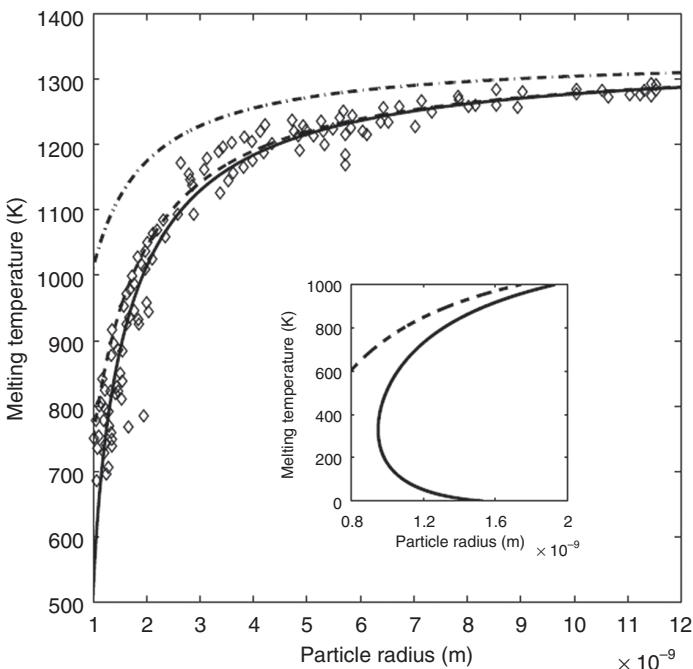


Figure 1.5 Size dependence of the melting temperature of gold nanoparticles. The subplot shows T_m from radius below 2 nm. Source: Reprinted with permission from Font and Myers [15], Copyright © 2013, Springer.

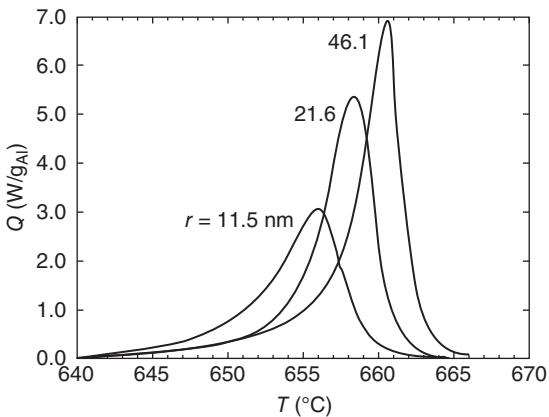


Figure 1.6 Melting response for three representative narrow-size distributed aluminum nanoparticles at 5 K/min under argon atmosphere; heat flows are normalized by mass of aluminum in the core of the nanoparticle, as determined from TGA. The radius indicated is the weight-average radius. Source: Reprinted with permission from Sun and Simon [17], Copyright © 2007, Elsevier.

was found to correlate linearly with the reciprocal of the diameter. Jackson and McKenna [16] studied a set of organic molecules inside pore glasses. The results shown in Figure 1.8 indicate the influence of small pores in reducing the melting points of the molecules.

As shown in Figure 1.9, the confinement is depending on the kind of nanomaterial, but it leads in any case to melting point depression.

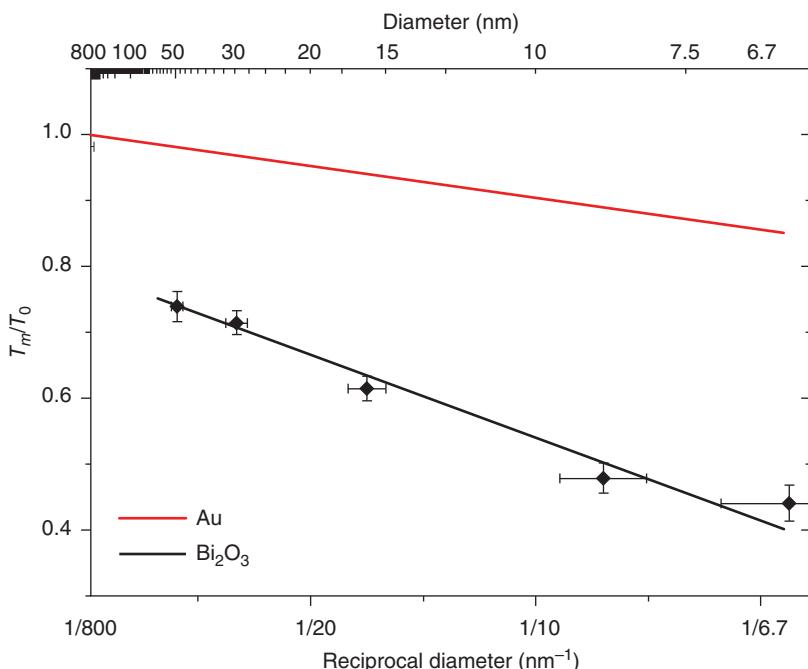
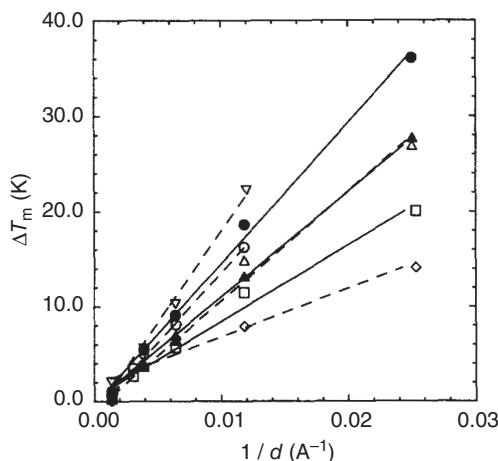


Figure 1.7 Comparison of the relative size-dependent melting point reduction between gold and bismuth oxide. Source: Reprinted with permission from Guenther et al. [18], Copyright © 2014, American Chemical Society.

Figure 1.8 Experimental values of ΔT_m plotted as a function of the reciprocal pore diameter. (O) *cis*-decalin, (●) *trans*-decalin, (▽) cyclohexane, (Δ) benzene, (▲) chlorobenzene, (◆) naphthalene, and (□) heptanes. Source: Jackson and McKenna 1990 [16]. Reprinted with permission from AIP Publishing.



Nanosponges can even suppress the melting point of a molecule, as reported in Figure 1.10 for meloxicam drug included in a cyclodextrin nanosponge. Meloxicam has a sharp melting point at 250 °C. This peak is absent when meloxicam is entrapped in nanosponges, thus indicating the formation of a complex between meloxicam and the nanosponges, and that meloxicam was protected by encapsulation in the nanosponges [20].

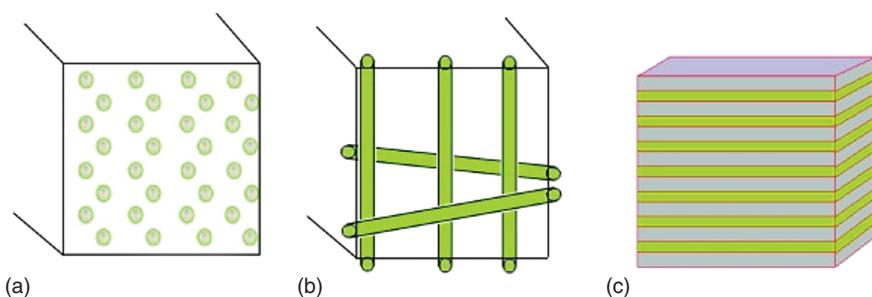


Figure 1.9 Schematic representation of (c) 1D, (b) 2D, and (a) 3D confinement. Source: Reprinted with permission from Singh et al. [19], Copyright © 2014, Elsevier.

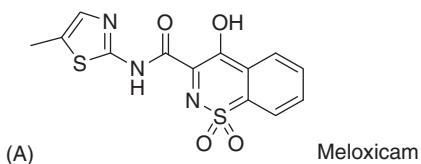
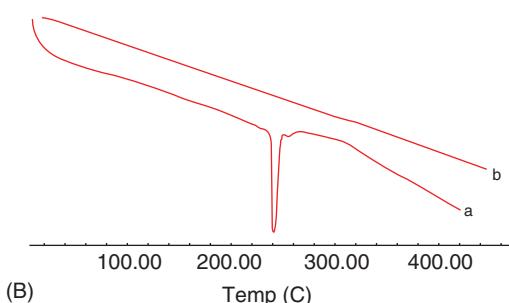


Figure 1.10 (A) Molecular structure of meloxicam. (B) DSC thermograms of (a) meloxicam and (b) meloxicam inclusion compound with CD-NS. Source: Reprinted with permission from Shende et al. [20], Copyright © 2015, Elsevier.



Further spectacular effects associated with the nanosize dimensions of the particles in a material are the change in color. It is well known that gold has the characteristic yellow, brilliant color, but when gold is produced in the nanosized dimension range, its color invariably changes to red. In other words, gold shows a color depending on the size of the gold particles. This phenomenon has an impressive example in the so-called Lycurgus cup now preserved at the British Museum in London (Figure 1.11) [21].

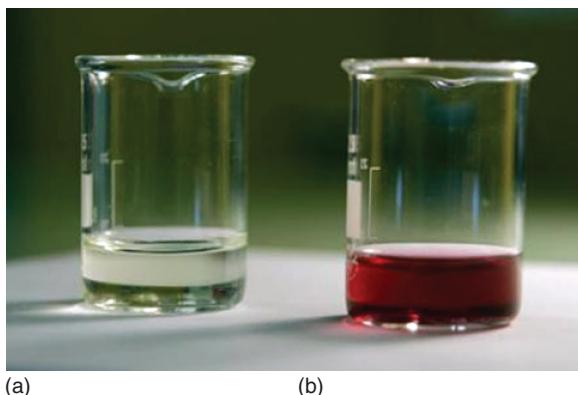
This cup was probably created in Rome during the fourth century CE and shows a different color changing the light from opaque green to bright red. This is the most famous example of the so-called dichroic glass. Actually, it presents some tiny amount of nanosized gold and silver that gives these unusual optical properties. This happens because at the nanoscale range, the electron cloud located on the surface of a gold nanoparticle has the possibility to resonate with different wavelengths of light depending on their frequency. This phenomenon is now well understood and reproduced even at laboratory demonstrative level as reported in Figure 1.12.

As mentioned above, this behavior is influenced by the size of the nanoparticle. The result is that a nanoparticle of about 90 nm in size will absorb color on



Figure 1.11 King Lycurus Cup at British Museum – London: (a) reflected light and (b) transmitted light. Source: Adapted under CC license from Freestone et al. 21. Published by SpringerNature.

Figure 1.12 Pale yellow Au(III) salt (1 mM) (a) and red Au NP (b) solutions. Source: Adapted under CC license from Pluchery et al. 22. Published by SpringerNature.



the red and yellow end of the color spectrum, making the nanoparticle appear blue-green. A small-sized particle, about 30 nm in size, absorbs blues and greens, resulting in a red appearance [23]. To date, it is proved that shape has also some influence in the color change. Figure 1.13, for example, reports the absorption spectra of several kinds of gold nanoparticles [24].

Although it appears unlikely that this knowledge was in the background of those ancient masters, however, the effect obtained is still impressive! Nevertheless, Lycurus cup was not the only one heritage that is connected with the presence of nanoparticles or nanomaterials in the ancient time. This is also the

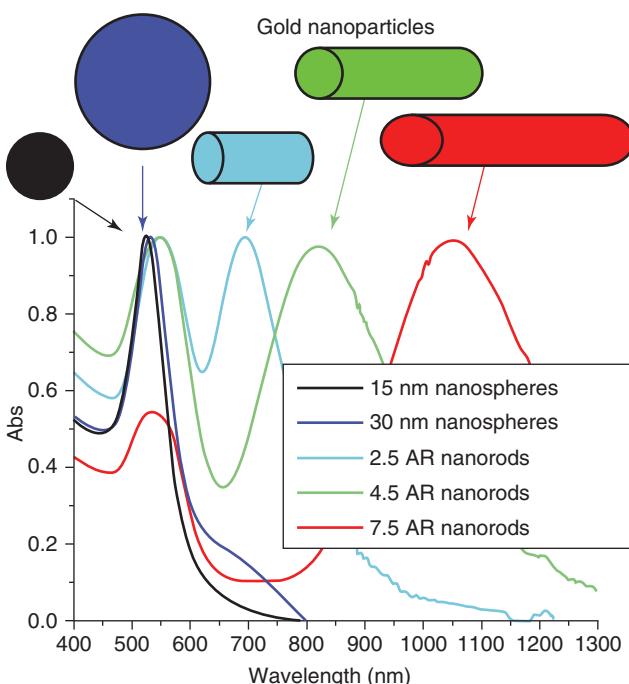


Figure 1.13 Influence of gold shape on color change. Source: Adapted with permission from Eustis and El-Sayed [24], Copyright © 2005, RSC.

case of the red-colored glasses of the Late Bronze Age (1200–1000 BCE) that were found to produce a plasmon surface resonance for the presence of copper nanoparticles. These latter were also used by Romans to produce mosaics. Finally, this expertise was not confined in the western part of the world but observed even in eastern countries. This is the case of the famous Japanese Satsuma glasses that appear ruby colored because of the presence of copper nanocrystals [24].

However, it should be pointed out that not only metallic nanoparticles show the above-mentioned effect but also some salts such as CdS or CdSe crystals, which are also known to change their color when reduced to a few nanometers [25]. A visual sketch is reproduced in Figure 1.14.

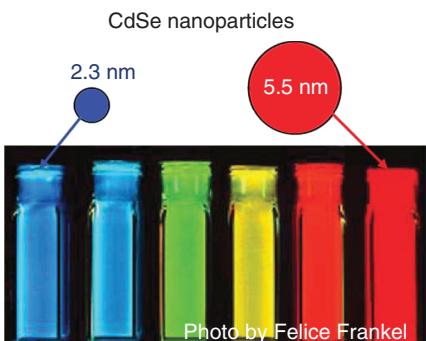


Figure 1.14 Color change of CdSe. Source: Adapted with permission from Eustis and El-Sayed [24], Copyright © 2005, RSC.

Nanosized gold has another very particular behavior. It is well known that gold is considered chemically inactive; however, it was recently reported that gold nanoparticles, i.e. less than 2 nm, show an unexpected antimicrobial effect toward Gram-positive and Gram-negative bacteria. This broad antimicrobial activity was attributed to the ability of ultrasmall gold nanoparticles to interact with bacteria leading to a metabolic imbalance and a high production of reactive oxygen species (ROS) that kills the bacteria [26]. It should be quite evident from the above reported examples that the behavior and the properties of nanomaterials are much more because of the size and surface area rather than to their chemical composition.

1.3 Manufacturing of Nanomaterials

Despite the arbitrary 100 nm limit for numerous classifications of nanomaterials, it is sometimes reported, and generally accepted, that more precisely 30 nm is the upper limit for the experimental detection of size-dependent property change. In fact, it is quite evident that the high increase in the surface area and new quantum effects are the two main factors driving the behavior of nanomaterials. A nanomaterial may be formed by just a single element or composed by a significant number of them. In addition, all nanomaterials can be further modified or functionalized. The choice of the method results to be different for 0D, 1D, 2D, and 3D nanomaterials. Generally, it is accepted that nanomaterials can be produced by physical, chemical, or bio-based methods [25]. Two basic manufacturing processes are known [27], graphically displayed in Figure 1.15.

The first approach is a defined “top-down,” and the most common example is the milling procedure of the starting large-sized material; this method requires relevant amounts of starting materials with a great loss of material

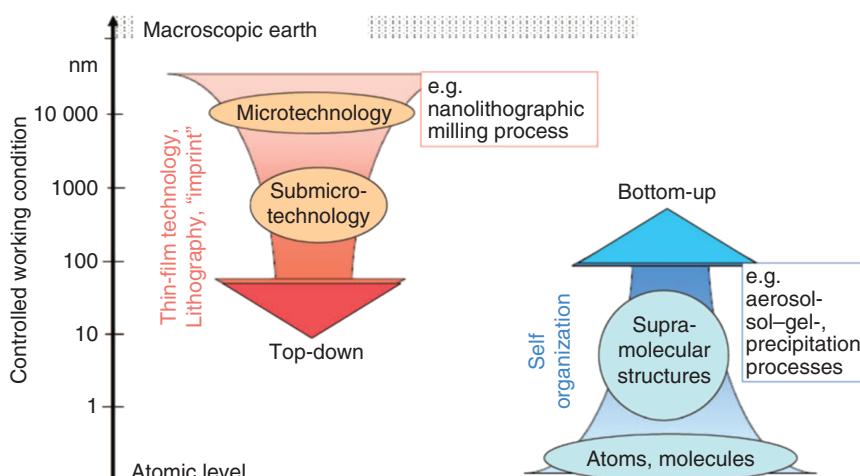


Figure 1.15 Methods of nanoparticle production: top-down and bottom-up. Source: Reproduced under CC license from Gleiter [27]. Published by Elsevier.

and, as a consequence, to a significant waste production. This technique is well applicable to metallic and ceramic nanomaterials. It has to take into account that prolonged milling procedure involves severe thermal stress to the material. Often, a cryogenic liquid is used to facilitate the milling process and to increase the brittleness. In addition, contamination by abrading the container often occurs. Nanoparticles obtained invariably show relevant polydispersity and poor uniformity in particle shape. Photolithography, anodization, and plasma etching are other examples of top-down methods used. Alternatively, nanomaterials can also be produced by a “bottom-up” route based on the assembling of atoms or molecules to get the desired nanomaterial. Reaction in the gas phase and liquid phase as well is involved. Often, this technique is time consuming, complex, and expensive. In any case, this method allows the production of a much more regular particles size and shape. Some examples are sol–gel process, gas-phase synthesis, flame-assisted ultrasonic spray pyrolysis, gas condensation processing, chemical vapor condensation, sputtered plasma processing, microwave plasma processing, and laser ablation. Among these, gas-phase process appears to be more prone to be used in industrial scale to produce nanomaterials both as powder and film. Fullerene and carbon nanotubes are the most known nanomaterials obtained in this way. On the other hand, the liquid-phase process has the advantage to be performed at lower temperature than the gas-phase process. Although it is possible to get almost completely monodisperse nanomaterials, nevertheless, often relevant polydispersity is observed. It has to be pointed out that the size distribution is a pivotal element to consider to classify the nanomaterials. In particular, the classification changes if the size distribution is considered on the number of particles or on the mass concentration. For safety concern, it is much more useful to consider the number distribution being a more cautious choice. The primary particle of the selected material can form larger unit formation, by adhesion phenomena, i.e. agglomerates or even more stable aggregates (Figure 1.16). The most important difference is that in agglomerates, the total surface area does not change to a great extent in comparison with the area of the single particles. On the contrary, aggregates always have a lower total surface

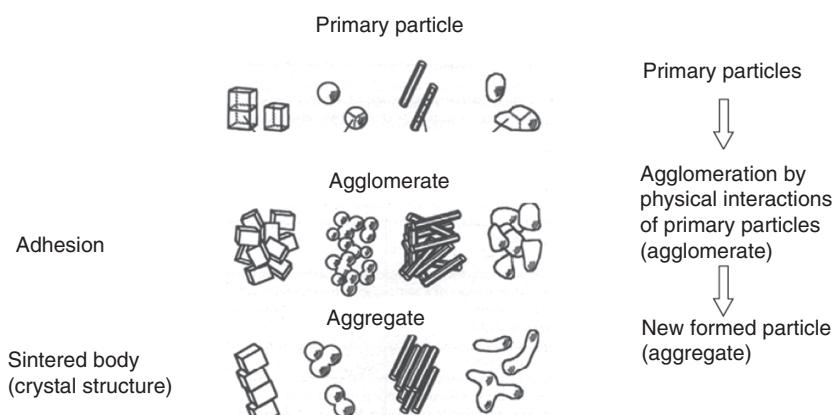


Figure 1.16 Relationships between primary particles, agglomerates, and aggregates. Source: Walter 2013 [28]. Reprinted with permission from John Wiley & Sons.

area if compared with the parent particles. Agglomerates are, for instance, responsive to ultrasound being easily divided into smaller agglomerates.

1.4 Nanomaterials and Health Concerns

The great interest toward nanomaterials in all aspects is well documented by the number of papers on this matter. For example, Figure 1.17 reports the number of articles published on some selected keywords dealing with nanomaterials in the article title (www.scopus.com).

Applications of nanomaterials are growing continuously. Today, about one-third of the nanomaterials produced in the world find applications in cosmetic products especially in sunscreen formulations. The broad range of applications of nanomaterials can be summarized in this nonexhaustive list of products containing nanomaterials of different origin:

- (1) Cosmetic and personal care products
- (2) Paints and coatings
- (3) Household products
- (4) Catalysts and lubricants
- (5) Sport products
- (6) Textiles
- (7) Medical and health care products
- (8) Food and nutritional ingredients
- (9) Food packaging
- (10) Agrochemicals
- (11) Veterinary medicines
- (12) Construction materials
- (13) Weapons and explosives
- (14) Consumer electronics

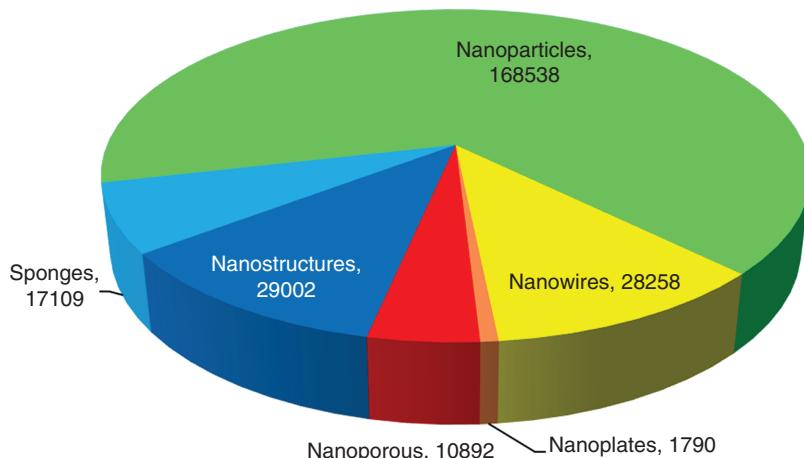


Figure 1.17 Distribution of scientific papers for types of nanomaterials. Source: Data obtained from www.scopus.com.

The wide and increased uses of nanomaterials rise the health and safety concerns for some major reasons: (i) nanomaterials are much more reactive than the molecular analogs in solvents or in condensed phase; (ii) their very small size allows them to migrate easier in biological systems; and (iii) they may pass the biological membranes in the lung, gut, and even in the brain causing damage to intracellular structures and cellular functions. Actually, lung is the preferred route to enter in the body by nanoparticles [7]. The 100 millions of alveoli present and their very high surface area in the lung highly facilitate the contact with the nanosized material. Fortunately, most of the introduced nano-objects are removed efficiently by mucociliary transport or by macrophages for the smaller particles. It seems likely that only prolonged overexposure or stress created by smoking for instance can provoke serious danger to health. In any case, less than 0.05% of the quantity administered by inhalation reaches the bloodstream. The second possibility for a nano-object to enter the body is to follow the olfactory nerve route. This latter route is much more effective, and it is directly connected to the brain; thus, in this case, the nanoparticle can reach the central nervous system despite the very low overall amount capable to reach the brain.

On the other hand, skin is an effective barrier to the penetration of nanoparticles, especially the nonlipophilic ones. Only very small particles, i.e. $<10\text{ nm}$, are reported to pass the skin, and the penetration can be influenced and promoted by particle surface coating, especially those used to prevent the agglomeration of the nanoparticles. Finally, gastrointestinal uptake of nanoparticles is minimal. In fact, the gastrointestinal tract is not efficient for nanoparticle adsorption, despite its large surface area. It was reported that 98% of the orally administered nanoparticles in animal tests was excreted [28–30].

Nanomaterials are recognized to produce the formation of ROS leading to severe inflammation processes and related consequences [31].

It should also point out that the factors of risk other than the particle size, e.g. the shape, contribute to the picture: this is the case, for example, of nanofibers that cannot be removed from the lung via mucociliary clearance, as happens with spherical particles, and they can generate fibrosis and even cancer. This is well known for asbestos fibers and probably also to carbon nanotubes [7].

A graphic summary of the possible pathologies associated with nanoparticle exposure is proposed in Figure 1.18. Risk assessment is defined as the product of hazard (toxicity) and exposure and determines the chronic and acute health concerns. This is also valid for adverse effects of nanomaterials toward CNS (central nervous system) [33, 34].

Figure 1.18 reports the known routes and the possible effects of inhaled or ingested nanoparticles. Although nanoparticles can reach CNS, it is reported that by inhalation, only a minor part of them reaches the bloodstream and the target organs or brain. Moreover, a very slow translocation rate was always observed. On the other hand, nanoparticles can reach CNS more efficiently through the olfactory nerve. Long-term exposure toward nonbiodegradable or nonexcreted nanoparticles is likely to accumulate in the brain with possible chronic toxic effects. Potential sources of exposure to nanoparticles are listed in Table 1.4.

In addition, several nanomaterials may act as chemical catalysts and produce unanticipated reactions increasing the level of risk for explosions and fires. Because it is well known that dust explosion occurs below $500\text{ }\mu\text{m}$ size of the

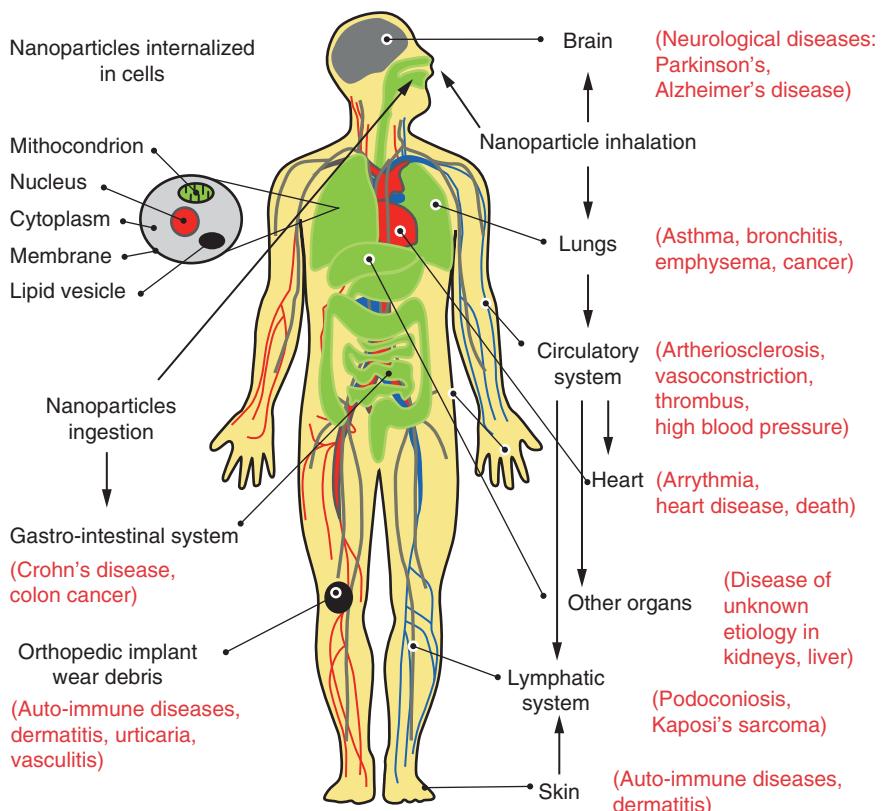


Figure 1.18 Diseases associated with nanoparticle exposure. Source: Buzea et al. 2007 [32]. Reprinted with permission from AVS.

powder and the risk is increasing reducing the particle dimension, nanoparticles may be combustible and require less energy to ignite, enhancing the risk of accidents in industrial plants. In addition, metallic nanoparticles such as aluminum, titanium, and magnesium are even pyrophoric. Thus, it is necessary to properly characterize the nanomaterial from physical and chemical point of view in order to prepare a safety profile. A possible flowchart for the risk analysis is proposed in Figure 1.19.

The most relevant physical properties to be monitored are size, shape, specific surface area, physical state, capability for aggregates via self-assembly, size distribution, smoothness of the surface, crystal structure, and facility to dissolve in solvents. From a chemical point of view, other parameters should be considered: molecular structure, presence of impurities or additives, surface chemistry, and interaction with water or other solvents.

1.5 Legislation on Nanomaterials

The EU adopted a definition of a nanomaterial in 2011 (2011/696/EU) [36]. Its provisions include a requirement for review “in the light of experience and of

Table 1.4 Potential sources of exposure to nanoparticles.

Process synthesis	Particle formation	Exposure source	Exposure route
Gas phase	In air	Leakage from reactor, especially if operated at positive pressure	Inhalation
		Product recovery from bag filters in reactors	Inhalation/dermal
		Processing and packaging of dry powder	Inhalation/dermal
		Equipment cleaning/maintenance (including reactor evacuation and spent filters)	Dermal (and inhalation during reactor evacuation)
Vapor deposition	On substrate	Product recovery from reactor/dry contamination of workplace	Inhalation
		Processing and packaging of dry powder	Inhalation/dermal
		Equipment cleaning/maintenance (including reactor evacuation)	Dermal (and inhalation during reactor evacuation)
Colloidal	Liquid suspension	If suspension is processed into a powder, potential exposure during spray drying to create a powder, and processing and packaging of dry powder	Inhalation/dermal
Attrition	Liquid suspension	Equipment cleaning/maintenance	Dermal
		If suspension is processed into a powder, potential exposure during spray drying to create a powder, and processing and packaging of dry powder	Dermal
		Equipment cleaning/maintenance	Dermal

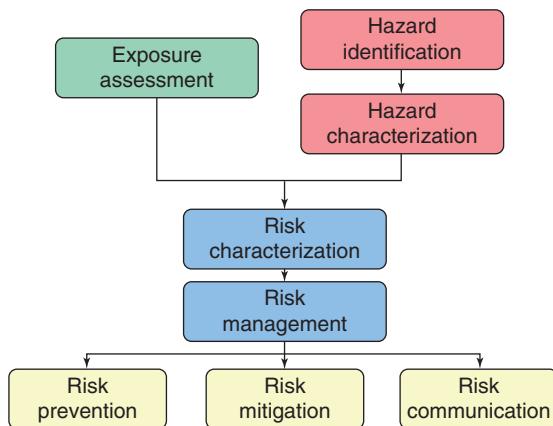
Note: Ingestion would be a secondary route of exposure from all sources/activities from the deposition of nanomaterials on food or mucous that is subsequently swallowed (primary exposure route inhalation) and from hand to mouth contact (primary exposure route dermal).

Source: Adapted from Safety & Wellbeing Team 2013 [35].

scientific and technological developments. The review should particularly focus on whether the number size distribution threshold of 50% should be increased or decreased.” The commission was expected to conclude the review in 2016 or shortly after. According to the Recommendation, “Nanomaterial” means:

A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm – 100 nm. In specific cases and where warranted by concerns for the environment, health, safety

Figure 1.19 Risk assessment and risk management regarding possible adverse substances or materials. Source: Krug and Wick 2011 [7]. Reprinted with permission from John Wiley & Sons.



or competitiveness the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%. By derogation from the above, fullerenes, graphene flakes and single wall carbon nanotubes with one or more external dimensions below 1 nm should be considered as nanomaterials.

The definition will be primarily used to identify materials for which special provisions might apply (e.g. for risk assessment or ingredient labeling). Those special provisions are not part of the definition but of specific legislation in which the definition will be used. Nanomaterials are not intrinsically hazardous per se, but there may be a need to take into account specific considerations in their risk assessment. Therefore, one purpose of the definition is to provide clear and unambiguous criteria to identify materials for which such considerations apply. It is only the results of the risk assessment that will determine whether the nanomaterial is hazardous and whether or not further action is justified. Today, there are several pieces of EU legislation, and technical guidance supporting implementation of legislation, with specific references to nanomaterials. To ensure conformity across legislative areas, where often the same materials are used in different contexts, the purpose of the Recommendation is to enable a coherent cross-cutting reference. Therefore, another basic purpose is to ensure that a material that is a nanomaterial in one sector will also be treated as such when it is used in another sector.

1.6 ISO Classification and Standards

ISO has shown interest in nanotechnologies and related fields: in 2005, ISO created the Technical Committee (TC) 299 – Nanotechnology – under the secretariat of BSI with the specific tasks of developing and spreading standards concerning materials, processes, and measurements on the matter in the size range 1–100 nm. The standards include nomenclature, terminology, reference materials, metrological aspects and characterization methods, and a large set

of standards and recommendations related to safety, health, environment, and risk assessment. TC 229 is structured in Joint Working Groups (JWG), Working Groups (WG), and Task Groups (TG) engaged in the following sectors:

- Terminology and nomenclature
- Products and applications
- Nanotechnology and sustainability
- Measurements and characterization
- Material specifications
- Health, safety, and environmental (HSE) aspects of nanotechnologies
- Consumer and societal dimensions of nanotechnologies

Since its establishment and until 2017, ISO TC 229 published 55 standards, listed on the ISO website at the address: www.iso.org/committee/381983/x/catalogue/p/1/u/0/w/0/d/0 and released at different stages. It is worth mentioning here the code for the stage classification of the international standards. The code is a four-digit number made of two couples of digits separated by a dot (e.g. 40.92). The first two digits identify the stage – ranging from “preliminary” to “withdrawal” – whereas the second two are associated with the substage – ranging from “registration” to “proceed.” The full matrix is reported in Table 1.5.

We just want to mention here the basic “tool-case” of ISO standards related to nanotechnology. The clear definition of the terms, lexicon, and basic concepts is contained in the large family of standards labeled as ISO/TS 80004, in turn articulated in 12 issues at different stages. As an example, it is suffice to mention ISO/TS 80004-6:2013 Nanotechnologies – Vocabulary – Part 6: Nano-object characterization, available as International Standard Confirmed (stage 90.93) or ISO/TS 80004-13 Nanotechnologies – Vocabulary – Part 13: Graphene and other two dimensional materials, under development (stage 30.60). Interestingly, ISO also provides significant efforts to a clear dissemination of the key concepts even to the audience not directly involved in nanotechnology practice; an example is the manual for ISO 80004 interpretation contained in the ISO/TR 18401 standard, titled “Nanotechnologies – plain language explanation of selected terms from the ISO/IEC 80004 series,” currently at stage 60.00.

Quite a large collection of standards is dedicated to the measurements of physicochemical properties of selected nanomaterials by using different spectroscopical, thermal, and imaging methods such as ICP mass spectrometry, GC–MS analysis, energy-dispersive X-ray spectrometry, UV–Vis–NIR spectroscopy, and transmission and scanning electron microscopy (EM).

The regulatory aspects concerning HSE are largely covered by the standards published or under development by the TC 229 Secretariat. Worth of mention are the following: health and safety practices in occupational settings relevant to nanotechnologies (ISO/TC 12885:2008, stage 90.92), health and safety practices in occupational settings relevant to nanotechnologies (ISO/NP TR 12885, under development, stage 10.99), preparation of material safety data sheet (MSDS) (ISO/TR 13329:2012, stage 60.60), nanomaterial risk evaluation (ISO/TR 13121:2011, stage 60.60), occupational risk management applied to engineered nanomaterials – Part 1: principles and approaches

Table 1.5 International harmonized stage codes.

Stage	Substage	90 Decision			
		20 Start of main action	60 Completion of main action	92 Repeat an earlier phase	93 Repeat current phase
00 Preliminary	00.00	00.20	00.60		
	Proposal for new project received	Proposal for new project under review	Close of review		
10 Proposal	10.00	10.20	10.60	10.92	
	Proposal for new project registered	New project initiated	Close of voting	Proposal returned to submitter for further definition	
20 Preparatory	20.00	20.20	20.60	20.98	
	New project registered in TC/SC work programme	Working draft (WD) study initiated	Close of comment period	Project deleted	
30 Committee	30.00	30.20	30.60	30.92	
	Committee draft (CD) registered	CD study/ballot initiated	Close of voting/comment period	CD referred back to Working Group	
40 Enquiry	40.00	40.20	40.60	40.92	
	DIS registered	DIS ballot initiated: 12 weeks	Close of voting	Full report circulated: DIS referred back to TC or SC	
				40.93	40.98
				Full report circulated: DIS approved for registration as FDIS	40.99

(Continued)

Table 1.5 (Continued)

Stage	Substage	90 Decision			
		20 Start of main action	60 Completion of main action	92 Repeat an earlier phase	93 Repeat current phase
50 Approval	50.00 Final text received or FDIS registered for formal approval	50.20 Proof sent to secretariat or FDIS ballot initiated: eight weeks	50.60 Close of voting. Proof returned by secretariat	50.92 FDIS or proof referred back to TC or SC	50.98 FDIS or proof approved for publication
60 Publication	60.00 International standard under publication	60.60 International standard published		90.93 International standard confirmed	90.99 Withdrawal of international standard proposed by TC or SC
90 Review		90.20 International standard under periodical review	90.60 Close or review	90.92 International standard to be revised	90.99 Withdrawal of international standard confirmed
95 Withdrawal		95.20 Withdrawal ballot initiated	95.60 Close of voting	95.92 Decision not to withdraw international standard	95.99 Withdrawal of international standard

Source: Printable version downloadable from www.iso.org/stage-codes.html.

(ISO/TS 12901-1:2012, stage 90.93) and Part 2: use of the control banding approach (ISO/TS 12901-2:2012, stage 90.20), considerations for the measurement of nano-objects, and their aggregates and agglomerates (NOAA) in the environment (ISO/AWI TR 21386, under development, stage 20.00).

1.7 EPA Regulatory Approach for Nanomaterials and Manufacturing

The U.S. Environmental Protection Agency (EPA) issued, at the beginning of 2017, the first rule for collecting information related to the risks associated with the production and manufacturing of nanomaterials. This is the (so far) ending of a long story started in 2005 with a declaration of intent toward a voluntary reporting programme and arriving to the 2017 reporting rule.

EPA inserted the control of nanoscale materials under the general Toxic Substances Control Act (TSCA). Nanomaterials are classified as “chemical substances” of dimensions in the 1–100 nm range expected to show different properties with respect to the same chemical substance in bulk and thus deserving attention for the possible unpredictable and unknown behavior under specific conditions. The main purpose of the EPA comprehensive regulatory approach is to avoid unreasonable risks to health and environment with the manufacturing and use of nanomaterials. This is achieved through two key steps: (i) premanufacture notifications for new nanomaterials and (ii) information gathering rule on new and existing nanomaterials.

The first point raises the issue of what is considered a “new” material or chemical for the purposes of TSCA. EPA lists the existing chemicals in the TSCA Inventory. The chemicals not present in the Inventory are regarded, by definition, as “new.” The nonconfidential inventory can be downloaded for free in .csv format at the EPA website. The main criterion used under TSCA to classify the chemicals as “new” or “existing” is the molecular identity, as clearly exemplified in the report “TSCA Inventory Status of Nanoscale Substances – General Approach” dated January 23, 2008, and freely downloadable from www.epa.gov/tscainventory. The particle size is thus not a parameter of molecular identity for the TSCA Inventory. It is worth reporting in quotes the part of the mentioned document dealing with the existing chemicals, either in molecular or in nanometric scale:

[...]a nanoscale substance that has the same molecular identity as a substance listed on the Inventory (whether or not reported to the Agency as being manufactured or processed in nanoscale form) is considered an existing chemical, i.e., the nanoscale and non-nanoscale forms are considered the same chemical substance because they have the same molecular identity.

EPA’s rationale for considering this group of nanoscale substances to be existing chemicals is based on the TSCA definition of “chemical substance.” Although a nanoscale substance that has the same molecular identity as a non-nanoscale substance listed on the Inventory differs in particle

size and may differ in certain physical and/or chemical properties resulting from the difference in particle size, EPA considers the two forms to be the same chemical substance because they have the same molecular identity. The Inventory listing in this case is considered to represent both the nanoscale and non-nanoscale forms of the substance and, as such, does not distinguish between two forms having the same molecular identity that differ only in particle size and/or physical/chemical properties resulting from the difference in particle size.

In this case, the nanomaterial is classified as a “new chemical,” and the TSCA requires the manufacturers to provide information before starting the activity. This allows the agency to review the process and establish suitable actions to avoid unreasonable risks for the community and for the environment. This step is referred to as Premanufacture Notifications.

The second point mentioned above – information gathering rule on new and existing nanomaterials – points to the final regulation issued on 11 January 2017, and titled “Chemical substances when manufactured or processed as nanoscale materials: TSCA reporting and recordkeeping requirements” (available by searching the docket identification number EPA-HQ-OPPT-2010-0572 at the www.regulations.gov website). The rule focuses on the requirements for recordkeeping and reporting information on the new chemical produced or processed at the nanoscale. The report is expected to list the chemical identity, the production volume, the way personnel and environment might be exposed to the nanomaterials, and all the existing information concerning the possible fallout on health and environment.

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