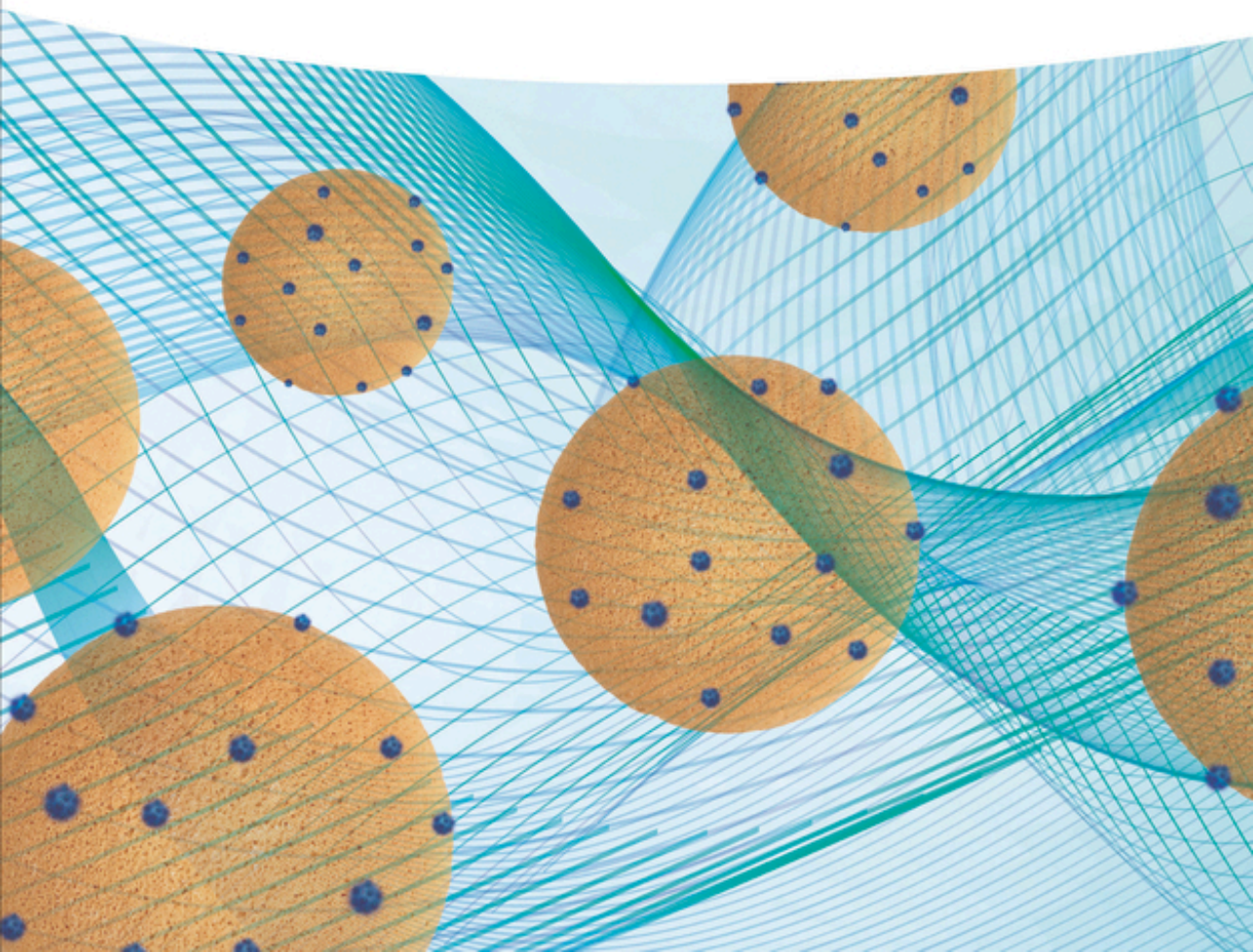


Edited by Francesco Trotta and Andrea Mele

# Nanosponges

Synthesis and Applications





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*Edited by*  
*Francesco Trotta*  
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## Preface

In the past few decades, the prefix “nano” was included in a great deal of words not only in the scientific language but also as part of everyday life vocabulary. Although the word “nanotechnology” was first introduced for the first time by Norio Toniguchi in 1974 during a talk at an international conference, the roots of this science is often linked to the Richard Feynman’s lecture at Caltech in 1959. The famous sentence “there is a plenty of room at the bottom” can be considered the first milestone of nanotechnology and a visionary horizon. To date, the word nano has been included 86 635 times in the title of scientific articles, according to Scopus, or 342 190 times if abstract (194 056) and keywords (194 281) are included too. These simple numbers give the taste of the tremendous importance of nanomaterials and nanotechnology. Nanoscience and nanotechnology have shown – and still continuously show – an incredible growth of application leading to impressive advancement of fundamental knowledge and performances in medicine, electronics, mechanics, optics, computer science, drug delivery, paint, sensors, photonics, robotics, artificial intelligence, cosmetics, textiles, food packaging, just to mention the main fields. Actually, there is no field of modern technology without the presence of nanomaterials. The growing of the number of applications of nanomaterials is impressive: It is estimated that about three to four new products reach the market every week, and the list of such materials are now quite astonishing. In the recent years, several Nobel laureates in chemistry or physics took the prize for the studies in the nanoworld.

As it is explained in the first chapter of this book, nano-world spans the range between 1 and 100 nm, i.e. below the submicron range (100–1000 nm) but above the quantum range (less than 1 nm), now referred to as the picorange.

A relevant limit on the applications and use of nanomaterials is derived from health concerns. This seems to be particularly true for nanofiber and, although to a lesser extent, for nanoparticles. On this basis, it is also understandable how nanocarriers for drug delivery still have limited applications.

Nanosponges do form a different class of nano-objects. In fact, from a morphological point of view, they can assume dimensions in the microrange or even larger. Nevertheless, they generally present a nanoporous structure providing these materials with unique properties and ruling out the health concern related to the nanometric dimensions of the particles. From this standpoint, nanosponges can be considered a relatively safe material.

Although the papers directly linked to the term nanosponges are not so numerous, nevertheless, the world of porous, nanostructured materials or highly cross-linked materials is quite large. In many cases, the synthetic processes leading to nanosponges are simple, especially if compared to classical nanomaterials. Nanosponges show tunable properties, high versatility, low-cost synthetic routes, high stability, and excellent absorption properties, making them ideal materials for the removal of unwanted molecules from the environment or, on the other hand, for the selective release of added value compounds, as in drug delivery or in targeted and controlled release.

The aim of this book is to provide the reader with state-of-the-art reviews of the fundamental and applicative aspects of nanosponges, thus filling the gap between nanomaterials and this new class of nanoporous, functional materials, underlining both basic and advanced information for those researchers willing to approach these fascinating, novel, and high-performance materials.

Torino-Milano  
November 2018

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## 1

## Nanomaterials: Classification and Properties

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### 1.1 Nanomaterial Classifications

The word “nano” derives from the latin word “*nanus*” and Greek word “*νάνος*,” 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.

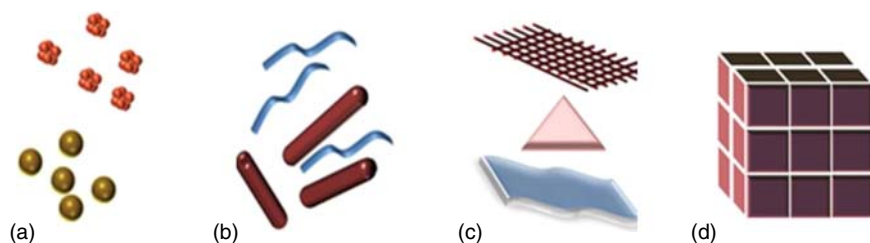
In other words, nanosponges can be counterintuitively classified as nanomaterials because of the presence of a network of nanometer-sized cavities in the bulk, despite the fact that the dimensions of a given specimen along the  $x$ -,  $y$ -, and  $z$ -axes can be larger than 100 nm. From this viewpoint, 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.

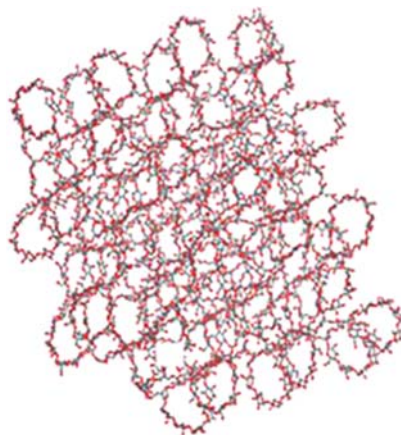
Method name (abbreviation)	Measurement range and medium (limiting factors)	Types of size distribution of raw data
Electron microscopy (EM)	1 nm or higher; dry (dynamic range)	Number based
Dynamic light scattering (DLS)	5–500 nm; suspension (sedimentation and scattering intensity)	(No distribution, or 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)

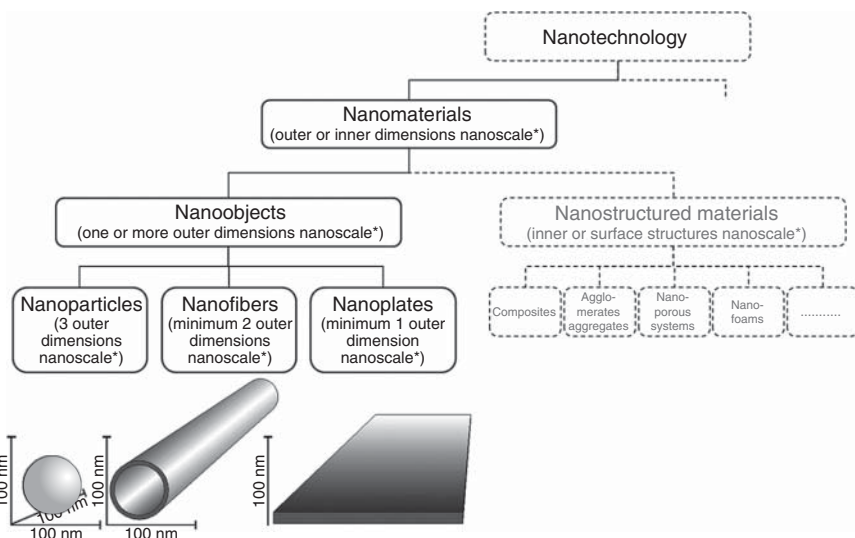
Source: Adapted from Lisinger et al. [2].



**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  $\text{TiO}_2$  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  $\text{m}^2/\text{cm}^3$  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

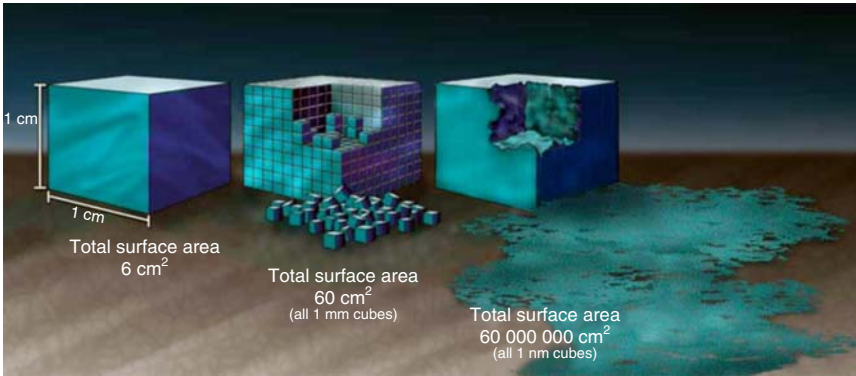
Despite the recent explosion of the term nanomaterials in the common language, it is important to point out that a lot of nanomaterials are of natural origin and largely diffused in the environment. For instance, dust volatilized, ocean spray, soot from forest fires, and volcanic eruptions are typical 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  $6\text{ cm}^2$ . 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  $1\text{ }\mu\text{m}$  on a side. As  $1\text{ cm} = 10^4\text{ }\mu\text{m}$ , the total number of little cubes is now  $(10^4)^3 = 10^{12}$  cubes. The overall surface area is now  $6 \times 10^{12}\text{ }\mu\text{m}^2$ , corresponding to  $6\text{ m}^2$ . 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  $6\text{ nm}^2$ . The sum of surface areas is  $6 \times 10^{21}\text{ nm}^2$ , i.e.  $6\text{ km}^2$ !

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](http://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]:

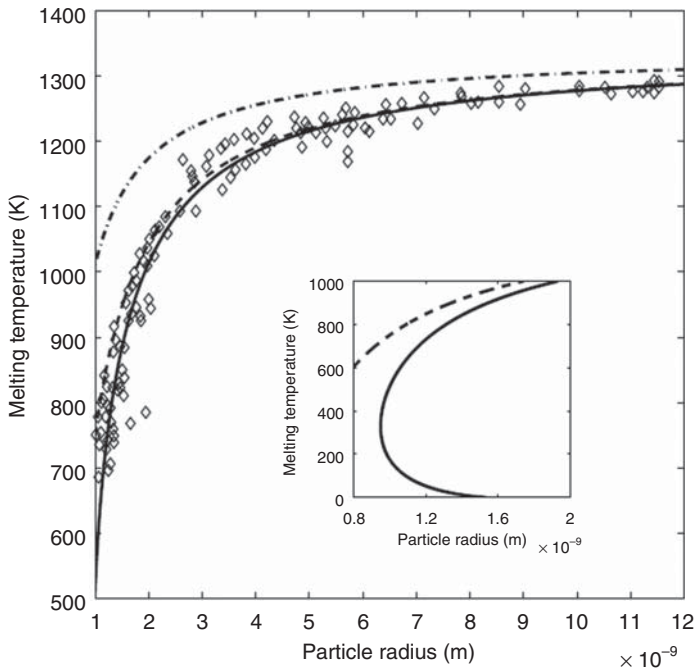
$$\Delta T_m(x) = T_{mB} - T_m(x) = T_{mB} \frac{4\sigma_{sl}}{H_f x \rho_s}$$

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

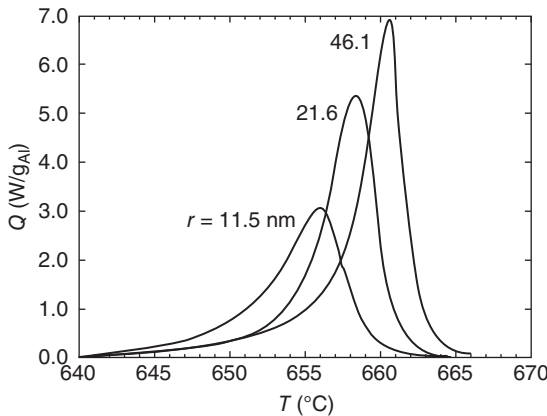
Very similar behavior can be observed with other elements such as aluminum as depicted in Figure 1.6.

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,  $\text{Bi}_2\text{O}_3$  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  $\text{Bi}_2\text{O}_3$  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



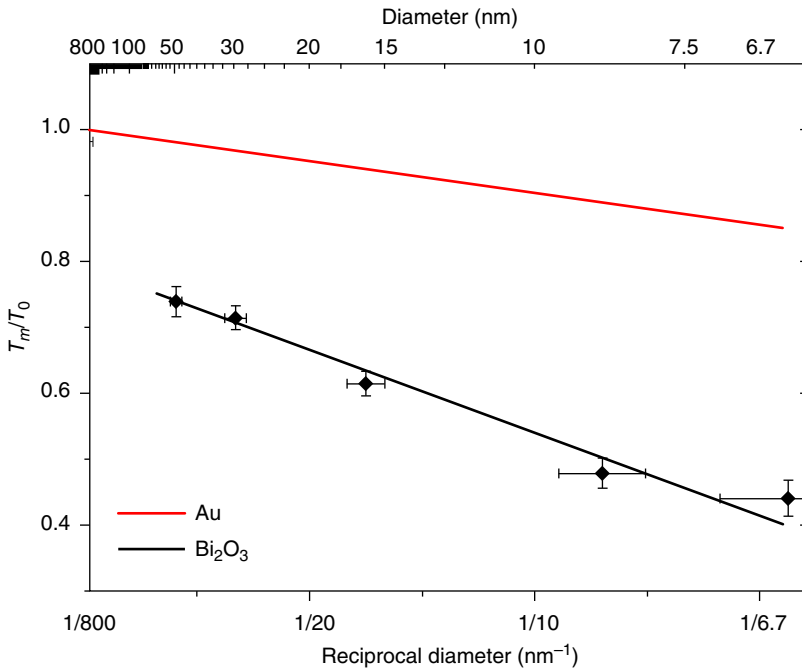
**Figure 1.5** Size dependence of the melting temperature of gold nanoparticles. The subplot shows  $T_m$  from radius below 2 nm. Source: Reprinted with permission from Font and Myers [15], Copyright © 2013, Springer.



**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.

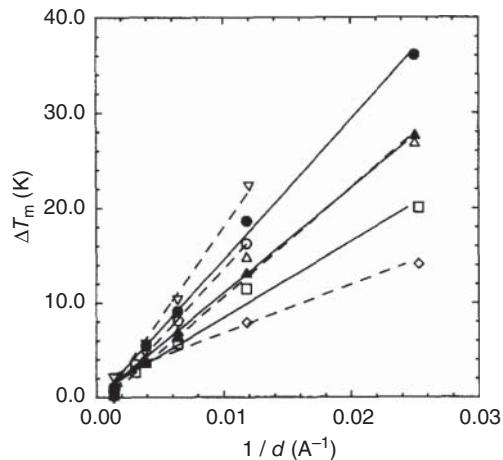
was found to correlate linearly with the reciprocal of the diameter. Jackson and McKenna [16] studied a set of organic molecules inside pore glasses. The results shown in Figure 1.8 indicate the influence of small pores in reducing the melting points of the molecules.

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.

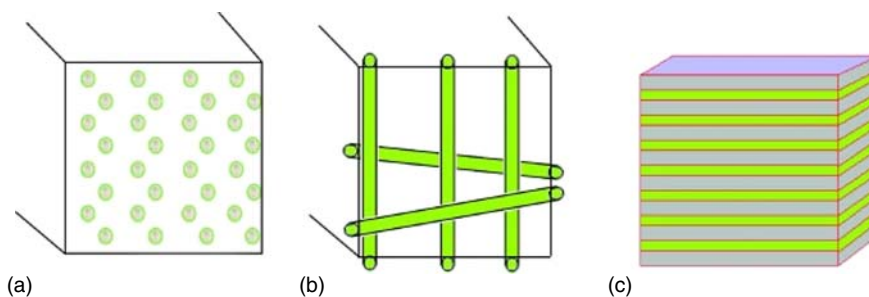


**Figure 1.7** Comparison of the relative size-dependent melting point reduction between gold and bismuth oxide. Source: Reprinted with permission from Guenther et al. [18], Copyright © 2014, American Chemical Society.

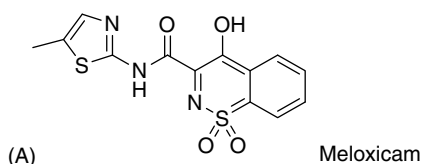
**Figure 1.8** Experimental values of  $\Delta T_m$  plotted as a function of the reciprocal pore diameter. (O) *cis*-decalin, (●) *trans*-decalin, (▽) cyclohexane, (Δ) benzene, (▲) chlorobenzene, (◆) naphthalene, and (□) heptanes. Source: Jackson and McKenna 1990 [16]. Reprinted with permission from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



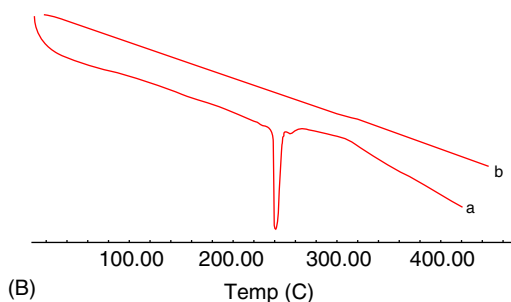
Nanosponges can even suppress the melting point of a molecule, as reported in Figure 1.10 for meloxicam drug included in a cyclodextrin nanosponge. Meloxicam has a sharp melting point at 250 °C. This peak is absent when meloxicam is entrapped in nanosponges, thus indicating the formation of a complex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

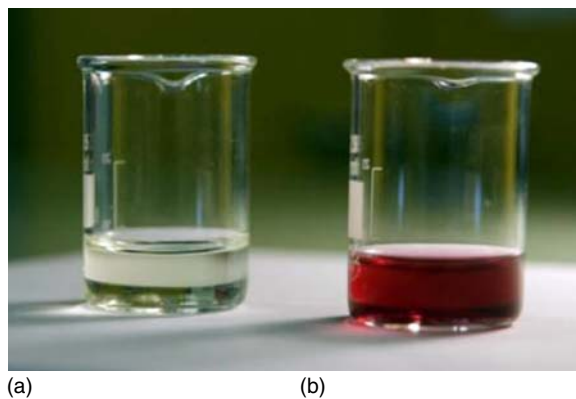
As mentioned above, this behavior is influenced by the size of the nanoparticle. The result is that a nanoparticle of about 90 nm in size will absorb color on





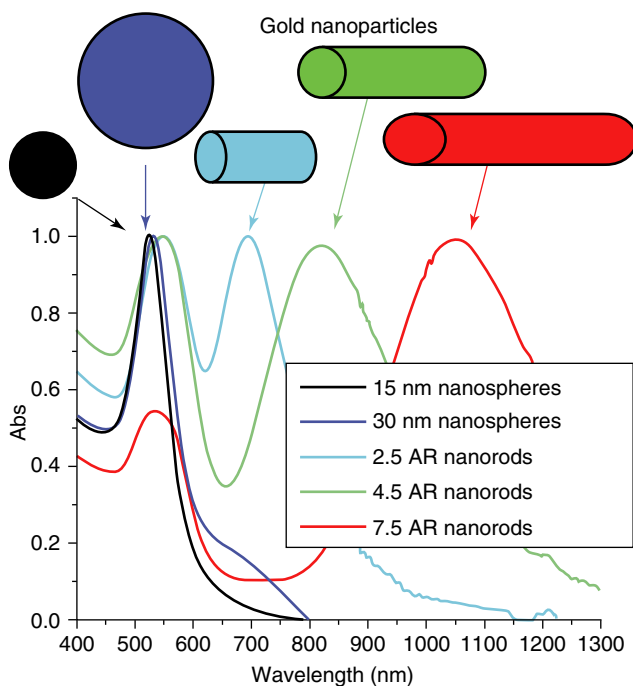
**Figure 1.11** King Lycurgus Cup at British Museum – London: (a) reflected light and (b) transmitted light. Source: Adapted under CC license from Freestone et al. 21. Published by SpringerNature.

**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].

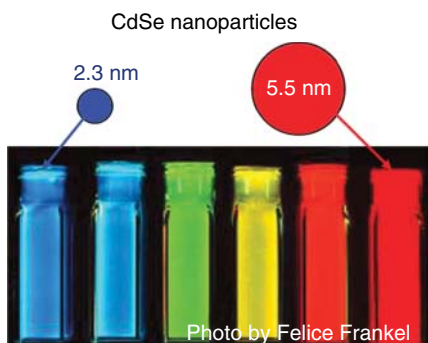
Although it appears unlikely that this knowledge was in the background of those ancient masters, however, the effect obtained is still impressive! Nevertheless, Lycurgus cup was not the only one heritage that is connected with the presence of nanoparticles or nanomaterials in the ancient time. This is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



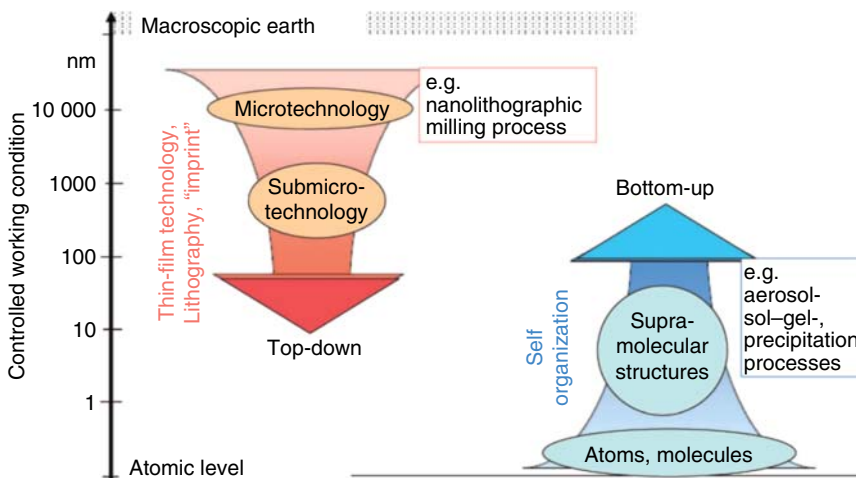
**Figure 1.14** Color change of CdSe. Source: Adapted with permission from Eustis and El-Sayed [24], Copyright © 2005, RSC.

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

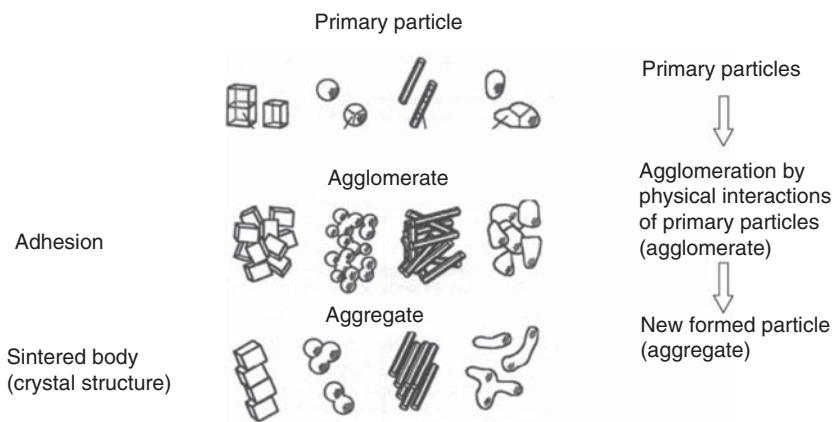
Despite the arbitrary 100 nm limit for numerous classifications of nanomaterials, it is sometimes reported, and generally accepted, that more precisely 30 nm is the upper limit for the experimental detection of size-dependent property change. In fact, it is quite evident that the high increase in the 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.

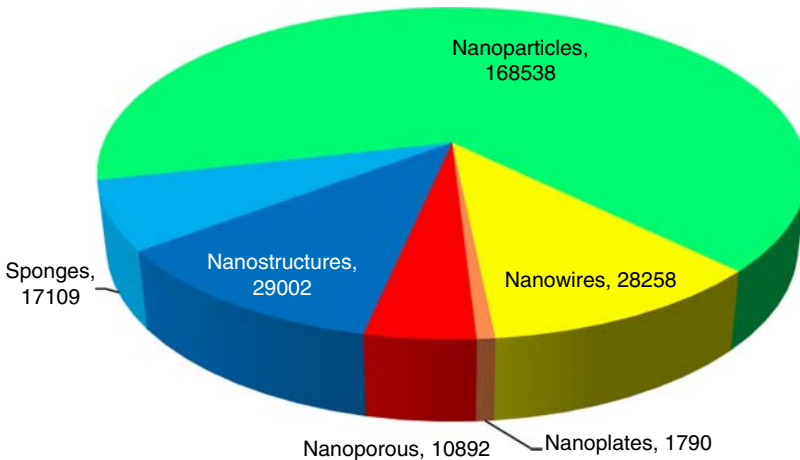
area if compared with the parent particles. Agglomerates are, for instance, responsive to ultrasound being easily divided into smaller agglomerates.

## 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](http://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](http://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 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  $\mu\text{m}$  size of the