Nanoparticle Uptake by Plants: Beneficial or Detrimental?

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1.1 Introduction

Nanoparticles can be defined as very small particles with size in the nanometer range. They can be as small as 1 nm and as large as hundreds of nm.

Due to their small size, nanoparticles can be internalized by plants, animals, and humans. Further, they can enter cells and organelles and affect cellular processes. Nanoparticles with selected compositions had shown some beneficial effects in selected plants, and, as a result, some scientists are promoting their use in agriculture. However, nanoparticles are phytotoxic for many other plants. In addition, nanoparticles are toxic to humans and animals, being associated to a multitude of diseases, ranging from respiratory and cardiovascular to neurological diseases. As a result of their toxicity, it is necessary to environmentally monitor man-made nanoparticles and to pass regulations and laws regarding the use and safe handling of nanoparticles.

What makes nanoparticles different from larger particles of the same material are surface and quantum effects (Buzea and Pacheco 2017). A material in nanoform exhibits different physical, chemical, and mechanical properties than the material in bulk form. Decreasing the size of a nanoparticle, the ratio between the atoms on its surface compared to those in its interior increases, leading to a smooth scaling of its physical and chemical properties. As a result, nanoparticles will have higher surface/volume ratio, increased chemical reactivity, and reduced melting point. Due to the

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small size of a nanoparticle, its electrons become confined and will have a quantized energy spectrum, resulting in quantum size effects. An example of quantum size effect is the appearance of magnetic moments. For example, there are nanoparticles of materials nonmagnetic in bulk that, when in nanoform, develop magnetic moments. Among these are gold, platinum, and palladium.

Nanoparticles can have various sizes, morphologies, and crystallinities, as illustrated in Fig. 1.1. They can have a short aspect ratio, with spherical or cubic morphologies, or a long aspect ratio, in the form of tubes or long whiskers (Soto et al. 2005; Murr and Soto 2004; Rui et al. 2015; Qiu et al. 2010).

Nanotoxicology is a branch of toxicology that studies the toxicity of nanoparticles in humans and animals. It encompasses in vitro studies performed on animal and human cell lines, in vivo experiments on animals and humans, epidemiological data related to particle pollution, and occupational exposure studies of workers involved in handling nanoparticles (welding, mining, etc.).

Nanoparticles are being increasingly used in applications, including agriculture. However, many types of nanoparticles are proved to be toxic, despite the fact that the same material in bulk form is harmless. It is impossible to predict the toxicity degree of a nanoparticle type without experimental data. As most of the nanotoxicity studies are published in very specialized journals, the dissemination of information on nanoparticle toxicity is not readily available for the scientists that are starting to use these nanoparticles in applications, including agrichemicals.

The researchers working in their application in agriculture, being unaware of nanoparticle toxicity, are likely to suffer health effects in the coming years due to incorrect handling and inadvertently exposure to nanoparticles. Due to their small size, nanoparticles can easily become airborne and be inhaled and ingested and enter in contact with the skin. Secondly, the use of agricultural nanoparticles poses a risk for the population and ecosystem.

Having remembered asbestos and the severe health effects due to its use in construction, we would like to prevent a similar situation from happening. However, nanoparticles use in agriculture might pose a higher environmental and toxic threat than asbestos. Asbestos use was limited mainly to the construction industry, being confined to buildings, and is now relatively easy to remove. Nanoparticles used in agriculture will not be confined to a specific place; they will enter the atmosphere and become respirable particles, pollute the water, and lead to devastating consequences for humans and other life species.

This chapter will focus on evaluating the beneficial and detrimental effects of nanoparticles on plants together with their toxicity in humans and animals. Weighting the pros and cons will allow the reader to form an idea whether or not nanoparticles should be used in agriculture. We show research regarding nanoparticle uptake and accumulation in plants, together with phytotoxicity studies. We also show selected beneficial effects in some plants. Following are subchapters dedicated to toxic effects of nanoparticles in humans and animals together with comparative toxicity for various compositions. After reading this chapter, the reader should be informed on the pros and cons of using nanoparticles in agriculture and the environmental risks and toxicity that they will pose for life.

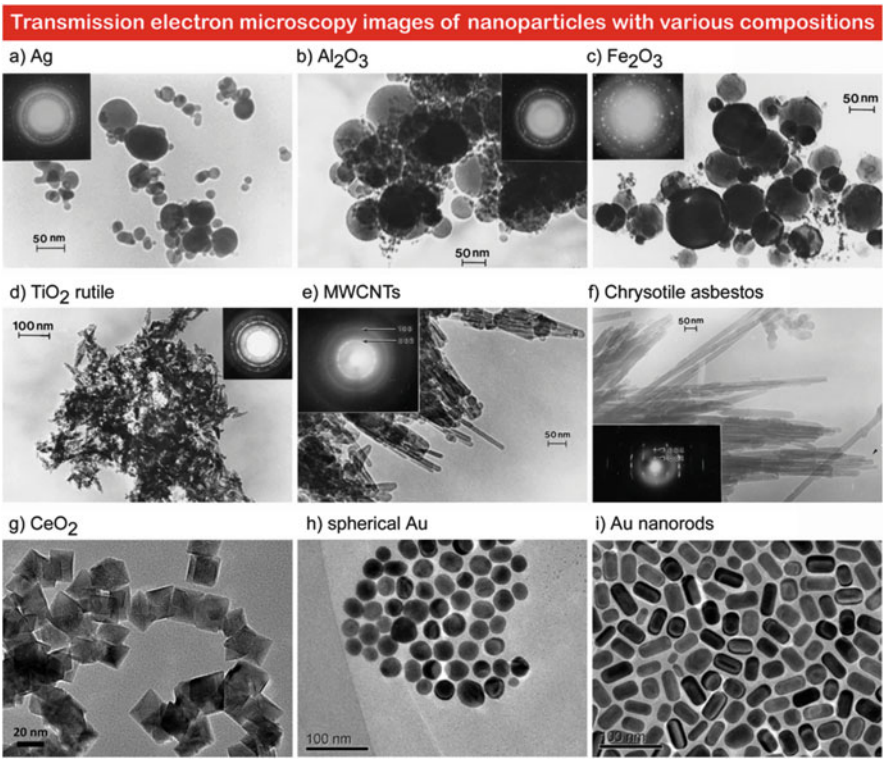

Fig. 1.1 Transmission electron microscopy images of nanoparticles of (**a**) Ag, (**b**) Al_2O_3, (**c**) Fe_2O_3, (**d**) TiO_2 rutile, (**e**) MWCNTs, and (**f**) chrysotile asbestos. Inserts are showing selected area electron diffraction (SAED) patterns that indicate the degree of crystallinity of nanoparticles. Notice the similarity between the morphology of MWCNTs and asbestos. Images (**a**–**d**) are reprinted from Soto K. F. et al. 2005. Comparative in vitro cytotoxicity assessment of some manufactured nanoparticulate materials characterized by transmission electron microscopy. Journal of Nanoparticle Research, 7, 145–169, with permission from Springer (Soto et al. 2005). Images (**e**–**f**) are reproduced from Murr L. E. & Soto K. F. 2004. TEM comparison of chrysotile (asbestos) nanotubes and carbon nanotubes. Journal of Materials Science, 39, 4941–4947. Copyright 2004 Kluwer Academic Publishers. With permission of Springer (Murr and Soto 2004). (**g**) CeO_2 nanoparticles. Reprinted from Environmental Pollution, vol. 198, Rui Y. et al., Transformation of ceria nanoparticles in cucumber plants is influenced by phosphate, pp. 8–14, Copyright (2015), with permission from Elsevier (Rui et al. 2015). (**h**) Gold nanospheres and (**i**) gold nanorods; images (**h**–**i**) adapted from Biomaterials, Vol 31, issue 30, Qiu Y. et al, Surface chemistry and aspect ratio mediated cellular uptake of Au nanorods, Pages 7606–7619, Copyright (2010), with permission from Elsevier (Qiu et al. 2010)

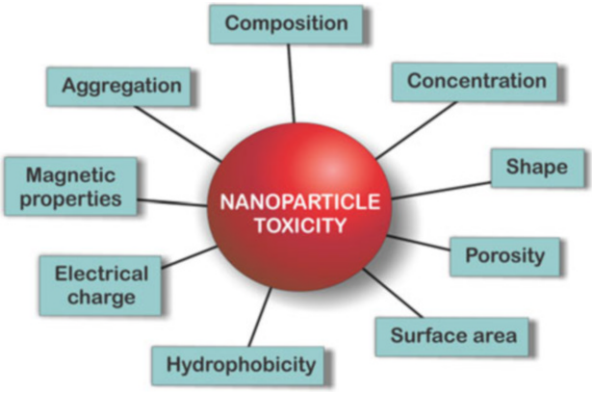

Fig. 1.2 Nanoparticle toxicity is determined by its physicochemical and morphological characteristics

1.2 Nanoparticle Physicochemical Properties

Nanoparticle interaction with their environment and uptake and toxicity in plants, humans, and animals depend on their size, aggregation, composition, concentration, shape, porosity, surface area, hydrophobicity, electrical charge, and magnetic properties, as illustrated schematically in Fig. 1.2.

It is important to note that nanoparticles suffer chemical transformation in the soil, within the plants, and within organisms in general. They are able to undergo various transformations, for example, acquiring a protein corona or changing their oxidation state, depending on their environment conditions. These transformations dictate ultimately their uptake, translocation, and toxicity. Even nanoparticles that may be considered stable are still able to change chemically, and their beneficial properties might become detrimental. For example, under hydroponic conditions Ce (IV)O_2 in cucumber plants is reduced to Ce(III) (Rui et al. 2015). CeO_2 nanoparticles in hydroponic cucumber plants treated with phosphate suffer chemical transformation, being located outside the epidermis, while in phosphate free plants, they were observed only in the intercellular spaces and vacuole of root (Rui et al. 2015).

1.3 Nanoparticles in Agriculture

1.3.1 Pesticides and Fertilizers

The topic of nanoparticle applications in agriculture emerged around the year 2000 (Gogos et al. 2012). Nanoparticles used in agriculture can be solid (such as metal and their oxides) or nonsolids (such as lipid or polymer) (Gogos et al. 2012). They are used for plant crop protection and for soil/water remediation (Fig. 1.3). Nanoparticles in plant protection are used as fungicides, herbicides, and insecticides, as depicted in Fig. 1.4. Nanoparticles can be the active ingredient or an additive that

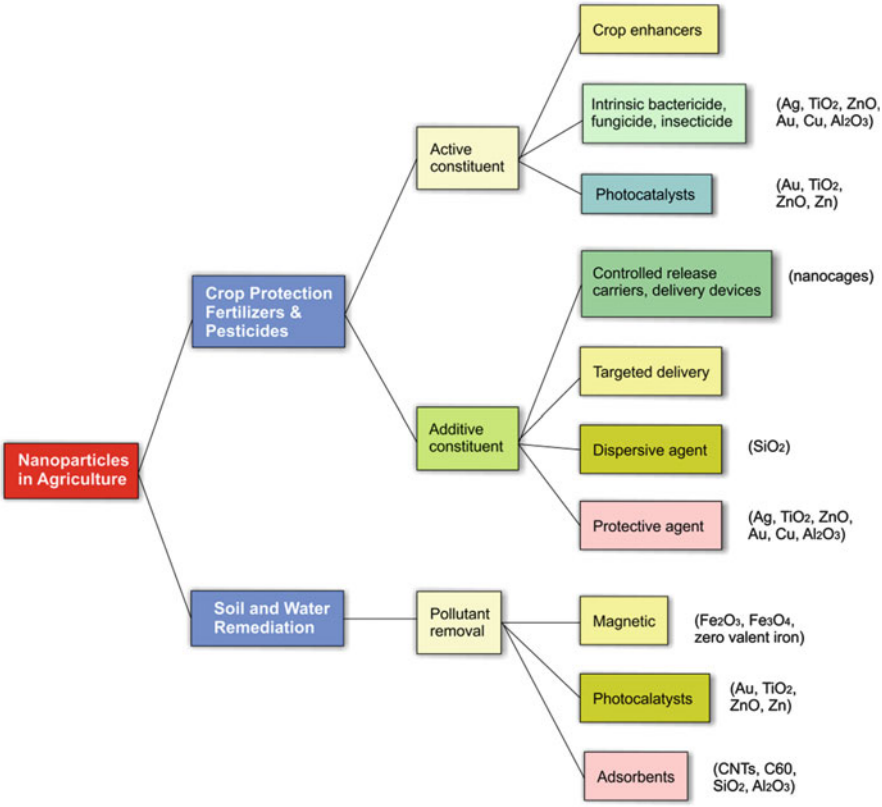

Fig. 1.3 Schematics for the applications of nanoparticles in agriculture for plant protection and soil and water remediation

can act for the controlled release of the main ingredient, as dispersing agent, targeted delivery agent, protective agent, or photocatalyst.

Figure 1.3 shows a schematic of nanoparticle function used in agriculture together with examples of nanoparticle compositions. Figure 1.4 shows comparative results of nanoparticles used in agriculture. Nanoparticles can act as active constituents and additives: they can serve as delivery devices that targeting specific tissues, nanopesticides (small particles of pesticides), and nanocages filled with pesticides act as controlled release devices. Nanoparticles themselves can have pesticidal properties when in nanoform, such as Ag, Au, TiO_2, Cu, and ZnO, several of these having photocatalytic properties. They can be pesticide additives that serve for enhancing the solubility of active ingredients. Some nanoparticles can also be used for soil and water remediation (Aragay et al. 2012). Due to their high surface area, adsorption capacity, and electromagnetic properties, nanoparticles are prospected for the adsorption of organic and inorganic pollutants from soil and water (Gupta and Saleh 2013). Among them are metal-containing particles, CNTs,

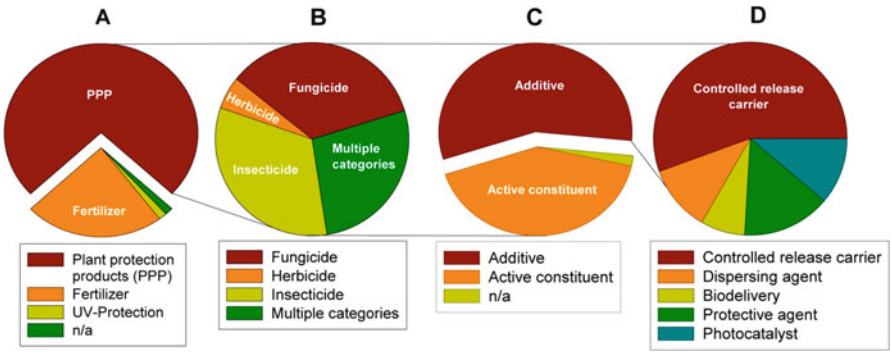

Fig. 1.4 Comparative results of nanoparticles used in agriculture. (**a**) Applications of nanoparticles in agriculture. (**b**) Types of plant protection products containing nanoparticles, (**c**) the function of nanoparticles within these products, (**d**) the role of the additive nanoparticles in plant protection products. Reprinted with permission from Gogos A. et al., Nanomaterials in Plant Protection and Fertilization: Current State, Foreseen Applications, and Research Priorities. Journal of Agricultural and Food Chemistry, vol. 60, pp. 9781–9792. Copyright (2012) American Chemical Society (Gogos et al. 2012)

C_{60}, and zeolites. Magnetic nanoparticles, such as iron oxide (Fe_3O_4) and zerovalent iron, are unique agents for water treatment (Xu et al. 2012; Deng et al. 2014). Magnetic nanoparticles are used for selected pollutant removal. Heavy metal pollutants are adsorbed by nanoparticles of Fe_2O_3, Fe_3O_4, SiO_2, and Al_2O_3 (Bakshi et al. 2015).

Some nanoparticles are found to be beneficial for plant protection and growth of selected plants, as discussed in Sect. 1.6. Unfortunately, the same types of nanoparticles are shown to be toxic to animals, humans, and some plants, such as carbon nanotubes (CNTs), Ag, titanium dioxide (TiO_2), silica (SiO_2), and alumina (Al_2O_3), as seen in Sect. 1.7.

The use of nanoparticles in agriculture should be limited by legislation. Very concerning is the increasing number of patents being filed related to nano-agrichemicals. The buildup of nanoparticles in plants, soil, water, and the environment, their trophic transfer, will detrimentally and irreversibly affect the health of humans and animals as well as plants. Many nanoparticles are shown to enter edible plants, and once they are in the food chain, they are likely to cause adverse health effects. It is imperative that regulatory agencies address and control the utilization of nanoparticles in agriculture (Kookana et al. 2014).

The reader interested in finding out more details about nanoparticles used in agriculture as agrichemicals, crop enhancers, crop protection, and soil and water remediation, can research the following reviews: Iavicoli et al. (2017), Khot et al. (2012), Liu and Lal (2015), Servin et al. (2015), Deng et al. (2014), Aragay et al. (2012), Gogos et al. (2012), Kah and Hofmann (2014), Ruttkay-Nedecky et al. (2017), and Wang et al. (2016).

1.3.2 Nanoparticle Soil Interaction and Accumulation

The use of nanoparticles in agriculture results in their accumulation in soil and the environment in general as well as trophic transfer. We must specify that when speaking about soil and nanoparticles, we are referring to man-made nanoparticles. Within the soil there are a multitude of natural nano- and microparticles, some of them having beneficial properties for the soil fertility. For example, clay nanoparticles may prevent leakage of nutrients in the groundwater by forming electrostatic bonds with them (Bernhardt et al. 2010).

Several types of nanoparticles are known for their antibacterial properties; hence their availability in soil is likely to affect soil bacteria, which are essential for their role in various ecosystems (Dinesh et al. 2012). The negative effects on endophytic bacteria symbionts are of special concern (Deng et al. 2014). Nanoparticles in soil will modify their properties in a dynamic manner, affecting their aggregation, dispersibility, dimensions, surface area, charge, and chemistry, which will affect their transport and availability.

Nanoparticle interaction with the soil and their bactericidal properties depends on the soil properties (Bakshi et al. 2015; Layet et al. 2017; Schlich and Hund-Rinke 2015). For example, silver nanoparticle toxicity against ammonia-oxidizing bacteria decreases for soils with higher clay content and larger pH. As a result, the toxicity of nanoparticles on plants may be affected by the soil type (Josko and Oleszczuk 2013).

The existence of nanoparticles with bactericidal properties in soil is likely to affect plants. It was found that the exposure of legumes to some nanoparticles severely lowers nitrogen fixation due to their bactericidal effects. Soybean plants exposed to ceria nanoparticles have a reduced nitrogen fixation correlated with almost absent bacteroids in its nodules (Priester et al. 2012).

1.4 Nanoparticle Uptake in Plants

1.4.1 Nanoparticle Uptake Routes

The interaction of nanoparticle with plants is a relatively new field of study. Nanoparticle uptake is plant specific. While the topic of uptake and transport of nanoparticles within plants is still not entirely understood, there is a consensus that it depends on the type of nanoparticle, their physicochemical properties, plant species, and the plant substrate—soil, hydroponics, or culture medium (Arruda et al. 2015; Aslani et al. 2014; Bakshi et al. 2015; Bernhardt et al. 2010; Chichiricco and Poma 2015; Deng et al. 2014; Dietz and Herth 2011; Ma et al. 2015; Miralles et al. 2012a, b; Navarro et al. 2008; Rico et al. 2011; Yadav et al. 2014; Schwab et al. 2015; Zuverza-Mena et al. 2017; Reddy et al. 2016).

It is known already that some nanoparticles translocate within the plants by forming complexes with membrane transporter proteins or root exudates (Yadav et al. 2014). Nanoparticle properties, such as size, porosity, hydrophobicity, and

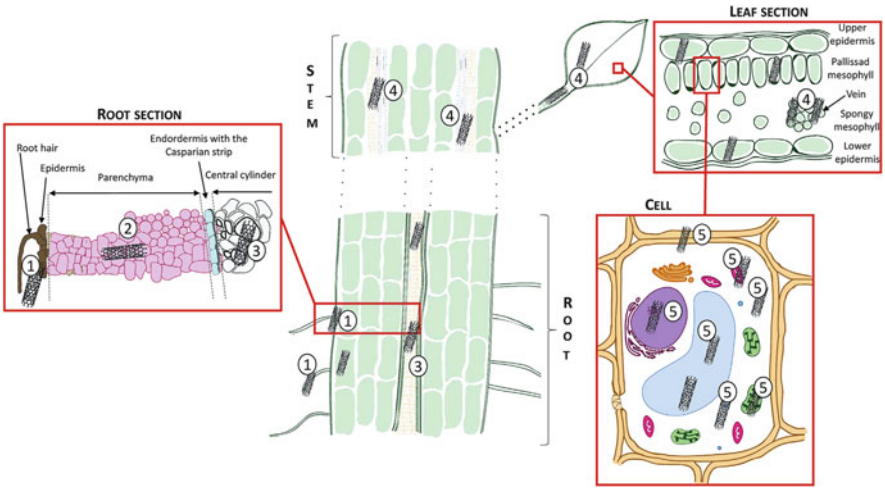

Fig. 1.5 Schematics of the uptake and translocation of CNTs in plants. Image not at scale. Within the cell blue represents vacuole; green, chloroplasts; purple, nucleus; orange, smooth endoplasmic reticulum; blue, plasmode. *1*. The uptake of CNTs by plant roots can occur via osmotic pressures, capillary forces, pores on cell walls, intercellular plasmodesmata, or through direct penetration. *2*. Endocytosis allows CNTs to cross both cell wall and cell membrane. *3*. CNTs may use the vascular system together with water and nutrients and can translocate to the upper parts of the plants. *4*. CNTs may reach the upper part of plants. Their preferential location in leaves is the xylem. *5*. Inside the cells CNTs can be found in cytoplasm, cell wall, cell membrane, chloroplast, mitochondria, and plasmodes. Reprinted from Carbon, vol. 123, Line C. et al., Carbon nanotubes: Impacts and behaviour in the terrestrial ecosystem—A review, pp. 767–785. Copyright (2017), with permission from Elsevier (Line et al. 2017)

surface, are modulating the interaction of nanoparticles with plants. A schematic of nanoparticle uptake in plants is shown in Fig. 1.5 (Line et al. 2017).

Roots can uptake small nanoparticles through pores (with size around 5–20 nm) within the root epidermal cell walls—called the apoplastic route (Deng et al. 2014). Particles larger than the pore size will be stopped. Small nanoparticles that cross the cell walls may be subjected to osmotic pressure and capillary forces and diffuse through the apoplast and reach the endodermis (Lin et al. 2009; Deng et al. 2014).

Another route of nanoparticle uptake in plants is the symplastic pathway via the inner side of the plasma membrane. The cell wall is a porous matrix of polysaccharide fibers that can be crossed by nanoparticles that bind to protein carriers, via aquaporins, ion channels, and endocytosis, or by piercing the cell membrane and creating new pores (Tripathi et al. 2017; Rico et al. 2011; Wild and Jones 2009). Nanoparticles can migrate to neighboring cells through plasmodesmata (20–50 nm diameter channels) (Deng et al. 2014).

Another way of entry of nanoparticle in plants is via foliar through stomatal pores (Larue et al. 2014a, b; Hong et al. 2014). From leaves nanoparticles can translocate to other parts of the plants, including roots (Hong et al. 2014). Examples of plants that internalize nanoparticles through leaves are rapeseed, wheat, beans, corn,

lettuce, and cucumber (Chichiricco and Poma 2015). Nanoparticles ranging from a few nanometers up to several hundred nanometers and with different compositions can be internalized through leaves, such as ceria, titania, iron oxide, zinc oxide, and silver (Chichiricco and Poma 2015).

Within the cells nanoparticles are shown to interact with cell organelles, and depending on their physicochemical properties, many produce oxidative stress, genotoxicity, and metabolic changes (Deng et al. 2014).

1.4.2 Nanoparticle Composition-Dependent Uptake in Plants

In the following, we will focus mostly on the nanoparticle uptake on crops due to their immediate trophic transfer to humans and animals. Many crops exposed to various nanoparticles have been shown to internalize them (Deng et al. 2014). Once inside, they translocate to various plant tissues: stems, leaves, petioles, flowers, and fruits (Deng et al. 2014). While there are some reports on beneficial effects on selected plants, there is an overwhelming evidence of adverse effects of nanoparticles on many crops.

Below are examples of studies showing the uptake of nanoparticles with various compositions in various edible plants:

- Au—tomato plants (Dan et al. 2015), tobacco (Judy et al. 2011; Sabo-Attwood et al. 2012), *Arabidopsis thaliana* (Avellan et al. 2017; Taylor et al. 2014), barley (Feichtmeier et al. 2015), rice, radish, pumpkin (Zhu et al. 2012)
- Ag—*Arabidopsis thaliana* (Geisler-Lee et al. 2013; Kaveh et al. 2013; Nair and Chung 2014), tomato (Antisari et al. 2015), wheat (Dimkpa et al. 2013b), lettuce (Larue et al. 2014a), mung bean and sorghum (Lee et al. 2012), rice (Mirzajani et al. 2013; Thuesombat et al. 2014), broad bean (Patlolla et al. 2012), corn, cabbage (Pokhrel and Dubey 2013), review (Cox et al. 2016)
- CeO_2—alfalfa, corn (Lopez-Moreno et al. 2010b; Wang et al. 2013b), cucumber (Zhang et al. 2011; Lopez-Moreno et al. 2010b; Rui et al. 2015; Hong et al. 2014), tomato (Antisari et al. 2015; Lopez-Moreno et al. 2010b; Wang et al. 2013b), soybean (Lopez-Moreno et al. 2010a), barley (Rico et al. 2015), lettuce (Gui et al. 2015; Zhang et al. 2015), wheat (Rico et al. 2014)
- MWCNTs—wheat (Miralles et al. 2012b; Larue et al. 2012b), rapeseed (Larue et al. 2012b), tomato (Khodakovskaya et al. 2013), red spinach (*Amaranthus tricolor* L), (Begum and Fugetsu 2012), lettuce, rice, cucumber (Begum et al. 2014), onion (Ghosh et al. 2015), alfalfa (Miralles et al. 2012b), corn (Yan et al. 2013), review (Line et al. 2017)
- TiO_2—corn (Asli and Neumann 2009), wheat (Du et al. 2011; Larue et al. 2012a, c), rapeseed (Larue et al. 2012a, c), lettuce (Larue et al. 2014b), *Arabidopsis thaliana* (Kurepa et al. 2010, Wang et al. 2011b), cucumber (Servin et al. 2012, 2013), tomato (Antisari et al. 2015), onion (Pakrashi et al. 2014; Ghosh et al. 2010), review (Cox et al. 2016; Jacob et al. 2013), tobacco (Ghosh et al. 2010)

- C60 or C70—*Arabidopsis thaliana* (Landa et al. 2012; Liu et al. 2010), bitter melon (Kole et al. 2013), rice (Lin et al. 2009), onion (Chen et al. 2010), review (Husen and Siddiqi 2014)
- Zn and ZnO—*Arabidopsis thaliana* (Landa et al. 2012), soybean (Lopez-Moreno et al. 2010a), radish, rape, lettuce, corn, cabbage (Pokhrel and Dubey 2013; Lin and Xing 2007), cucumber (Lin and Xing 2007), wheat (Dimkpa et al. 2013a; Du et al. 2011), cress (Josko and Oleszczuk 2013), onion (Kumari et al. 2011), garlic (Shaymurat et al. 2012)
- Carbon-Fe—pea, sunflower, tomato, wheat (Cifuentes et al. 2010)
- Fe_3O_4—pumpkin (Zhu et al. 2008), soybean (Ghafariyan et al. 2013), tomato (Antisari et al. 2015)
- Al_2O_3 or Al—onion, cress (Asztemborska et al. 2015), corn (Lin and Xing 2007; Asztemborska et al. 2015), review (Singh et al. 2017b)
- Co—tomato (Antisari et al. 2015), onion (Ghodake et al. 2011)
- Ni—tomato (Antisari et al. 2015; Faisal et al. 2013)
- SnO_2—tomato (Antisari et al. 2015)
- CuO_2—radish (Atha et al. 2012), wheat (Dimkpa et al. 2013a), rice (Shaw and Hossain 2013), review (Anjum et al. 2015)
- CdSe quantum dots—rice (Nair et al. 2011)
- Rare-earth La_2O_3, Gd_2O_3, Yb_2O_3—rape, radish, wheat, lettuce, cabbage, tomato, cucumber (Ma et al. 2010)

The accumulation of nanoparticles in plants is not yet entirely understood; however several trends are emerging (Deng et al. 2014). Nanoparticle uptake in plants is species specific and depends on the nanoparticle composition and their size. For example, tobacco uptakes Au nanoparticles, while wheat does not (Judy et al. 2012). One must emphasize that future research might show a different picture of nanoparticle uptake, as various researchers uses nanoparticles with different sizes, surface charge and functionalization, crystallinity, etc.

Nanoparticle uptake and toxicity in plants is composition specific. For example, the exposure of tomato plants to nanoparticles with various compositions (CeO_2, Fe_3O_4, SnO_2, TiO_2, Ag, Co, and Ni) has different effects on root growth, accumulation site, and fruit yield (Antisari et al. 2015). Longer roots are achieved after exposure to iron oxide nanoparticles, while the opposite effect is obtained by using tin oxide. While most metal nanoparticles accumulate in roots, silver and cobalt nanoparticles were found in below- and aboveground plant organs. Tomato fruits had higher amount of silver nanoparticles compared to other compositions (Antisari et al. 2015).

The uptake of nanoparticle by plants is a function of exposure condition, nanoparticle physicochemical properties, and plant species. Similar to the process in humans, the uptake and translocation of nanoparticles within plants can be very swift. The time of translocation from roots to shoots of carbon-coated magnetic nanoparticles in sunflower, tomato, pea, and wheat is less than 24 h (Cifuentes et al. 2010).

1.4.3 Nanoparticle Size-Dependent Plant Uptake

Particle size is one of the most important factors that determine the uptake of nanoparticles in plants. Smaller nanoparticles are internalized by plants, while larger ones are not (Zhu et al. 2008; Wang et al. 2011a). For example, in the case of TiO_2 nanoparticles with sizes between 14 and 655 nm, only the smallest ones are able to translocate through the entire wheat plant (Larue et al. 2012a). The ones smaller than 140 nm pass through wheat root epidermis, while those smaller than 36 nm can transfer through root parenchyma and translocate from root to shoot (Larue et al. 2012a). Another example is the uptake of ceria nanoparticles in cucumber (Zhang et al. 2011). Nanoparticles with sizes of 7 and 25 nm are both absorbed by cucumber roots and translocate to leaves; however a larger number of smaller nanoparticles are absorbed compared to larger ones (Zhang et al. 2011).

1.4.4 Nanoparticle Crystalline Structure-Dependent Plant Uptake

Nanoparticles with the same composition but different crystalline structure can suffer a different uptake and translocation in plants. For example, titanium dioxide nanoparticles in anatase and rutile crystalline form are differentially translocated in cucumber plants (Servin et al. 2012). The anatase nanoparticles remained mainly in the roots, while the rutile nanoparticles translocated and accumulated mostly in the aerial tissue of cucumber.

1.4.5 Nanoparticle Charge-Dependent Plant Uptake

Studies show that the uptake of nanoparticles in plants is a function of nanoparticle surface charge or functionalization. Nanoparticles can be neutral; have a positive charge, in which case are called cationic; or have a negative charge—being called anionic. There seems to be a different behavior in the uptake of nanoparticles according to their charge by woody plants compared to herbaceous plants.

Woody Plants A recent study on the uptake of CdSe/CdZnS quantum dots coated with cationic polyethylenimine (PEI) or poly(ethylene glycol) of anionic poly (acrylic acid) (PAA-EG) in poplar trees shows that both types of nanoparticles are internalized after 2-day exposure (Wang et al. 2014). Cationic quantum dot absorption is tenfolds faster than anionic nanoparticles, most likely due to electrostatic forces between positively charged quantum dots and the negatively charged root cell wall (Wang et al. 2014). Slower absorption of anionic quantum dots might be a result of the repulsive electrostatic forces between the negatively charged root surface and the negatively charged nanoparticles.

Herbaceous Plants Interestingly, the uptake of cationic and anionic nanoparticles in herbaceous plants differs from the one in woody plants (Koelmel et al. 2013; Zhu et al. 2012).

Rice under hydroponic conditions uptakes and bioaccumulates 2 nm gold nanoparticles. Their distribution is a function of the nanoparticle surface charge (Koelmel et al. 2013). The accumulation in roots follows the order AuNP (+) > AuNP(0) > AuNP(−), where "+," "0," and "−" denoted positive, zero, and negative electrical charged nanoparticles, respectively. In contrast, the rice shoots showed a reverse order of nanoparticle charge uptake compared to the roots, having a preferential uptake of anionic nanoparticles.

Similar results were obtained in a study on the uptake of (6−10 nm) gold nanoparticles with different surface charge under hydroponic conditions in rice, radish, pumpkin, and perennial ryegrass (Zhu et al. 2012). Nanoparticle uptake is surface charge and plant specific. Cationic nanoparticles translocate mainly in plant roots, while anionic nanoparticles suffer uptake mainly in plant shoots. A larger number of nanoparticles are found in radish and ryegrass roots than rice and pumpkin roots. Nanoparticles accumulate in rice shoots in larger amounts compared to none in radish and pumpkin shoots (Zhu et al. 2012).

Cerium oxide nanoparticles (4 nm in size) also have a preferential uptake and tissue localization in wheat according to their surface charge (Spielman-Sun et al. 2017). Positively charged CeO_2 adhere to wheat roots the strongest, while negatively charged and neutral nanoparticles have higher concentrations in leaves compared to plants exposed to cationic CeO_2.

Therefore, the trend for herbaceous plants is to absorb positively charged nanoparticles in roots, while the shoots, stems, and leaves uptake mainly negatively charged nanoparticles.

1.5 Detrimental Effect of Nanoparticles in Plants

1.5.1 Composition and Plant-Specific Phytotoxicity

The interaction between plants and nanoparticles may range from subtle to notable changes in plant morphology, physiology, biochemistry, and genetics (Deng et al. 2014). Plant morphology changes include germination index (germination time and rate), root elongation, shoot and root biomass, root tip morphology, etc. (Deng et al. 2014).

Many studies indicate a detrimental effect of nanoparticles in many plant species, while a minority is trying to promote the use of nanoparticles for selected beneficial effects in a few plants. It is important to note that while some plants will have beneficial effects as a result of exposure to a type of nanoparticle, other plants are negatively affected by the same nanoparticles.

Many types of nanoparticles are phytotoxic, inhibiting plant growth and physiological, biochemical, and genetic traits (Tripathi et al. 2017; Brar et al. 2010; Deng et al. 2014). Table 1.1 shows examples of edible plants adversely affected by

Table 1.1 Detrimental effects of nanoparticles on selected crops

	Au	Ag	CNT	C_{60}	TiO_2	CeO_2	ZnO	CuO_2	Fe_3O_4
Alfalfa (*Medicago sativa*)					D	D	D	D	
Arabidopsis thaliana	D	D	D			D	D	*D*	D
Barley (*Hordeum vulgare*)	D	D				D		D	D
Corn (*Zea mays*)		D		D	D	D	D	D	
Cress (*Lepidium sativum*)					D		D		D
Cucumber (*Cucumis sativus*)		D	D		D	D	D	D	D
Lettuce (*Lactuca sativa*)		D	D		D	D	D	D	D
Onion (*Allium cepa*)		D	D	D	D		D	D	
Pumpkin (*Cucurbita*)									D
Radish (*Raphanus raphanistrum*)		D			D	D	D	D	D
Red spinach (*Amaranthus tricolor*)			D					D	D
Rice (*Oryza sativa*)	D	D	D	D	D	D	D	D	
Soybean (*Glycine max*)	D		D	D		D	D	D	D
Tomato (*Lycopersicon esculentum*)	D	D	D		D	D	D		D
Wheat (*Triticum aestivum*)		D	D		D	D	D	D	D

D—found detrimental in at least one of the growth inhibition, physiological and biochemical traits, and toxicity at genetic level

nanoparticles with several compositions that are promoted or already being used as agrichemicals (Au, Ag, CNT, C_{60}, CeO_2, ZnO, CuO_2, Fe_3O_4). Here "D" refers to detrimental.

Table 1.2 shows examples of plant-specific detrimental effects of nanoparticles as a result of plant exposure to nanoparticles with several compositions. These range from adverse effects in their physiological, biochemical, and genetic traits. Noble metal nanoparticles, such as Au, induce necrosis in tobacco plants (Sabo-Attwood et al. 2012). Exposure to Ag nanoparticles leads to retarded germination in rice and corn (Thuesombat et al. 2014; Pokhrel and Dubey 2013) and reduction in mitotic index and fragmented chromosomes in onion (Kumari et al. 2009). Carbon-based nanoparticles (CNTs, C_{60}) lead to cellular toxicity in rice, spinach, and onion (Shen et al. 2010; Begum and Fugetsu 2012; Chen et al. 2010), reduction in biomass for zucchini (Stampoulis et al. 2009), and delayed flowering together with decreased yield (Lin et al. 2009). Exposure to TiO_2 nanoparticle results in damaged chloroplast and reduced photosynthetic rate in spinach (Lei et al. 2008), stress in cucumber

Table 1.2 Examples of detrimental effects as a result of plant exposure to different nanoparticles

NPC	Size (nm)	Plant	Effect	References
Au	3	Tobacco	Necrosis	Sabo-Attwood et al. (2012)
Ag	20	Rice	Seed germination	Thuesombat et al. (2014)
	11	Corn	Retarded germination	Pokhrel and Dubey (2013)
	<100	Onion	Fragmented chromosomes, reduction in mitotic index	Kumari et al. (2009)
CNT	1–2	Arabidopsis	Cell death	Shen et al. (2010)
		Rice	Delayed flowering, decreased yield	Lin et al. (2009)
		Rice	DNA damage, cell viability	Shen et al. (2010)
		Zucchini	60% reduction in biomass	Stampoulis et al. (2009)
		Spinach	Cell damage	Begum and Fugetsu (2012)
C_{60}		Onion cells	Necrosis	Chen et al. (2010)
TiO_2	27	Cucumber	Stress	Servin et al. (2013)
	30	Corn	Inhibited leaf growth	Asli and Neumann (2009)
		Corn	DNA damage	Castiglione et al. (2011)
	5	Spinach	Damaged chloroplast, reduced photosynthetic rate	Lei et al. (2008)
	100	Onion	DNA damage	Ghosh et al. (2010)
CeO_2	7	Soybean	Genotoxicity	Lopez-Moreno et al. (2010a)
	8	Cucumber	Stress	Hong et al. (2014)
	8	Rice	Stress	Rico et al. (2013)
	8	Wheat	Nutrition	Rico et al. (2014)
	10	Cucumber	Nutrition	Zhao et al. (2014)
	10–30	Tomato	Detrimental effects on second-generation plants	Wang et al. (2013b)
ZnO	20	Corn	Plant growth	Lin and Xing (2007)
	<100	Onion	Genotoxicity	Kumari et al. (2011)
	8	Soybean	Plant growth	Lopez-Moreno et al. (2010a)
	<50	Soybean	Seed formation	Yoon et al. (2014)
	4	Garlic	Genotoxicity	Shaymurat et al. (2012)
	10	Green peas	Chlorophyll/stress	Mukherjee et al. (2014)
	100	Rice	Root length/formation	Boonyanitipong et al. (2011)
	30,50	Chinese cabbage	Root and shoot formation	Xiang et al. (2015)
	<50	Buckwheat	Genotoxicity	Lee et al. (2013)

(continued)

Table 1.2 (continued)

NPC	Size (nm)	Plant	Effect	References
CuO, Cu	<50	Rice	Stress	Shaw and Hossain (2013)
		Zucchini	77% reduced root length 90% reduced biomass	Stampoulis et al. (2009)
	<100	Radish	Decreased root growth, DNA damage	Atha et al. (2012)
	<50	Buckwheat	Genotoxicity	Lee et al. (2013)
Ni	23,34	Tomato	Stress, mitochondria, cell damage	Faisal et al. (2013)

NPC nanoparticle composition

(Servin et al. 2013), inhibited leaf growth, and DNA damage in corn (Asli and Neumann 2009; Castiglione et al. 2011). CeO_2 nanoparticle adversely affects the nutrition and genetics of soybean, cucumber, rice, and wheat (Lopez-Moreno et al. 2010a; Hong et al. 2014; Rico et al. 2013, 2014; Zhao et al. 2014). ZnO is genotoxic to onion, garlic, and buckwheat (Kumari et al. 2011; Shaymurat et al. 2012; Lee et al. 2013); affects the seed formation in soybean (Yoon et al. 2014); inhibits plant growth in corn, soybean, rice, and cabbage (Lin and Xing 2007; Lopez-Moreno et al. 2010a; Boonyanitipong et al. 2011; Xiang et al. 2015); and affects chlorophyll in green peas (Mukherjee et al. 2014). CuO is genotoxic to radish and buckwheat (Atha et al. 2012; Lee et al. 2013), produces stress in rice (Shaw and Hossain 2013), and severely reduces root length (77%) and biomass (90%) in zucchini (Stampoulis et al. 2009). Nickel nanoparticles induce stress and damage of mitochondria and cells in tomato (Faisal et al. 2013).

A type of nanoparticle can sometimes have both beneficial and detrimental effects on the same plant. For example, barley exposed to CeO_2 nanoparticles (500 mg/kg) led to a more than 300% increase in shoot biomass; however it formed no grain (Rico et al. 2015).

In the following subchapters, we will elaborate on the adverse effects of nanoparticles on plant physiological, biochemical, and genetic traits.

1.5.2 Plant Growth Inhibition

Phytotoxicity related to growth inhibition manifests in reduced biomass; decreased germination and leaf growth; reduced root elongation, root biomass, root tip morphology, and shoot growth; delayed flowering; and decreased yield among others (Tripathi et al. 2017). The adverse biochemical traits involve the generation of reactive oxygen species, lipid peroxidation, decreased rate of transpiration, disturbed mitosis, breakdown of cell wall, reduction in chlorophyll content, and reduced photosynthesis (Tripathi et al. 2017). Toxicity at genetic level involves reduction in mitotic index, sticky and fragmented chromosomes, chromosome aberrations, alteration of genes, damaged DNA structure, and decreased cell viability (Tripathi et al. 2017). Examples of toxic effects of nanoparticle on plants are given in Table 1.2.

Some adverse effects of nanoparticles on plant growth are easily assessed by measuring the germination index, the elongation of roots and shoots, root biomass, root tip morphology, total biomass, and flowering (Deng et al. 2014).

For plants exposed to nanoparticles from soil or hydroponically, an important indicator of toxicity is the shoot and root biomass. While studies use different exposure times and doses, the general conclusion is that phytotoxicity is plant and nanoparticle specific. This toxicity can be due to the release and subsequent accumulation of ions in plant tissue and/or nanoparticle uptake and translocation (Deng et al. 2014). Nanoparticles with various compositions have an adverse effect on seedling roots and shoot elongation, mainly due to the adsorption of nanoparticles into the roots. Among phytotoxic materials to roots and shoots are gold, silver, zinc oxide, copper oxide, alumina, and carbon nanotubes (Begum and Fugetsu 2012; Begum et al. 2012; Burklew et al. 2012; Feichtmeier et al. 2015; Deng et al. 2014; Dimkpa et al. 2013b; Ghodake et al. 2011).

Figure 1.6 shows photographs of plants detrimentally affected by exposure to nanoparticles. Figure 1.6a–h illustrates the trend of decreased shoot and root length in a concentration-dependent manner in tomato and cauliflower exposed to CuO nanoparticles (Singh et al. 2017a), wheat exposed to Ag nanoparticles (Dimkpa et al. 2013b), barley seedlings exposed to Au nanoparticles (Feichtmeier et al. 2015), red spinach exposed to MWCNTs (Begum and Fugetsu 2012), rice exposed to MWCNTs (Begum et al. 2012), and rice exposed to CuO nanoparticles (Shaw and Hossain 2013). Figure 1.6i–j shows various aberrant features observed in onion after exposure to titanium dioxide nanoparticles, such as chromosome break and nuclear blebbing (Pakrashi et al. 2014).

It is important to note that nanophytotoxicity is material and species specific. This can be seen in a study comparing the toxic effects of several rare-earth oxide nanoparticles (CeO_2, La_2O_3, Gd_2O_3, Yb_2O_3) on several crops (cabbage, cucumber, lettuce, radish, rape, tomato, wheat) (Ma et al. 2010). For example, only the root elongation of lettuce is affected by CeO_2, while all remaining (La_2O_3, Gd_2O_3, Yb_2O_3) nanoparticles lead to a large reduction in root elongations for all studied plants.

Silver nanoparticles are known for their antibacterial, antifungal activity and are consequently used extensively as agrichemicals. As a result, the existence of Ag nanoparticles in soil can have an effect upon soil microbiota (such as nitrogen-fixing bacteria) that will in turn affect the physicochemical characteristics of soil and plants (Anjum et al. 2013). Silver nanoparticles can be internalized and accumulate in edible plants and consequently enter the food chain. Some plants exposed to silver nanoparticles show reduced germination, biomass, transpiration, shoot and root length, and cytotoxicity involving modifications in gene expression, oxidative stress, decreased mitosis, chromosomal abnormalities, and cell death (Anjum et al. 2013; Arruda et al. 2015; Thuesombat et al. 2014; Pokhrel and Dubey 2013; Kumari et al. 2009). Silver nanoparticles have a concentration-dependent growth inhibition effect upon mung bean and sorghum (Lee et al. 2012).

MWCNTs are the type of nanoparticle that shows the entire array of effects on plants, ranging from beneficial to detrimental. They are promoted for their use in

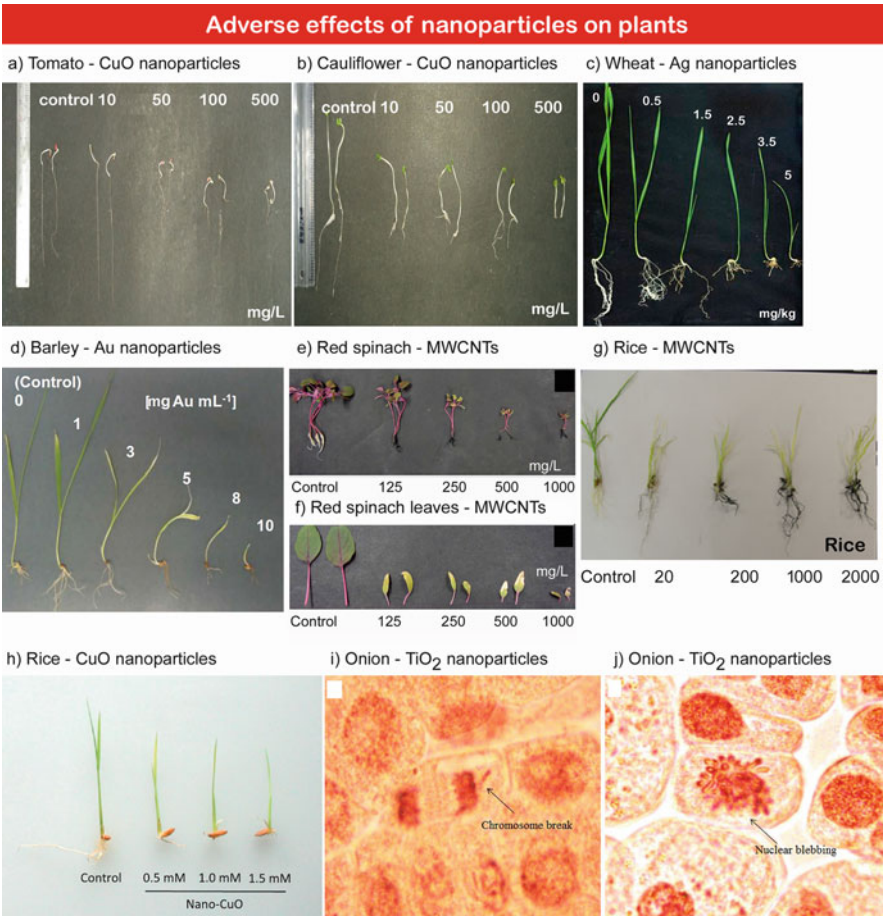

Fig. 1.6 Photographs showing detrimental effects following the exposure to different concentrations of various nanoparticles of selected crops. (**a**) Tomato exposed to CuO nanoparticles, (**b**) cauliflower exposed to CuO nanoparticles. Images (**a**–**b**) are reprinted from Singh A. et al., Effect of biologically synthesized copper oxide nanoparticles on metabolism and antioxidant activity to the crop plants *Solanum lycopersicum* and *Brassica oleracea* var. botrytis. Journal of Biotechnology, 262, 11–27, Copyright (2017), with permission from Elsevier (Singh et al. 2017a). (**c**) Wheat exposed to Ag nanoparticles. Reprinted with permission from Dimkpa C. O. et al, Silver Nanoparticles Disrupt Wheat (*Triticum aestivum* L.) Growth in a Sand Matrix. Environmental Science & Technology, 47, 1082–1090. Copyright (2013) American Chemical Society (Dimkpa et al. 2013b). (**d**) Barley seedlings exposed to Au nanoparticles. Reprinted from Feichtmeier, N. S. et al, Uptake, effects, and regeneration of barley plants exposed to gold nanoparticles. Environmental Science and Pollution Research, vol. 22, 2015, pp. 8549–8558, with permission from Springer (Feichtmeier et al. 2015). (**e**–**f**) Red spinach exposed to MWCNTs. Images (**e**–**f**) reprinted from Begum P and Fugetsu B, 2012, Phytotoxicity of multi-walled carbon nanotubes on red spinach (*Amaranthus tricolor* L) and the role of ascorbic acid as an antioxidant, Journal of Hazardous Materials, 243, 212–222, Copyright (2012), with permission from Elsevier (Begum and Fugetsu 2012). (**g**) Rice exposed to MWCNTs. Image reprinted from Begum P. et al., Applied Surface Science, vol. 262, Phytotoxicity of multi-walled carbon nanotubes assessed by selected plant species in the seedling stage, pp. 120–124, Copyright (2012), with permission from Elsevier (Begum et al. 2012). (**h**) Rice exposed to CuO nanoparticles. Reprinted from Shaw A. K. &

aiding germination of some seeds (Khodakovskaya et al. 2011). CNTs are phytotoxic to red spinach, lettuce, and cucumber, showing decreased roots and shoot lengths, while no negative effects were observed for chili and soybeans (Begum et al. 2014). They accumulate in onion plants and are cytotoxic and genotoxic, altering cellular morphology, affecting membrane integrity and mitochondrial function, resulting in DNA damage and chromosome aberration (Ghosh et al. 2015).

1.5.3 Nutrient Depletion in Nanoparticle-Contaminated Plants

The intake of plants and fruits is important for the mineral and nutrients they contain. Plant exposure to nanoparticles results in modified content of nutrients, fruit flavor, antioxidant content, and growth performance (Antisari et al. 2015; Deng et al. 2014; Petersen et al. 2014; Rico et al. 2011; Zhao et al. 2014).

Therefore, the use of nanoparticles as agrichemicals raises some serious concerns.

Cerium oxide nanoparticles affect the amounts of nutrients for important crops, such as rice, corn, soybean, tomato, and cucumber (Antisari et al. 2015; Peralta-Videa et al. 2014; Rico et al. 2013; Zhao et al. 2014, 2015). Rice exposed to ceria nanoparticles yields grains with compromised nutritional value, showing smaller amounts of iron, glutelin, lauric and valeric acids, starch, and some antioxidants (Rico et al. 2013). Cucumber fruits of plants exposed to nanoceria have an altered Mo micronutrient, sugar, and phenolic content in addition to protein fractionation (Zhao et al. 2014). Corn exposed to nanoceria has 38% reduced yield and less calcium translocation from the cob to the kernels compared to control (Zhao et al. 2015).

Zinc oxide nanoparticles have a profound effect on corn plants, accumulating in corncobs, alter its nutrient contents, and reduce photosynthesis and relative chlorophyll content, resulting in a reduced yield by 49% (Zhao et al. 2015).

The fruits of tomato plants exposed to CeO_2, Fe_3O_4, SnO_2, TiO_2, Ag, Co, and Ni nanoparticles exhibit a depletion of Mg, P, and S (Antisari et al. 2015).

1.5.4 Nanoparticle-Induced Genotoxicity

Due to their small size, nanoparticles are able to enter cells and elicit a genetic response from plants. Nanoparticles with many compositions (CuO, Ag, ZnO, CeO_2, TiO_2, carbon nanotubes, etc.) induce genotoxicity in various plants (radish, onion,

Fig. 1.6 (continued) Hossain Z. 2013. Impact of nano-CuO stress on rice (*Oryza sativa* L.) seedlings. Chemosphere, 93, 906–91, Copyright (2013), with permission from Elsevier (Shaw and Hossain 2013). (**i**, **j**) Various aberrant features observed in *Allium cepa* after exposure to titanium dioxide nanoparticles: (**i**) chromosome break, (**j**) nuclear blebbing. Images (**i**–**j**) reprinted from Pakrashi S. et al., 2014. In Vivo Genotoxicity Assessment of Titanium Dioxide Nanoparticles by *Allium cepa* Root Tip Assay at High Exposure Concentrations. Plos One, 9, 12 (Pakrashi et al. 2014)

soybean, buckwheat, fava beans, ryegrass, tobacco, etc.) (Atha et al. 2012; Chichiricco and Poma 2015; Ghosh et al. 2015; Kumari et al. 2009, 2011; Lee et al. 2013; Lopez-Moreno et al. 2010a; Pakrashi et al. 2014; Patlolla et al. 2012; Shaymurat et al. 2012; Burklew et al. 2012). The plants with inhibited roots displayed errors in cell division, chromosomal abnormalities, microRNA deregulation, and DNA damage.

1.5.5 Nanoparticle Transgenerational Effects in Plants

As shown previously, nanoparticles can accumulate in plants within various tissues, such as leafs, roots, fruits, and seeds. Nanoparticle uptake in seeds has been shown to cause transgenerational effects in some plants (Lin et al. 2009; Wang et al. 2013b). These studies raise the questions if other nanoparticles might cause long-term multigenerational effects in plants.

Nanoparticles can be transmitted to plant progenies through seeds, in the absence of external nanoparticle exposure. For example, C_{70} can be found in second-generation rice plants (Lin et al. 2009). Seeds harvested from plants exposed to C_{70} were planted in a media free of C_{70} nanoparticles. The germinated rice plants (second-generation plants) were found to contain C_{70} black aggregates near the stem's vascular system and in leaf tissue.

Some authors found that ceria nanoparticles might have a beneficial effect on some plants. Exposure to ceria nanoparticles had a minor beneficial effect on first-generation seedlings and, however, had a detrimental effect on the growth of second-generation plants (Wang et al. 2013b). Second-generation tomato plants grown from seeds harvested from parent plants exposed to ceria nanoparticles were weaker and had a lower biomass, lower water transpiration, and a higher reactive oxygen species amount (Fig. 1.7).

1.6 Beneficial Effects of Nanoparticles in Plants

Nanoparticles can influence plant phenotype, some plants will be negatively affected, others will show beneficial effects, while others will show no response.

Some nanoparticles are used for their beneficial effects as crop enhancers or/and inhibiting plant pathogens. Several reviews report positive effects of some nanoparticles as crop enhancers in selected plant species, such as enhanced seed germination, crop yield, improved photosynthesis, increased resistance against stress, and suppressed plant disease (Rico et al. 2011; Du et al. 2017; Siddiqi and Husen 2017; Rizwan et al. 2017; Ruttkay-Nedecky et al. 2017; Gardea-Torresdey et al. 2014; Zuverza-Mena et al. 2017; Wang et al. 2016; Khan et al. 2017; Arruda et al. 2015). The composition of nanoparticles that show beneficial effects includes Au, Pd, Cu, Si, CeO_2, TiO_2, Fe_2O_3, MWCNTs, and fullerol $C_{60}(OH)_{20}$ (Arruda et al. 2015; Chichiricco and Poma 2015; Siddiqui and Al-Whaibi 2014; Zheng et al. 2005).

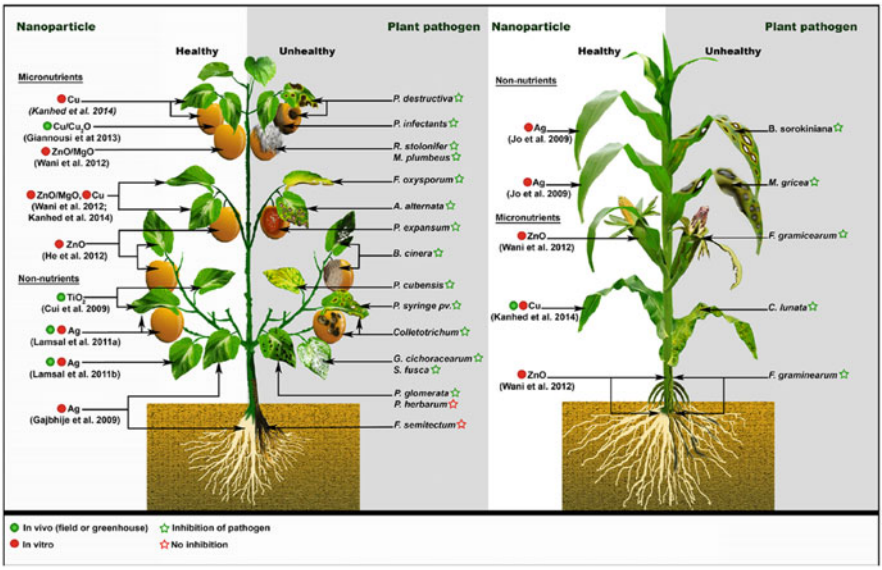

Fig. 1.7 Effect of nanoparticle used as micronutrients (left) and non-nutrients (right) on crop disease. Reproduced from Journal of Nanoparticle Research, A review of the use of engineered nanomaterials to suppress plant disease and enhance crop yield, Servin A. et al, vol. 17, 2015. Copyright (2015) with permission of Springer (Servin et al. 2015)

While some authors chose to focus mainly on the positive aspects of nanoparticle in plants, promoting their use as plant growth enhancers (Servin et al. 2015; Khodakovskaya et al. 2012, 2013; Lahiani et al. 2013; Lyu et al. 2017), it is difficult to predict what is the effect of nanoparticle progressive accumulation in soil. Here we must mention hormesis, which describes a beneficial effect for a low-dose agent, while a higher dose is toxic or inhibits growth.

Nanoparticles with selected compositions have been shown to inhibit plant pathogens as a result of their antimicrobial properties (Servin et al. 2015). Examples of pathogen inhibitor nanoparticles are Ag (Lamsal et al. 2011b; Gajbhiye et al. 2009), Cu (Giannousi et al. 2013; Kanhed et al. 2014), ZnO (Wani and Shah 2012; He et al. 2011), MgO (Wani and Shah 2012), and TiO_2 (Cui et al. 2009).

MWCNTs Several authors describe the positive effects of MWCNTs related to increased germination of tomato, barley, soybean, and corn and increased growth of tobacco cells (Khodakovskaya et al. 2009; 2011, 2012, 2013; Lahiani et al. 2013; Alexandru et al. 2012).

MWCNT exposure leads to enhanced germination and growth of tomato seedlings (Khodakovskaya et al. 2009, 2011) and enhanced flowering and fruit yield for tomato plants (Khodakovskaya et al. 2013). Raman spectroscopy detected MWCNT nanoparticles in the fruits of tomato plants (Khodakovskaya et al. 2011), which raises questions about the safety of their consumption. The presence of these

nanoparticles in the edible parts of plants together with the increased evidence of their toxicity in humans should not justify their use for increased flowering and fruit yield.

MWCNTs penetrate tomato seeds and increase their germination and growth rates compared to control (Khodakovskaya et al. 2009). The exposure of tomato plants to MWCNTs results in significant changes in total gene expression in leaves and roots (Khodakovskaya et al. 2011). The enhanced germination and growth of tomato plants are due to the upregulation of the stress-related genes, such as those induced by pathogens and water-channel LeAqp2 gene (Khodakovskaya et al. 2011). There are a large number of altered genes with various functions in the leaves of first-generation plants exposed to MWCNTs: 29 genes involved in cellular responses, 39 genes in stress response, 14 genes in transport, 13 genes in signal transduction, and 25 genes in metabolic processes. Similarly, there are a large number of genes in the roots: 19 genes involved in stress responses, 9 genes in cellular processes, 6 genes in transport, and 22 genes related to catabolic, metabolic, and biosynthetic processes.

The biochemical mechanism of MWCNT hormesis in plants is not yet understood. Cell culture experiments indicated that small concentrations (5 μg/ml) of MWCNTs lead to an augmented growth of tobacco cell, while higher concentrations (100–500 μg/ml) showed the opposite effect (inhibited cell growth) (Khodakovskaya et al. 2012).

Some authors studied the effects of CNTs on crops (such as corn, barley, soybean) and observed that they lead to accelerated seed germination also concluding that they have no negative effect on the biological endpoints showing the development of plants grown from the exposed seeds (Lahiani et al. 2013).

One must emphasize that while beneficial effects of nanoparticles were reported for first-generation plants, the nanoparticles accumulated in the seeds might be detrimental to second-generation plants (Wang et al. 2013b).

One must remind that the beneficial effects of carbon nanotubes are plant species specific. While CNTs might be beneficial for tomato plants, they inhibit the growth of red spinach, lettuce, cucumber, and rice in a dose-dependent manner (Begum and Fugetsu 2012; Begum et al. 2012, 2014).

In addition, taking into account their similarities to asbestos, CNTs are believed to have comparable toxicity to humans (Stella 2011).

C60 Fullerenes The use of C60-based nanoparticles in the growth of bitter melon was reported to increase biomass, water content, and fruit yield (Kole et al. 2013). The authors show that C60 nanoparticles biodistribute to petioles, leaves, flowers, and fruits. Again, the accumulation of nanoparticles in the edible part poses risks for human exposure to this nanoparticle.

Au, Pd, Si, and Cu Nanoparticles Low concentration of nanoparticles made of Au and Pd and higher concentrations of Si and Cu nanoparticles were found to increase the shoot ratio for lettuce after 15 days of incubation (Shah and Belozerova 2009). Nanoparticles with these compositions are shown to be toxic to humans and animals.

Ag Silver nanoparticles are used in agriculture for their bactericidal effects. Silver nanoparticles in small concentrations (30 μg/ml) accelerated root growth in rice plants while just doubling the concentration inhibited root growth (Mirzajani et al. 2013). Silver nanoparticles were shown to enter cell wall, damaged cells and produce reactive oxygen species.

TiO_2 Titania nanoparticles had some beneficial effects on seeds, especially those with low germination (Zheng et al. 2005; Feizi et al. 2013). Some authors believe that the induction of reactive oxygen species by nanoparticles results in subsequent enhancement of stress resistance and facilitation of seed penetration of water and oxygen (Khot et al. 2012).

Spinach exposed to titania nanoparticles shows increased plant dry weight, chlorophyll, and photosynthetic rate (Zheng et al. 2005).

Another example of hormesis is titanium dioxide in fennel plants. Titania nanoparticles were found to increase fennel seed germination, while larger particles lowered by 50% the shoot biomass compared to the control (Feizi et al. 2013). This fact is important as small nanoparticles can aggregate into larger particles, which can in turn become phytotoxic to the same plant species.

It seems that increased root length is an adaptation process of roots clogged with nanoparticles (Asli and Neumann 2009). Titania nanoparticles are shown to accumulate in roots and block pores in hydroponic maize treated with nanoparticles. As a result, the plants have lower water supply, leaf growth, and transpiration rate (Asli and Neumann 2009). In order to survive, the maize plant adapts by forming a larger root system.

Rare Earth Rare-earth additives are used in fertilizers for their promotion of larger yields, longer rots, darker green foliage, and better fruit color (Yuan et al. 2001).

1.7 Nanoparticle Toxicity in Humans and Animals

Unfortunately, many of the nanoparticles that have some agricultural benefits, including those shown to be internalized by crops, have varying degrees of toxicity in humans and laboratory animals. A multitude of reviews discuss the topic of nanoparticle toxicity in humans and animals (Buzea et al. 2007; Ema et al. 2016, 2017; Sohaebuddin et al. 2010; Kendall and Holgate 2012; He et al. 2017; Shah et al. 2015).

While the discipline of nanotoxicology is a fairly new, some older epidemiological studies give a plethora of information on environmental nanoparticle (particulate matter) toxicity on humans. What makes nanoparticles toxic is their size and, as a result, their ability to enter organisms; enter circulatory system; translocate to organs, such as the liver, spleen, kidneys, brain, and heart; enter cells; and go further into organelles (Buzea et al. 2007). They are able to be internalized, depending on their entry and size, within several minutes to several hours following exposure (see Fig. 1.8d) (Nemmar et al. 2002). Once inside cells and organelles, they produce

cytotoxicity and genotoxicity. They are associated to inflammation and various diseases, including cancer. In the following we will give examples of such adverse effects of nanoparticles on humans. While our examples are not comprehensive, we expect to be compelling and inform the scientists planning to use nanoparticles in agriculture of the potential adverse effects on humans, including themselves.

1.7.1 Nanoparticle Physicochemical Characteristic-Dependent Toxicity

Nanoparticle toxicity depends on their physical and chemical properties, such as size, aggregation, composition, concentration, shape, porosity, surface area, hydrophobicity, electrical charge, and magnetic properties (Buzea et al. 2007; Podila and Brown 2013; Silva et al. 2014, 2015; Hanley et al. 2009; Chithrani et al. 2006; Naqvi et al. 2010; Schlinkert et al. 2015; Sharma et al. 2014; Li et al. 2015b; Teske and Detweiler 2015). A schematic illustrating this idea is given in Fig. 1.2.

There is no universal law for determining the toxicity of nanoparticles, which cannot be extrapolated from the behavior of the bulk material. Each type of nanoparticles has to be tested in order to assess its toxicity. Nanoparticles of the same material can have different toxicities for different sizes, surface functionalization, or surface charge. Nanoparticles with the same size but made of different materials will also have different toxicities.

Usually nanoparticles with smaller size have higher toxicity than larger ones (Buzea et al. 2007).

Nanoparticles with the same composition but different crystalline form can exhibit different properties and toxicity, such as titanium dioxide in rutile and anatase forms. Rutile titania 200 nm in size induced oxidative DNA damage and other cytotoxic effects in human bronchial epithelial cell, while anatase titania did not (Gurr et al. 2005).

Some nanoparticles are hydrophobic, while others are hydrophilic (Garcia-Ivars et al. 2015). This property can be modulated by coating of nanoparticles of various substances (Podila and Brown 2013). For example, coating with polyethylene glycol (PEG) renders nanoparticles highly hydrophilic (Kettler et al. 2014).

Nanoparticles can have positive, negative, or neutral charge. Nanoparticle surface charge is very important in deciding how a nanoparticle interacts with biological systems (Gatoo et al. 2014; Salatin et al. 2015). Positively charged nanoparticles are attracted to the negatively charged cell membrane and have a higher cellular uptake versus negatively charged or neutral nanoparticles (Kettler et al. 2014). Nanoparticle toxicity depends on whether or not nanoparticles are internalized within cells. For example, cationic gold nanoparticles are toxic, while anionic nanoparticles are nontoxic (Goodman et al. 2004). Studies also show that nanoparticles with large surface charge, either negative or positive, show an increased receptor-mediated endocytic uptake of nanoparticle compared to neutral nanoparticles (Kettler et al. 2014).

1.7.2 Nanoparticle Internalization and Biodistribution

1.7.2.1 Inhalation, Ingestion, and Dermal Exposure

Due to their minute size, nanoparticles can be inhaled and ingested or penetrate through the skin. From the respiratory and gastrointestinal systems, they can rapidly enter blood and lymphatic system (Landsiedel et al. 2012).

Numerous studies indicate that inhaled nanoparticles accumulate in lungs, and some nanoparticles, depending on their size and other physicochemical properties, can reach the alveoli, translocate to organs, and become systemic. They can be found in the circulatory system and lymphatic system and in the brain, heart, thyroid, liver, spleen, colon, bones, and kidney (Anderson et al. 2015; Bakand et al. 2012; Bruinink et al. 2015; Buzea et al. 2007; Davidson et al. 2015; Fischer and Chan 2007; Geiser and Kreyling 2010; Gosens et al. 2014, 2015; Khlebtsov and Dykman 2011, Johnston et al. 2010; Lin et al. 2015; Landsiedel et al. 2012; Nakane 2012; Theodorou et al. 2014).

From lungs, nanoparticles can go further to the circulatory system. Nanoparticles with various compositions have been collected from the blood of patients with various diseases (Gatti and Montanari 2006). In the circulatory system, they interact with plasma and form a protein corona that will determine their toxicity and translocation. Next, nanoparticles move to and accumulate in various organs and tissues: the liver, spleen, pancreas, heart, kidneys, brain, lymph nodes, bone marrow, etc. (Landsiedel et al. 2012; Sonavane et al. 2008). The smaller the nanoparticles, the greater their accumulation in tissues (Sonavane et al. 2008).

Ingested nanoparticles that enter the gastrointestinal tract are partly excreted in feces, and some are absorbed and become systemically available (Hillyer and Albrecht 2001).

The site of accumulation in the body depends on the composition and surface functionalization of the nanoparticles. Metallic nanoparticles usually localize in the liver, spleen, and lymph node (Lin et al. 2015; Johnston et al. 2010).

Nanoparticles are able to cross the placental barrier, reach fetus, and have adverse effects on pregnancy and fetuses, as shown by in vivo and ex vivo studies on animals (Kulvietis et al. 2011; Wick et al. 2010; Semmler-Behnke et al. 2014; Snyder et al. 2015; Melnik et al. 2013; Yamashita et al. 2011).

1.7.2.2 Nanoparticle Persistence and Disease

Nanoparticles can persist in the body for longer than 6 months (Lin et al. 2015). Long-term residence of nanoparticles in the body will produce tissue injuries and inflammation which is the precursor to cancer and other diseases. The residence of metallic nanoparticles within a tissue favors tumorigenesis (Sighinolfi et al. 2016). Indeed, recent studies indicate that nanoparticles accumulate in tissue of patients with various diseases, such as deep-vein thrombosis, pulmonary embolism, colon cancer, prostate cancer, stroke, asthma, emphysema, lung cancer, Crohn's disease, ulcerative colitis, liver necrosis, renal failure, and Hodgkin's lymphoma (Gatti 2004; Gatti and Montanari 2006; Gatti and Rivasi 2002; Roncati et al. 2015a, b; Ballestri et al. 2001; Iannitti et al. 2010).

Figure 1.8a–c shows nanoparticles persistent in the lungs that are likely to be the cause of the disease observed in the respective subjects. Figure 1.8a shows images of MWCNTs inside lung cells and in the bronchoalveolar lavage fluids of asthmatic children living in Paris (Kolosnjaj-Tabi et al. 2015). The carbon nanotubes found inside the lungs of asthmatic children are very similar in morphology and shape to those from Fig. 1.8b, which shows MWCNTs from vehicle exhausts and from pollution dust collected near a busy traffic intersection in Paris. Figure 1.8c shows black carbon deposits inside the lung of a patient diagnosed with emphysema, which are likely to be the cause of his emphysema. Figure 1.8d illustrates very fast internalization of inhaled ^{99m}Tc-labeled carbon nanoparticles in a human volunteer, nanoparticles being detected within 5–60 min of exposure (Nemmar et al. 2002).

In some of the following paragraphs, we will discuss in more detail various diseases associated to nanoparticle exposure.

1.7.2.3 Nanoparticle Size-Dependent Accumulation

Experiments on mice with orally ingested gold nanoparticles having size between 4 and 28 nm show translocation to the blood, brain, lung, heart, kidney, spleen, liver, small intestine, and stomach, while nanoparticles with larger size (58 nm) were not detected in most studied tissue (Hillyer and Albrecht 2001).

Inhaled nanoparticles smaller than 50–100 nm can travel to and accumulate in the brain, through olfactory nerves and blood-brain barrier (Buzea et al. 2007; Lin et al. 2015; Sonavane et al. 2008).

The maximum size of nanoparticles that can enter and be cleared from the body is between 200 and 250 nm (Bruinink et al. 2015). If nanoparticles existent in tissues aggregate in complexes with larger size, their clearance becomes less likely. Consequently, long-term exposure to small amounts of nanoparticles can lead to adverse health effects due to their accumulation without clearance.

Experiments on human volunteers show fast internalization and long-term persistence of gold nanoparticles in humans (Miller et al. 2017). Within 15 min following inhalation, gold nanoparticles are detected in the blood of human volunteers. They can persist 3 months following inhalation exposure. Smaller nanoparticles (5 nm diameter) are more persistent than the larger ones (30 nm).

1.7.2.4 Nanoparticle Corona

When in contact with organic matter, nanoparticles will interact dynamically with biomolecules via electrostatic and van der Waals forces (Kumar et al. 2014). This interaction will result in acquiring a corona formed of biomolecules, which will determine their subsequent interaction with cells and tissue/organ accumulation (Grillo et al. 2015; Khlebtsov and Dykman 2011). This corona will dictate the degree of nanoparticle toxicity in addition to the intrinsic properties of the nanoparticle (Foroozandeh and Aziz 2015). There are cases when nanoparticle corona might be more important than the intrinsic physical properties of a nanoparticle in deciding its toxicity (Walkey et al. 2014). In general, nanoparticle physicochemical properties determine to some extent the composition of its corona together with the composition of the biological environment (Kreyling et al. 2014). It is believed that the

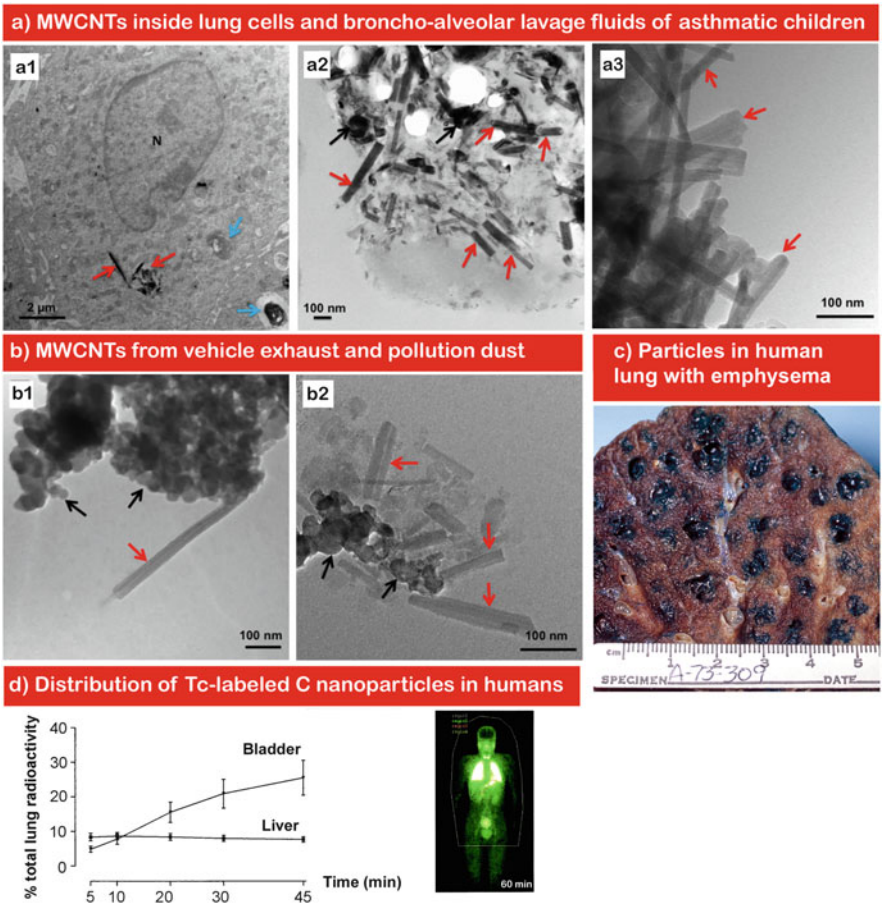

Fig. 1.8 High-resolution TEM images showing MWCNTs inside lung cells (**a1**) and in the bronchoalveolar lavage fluids (**a2**–**a3**) of asthmatic children together with MWCNTs from vehicle exhausts (**b1**) and pollution dust collected near a busy traffic intersection in Paris (**b2**). N indicates nucleus; blue arrows, lamellar bodies; black arrows, nanospheres; red arrows, MWCNTs. Image (**a2**) is a magnified view of (**a1**). Image (**b2**) is a magnified view of (**b1**). Reprinted from Kolosnja-Tabi J. et al., Ebiomedicine, vol. 2, Anthropogenic Carbon Nanotubes Found in the Airways of Parisian Children, pp. 1697–1704, Copyright (2015), with permission from Elsevier (Kolosnjaj-Tabi et al. 2015). (**c**) Pathology of lung with centrilobular emphysema with multiple cavities heavily lined by black carbon deposits. Courtesy of Dr. Edwin P. Ewing, Jr., http://phil.cdc.gov/phil_images/20040517/4/865_lores.jpg. (**d**) (left) Radioactivity on the bladder and liver compared to lungs versus time of exposure to ^{99m}Tc-labeled carbon nanoparticles in humans. (Right) Radioactivity in the body of a human volunteer after 1 h of exposure to ^{99m}Tc-labeled carbon nanoparticles. Image reproduced from Nemmar A. et al., Passage of inhaled particles into the blood circulation in humans. Circulation, vol. 105, pp. 411–414. Copyright (2002) American Heart Association, Inc. with permission of Wolters Kluwer Health, Inc. (Nemmar et al. 2002)

existence of a corona, with its overall negative charge, will diminish nanoparticle toxicity due to a reduced interaction with the negatively charged cell wall (Docter et al. 2015). On the other side, nanoparticles with a positive charge (without a corona), being electrostatically attracted to the negatively charged cell membrane, will have an increased cellular uptake.

1.7.2.5 Nanoparticle Uptake by Cells

Depending on their physicochemical properties, nanoparticles can be internalized by cells and locate within various organelles, cytoplasm, mitochondria, nucleus, lysosomes, endoplasmic reticulum, etc. (Singh et al. 2010; Huk et al. 2015; Sathuluri et al. 2011). The cellular uptake of nanoparticles is also cell specific and depends on the experimental conditions (Kettler et al. 2014). Cell internalization of nanoparticles usually results in cytotoxicity. Inside the cells, nanoparticles have been observed to affect cellular processes; produce reactive oxygen species, DNA damage, and epigenetic changes; and even cause cell death (Gatoo et al. 2014; Karlsson et al. 2008; Stoccoro et al. 2013). Nanoparticles can be genotoxic simply by their direct interaction with the genetic material or due to generating reacting oxygen species (Tortiglione 2014).

1.7.3 Nanoparticle Association to Respiratory Diseases

Epidemiological studies indicate that exposure to particulate pollution is associated with different respiratory diseases, such as chronic obstructive pulmonary disease (COPD), respiratory infections, lung cancer, and asthma (Mannucci et al. 2015; Rückerl et al. 2011). For each 10 $\mu g/m^3$ increase in particulate pollution, there is a 2.5% increase in hospital admissions of patients with COPD (Mannucci et al. 2015). Children exposed to air pollution have more respiratory tract infections and asthma episodes. Figure 1.8 shows nanoparticles accumulated in the lung of subjects with asthma and emphysema.

Nanoparticles with composition of iron, manganese, and chromium were found in the lungs of welders suffering from various respiratory diseases (Andujar et al. 2014). Welders that are exposed to welding fumes for a long time have higher incidence of high blood pressure (Li et al. 2015a; Xu et al. 2017).

1.7.4 Nanoparticle Association to Cardiovascular Diseases

In vivo, in vitro, and epidemiological studies show that exposure to nanoparticles of various compositions is associated to cardiovascular diseases (Franklin et al. 2015; Yu et al. 2016; Savi et al. 2014; Cosselman et al. 2015; Rückerl et al. 2011). Epidemiological studies show a relationship between particulate pollution and a gamut of cardiovascular diseases. Among them are blood clot formation, pulmonary embolism, increased blood pressure, atherosclerosis, arrhythmia, ischemic heart disease, myocardial infarction, and heart failure; stroke and stroke mortality correlate

to particulate pollution in a dose-dependent manner (Mannucci et al. 2015; Cosselman et al. 2015; Shah et al. 2015; Yu et al. 2016).

The composition of nanoparticles that are associated to adverse cardiovascular effects includes, but is not limited to, titanium dioxide, silver, silicon, silica, carbon black, carbon nanotubes, zinc oxide, etc. (Many of these nanoparticles are promoted for their use in agriculture due to some benefits on selected plants.)

Nanoparticles of metal oxide produce clotting irrespective of their charge (Steuer et al. 2014). Studies show that environmental nanoparticles are associated with an increased risk of thrombotic complications that lead to an increased and worse prognosis of cardiovascular events (Ilinskaya and Dobrovolskaia 2013).

Nanoparticles are found in biopsies and various human specimens of diseased tissue or collected from the blood of patients with various diseases (Gatti 2004; Gatti and Montanari 2006; Gatti and Rivasi 2002; Bitounis et al. 2016; Rinaldo et al. 2015; Ballestri et al. 2001). Nanoparticles tend to accumulate at the site of vascular lesions (Miller et al. 2017).

Figure 1.9a shows microscopy images of nanoparticles found in blood clots collected from diseased patients by using a vena cava filter (Gatti and Montanari 2006). With the help of environmental scanning electron microscopy (ESEM) and energy-dispersive spectroscopy (EDS), nanoparticles and their composition are identified in thrombi and fibrotic tissue taken from patients at risk of developing deep-vein thrombosis or to prevent pulmonary embolisms in potentially relapsing patients (Gatti et al. 2005; Gatti and Montanari 2006). The composition of micro- and nanoparticles collected from the tissue of the patients had various compositions, such as Fe, Cr, Cu, W, and Al. It is likely that the particles within the thrombi are the sole cause for thrombosis (Gatti et al. 2005).

Nanoparticles from automobile exhaust pollution lead to adverse cardiovascular effects which can occur as fast as within a few hours in the case of acute exposure, or within a few years for chronic exposure (Donaldson et al. 2013). Living near highway is associated with increased risk of high blood pressure (Chung et al. 2015).

Each 10 $\mu g/m^3$ increased in particulate pollution is associated with a 21% increase in fatal and nonfatal coronary artery disease according to an epidemiological study in more than 65,000 postmenopausal US women (Mannucci et al. 2015). An increase in the levels of particulate matter of 10 $\mu g/m^3$ results in a 35–85% increase in nonfatal and fatal strokes for population suffering a long-term exposure to particulate pollution (Mannucci et al. 2015).

Particulate pollution is also associated to higher mortality due to cardiovascular and respiratory events (Cohen et al. 2017; Chen et al. 2012; Brook 2008). The segment of population exposed to particulate pollution has a lower life expectancy, the life span being reduced by several months to several years (Brook 2008).

High concentration of particulate pollution is associated with increased hospital admission, stroke, acute myocardial infarction, and mortality (Shah et al. 2015). Even small increases in particulate pollution were associated with a large (19%) increase for developing cerebrovascular disease (ischemic and hemorrhagic) (Shah et al. 2015).

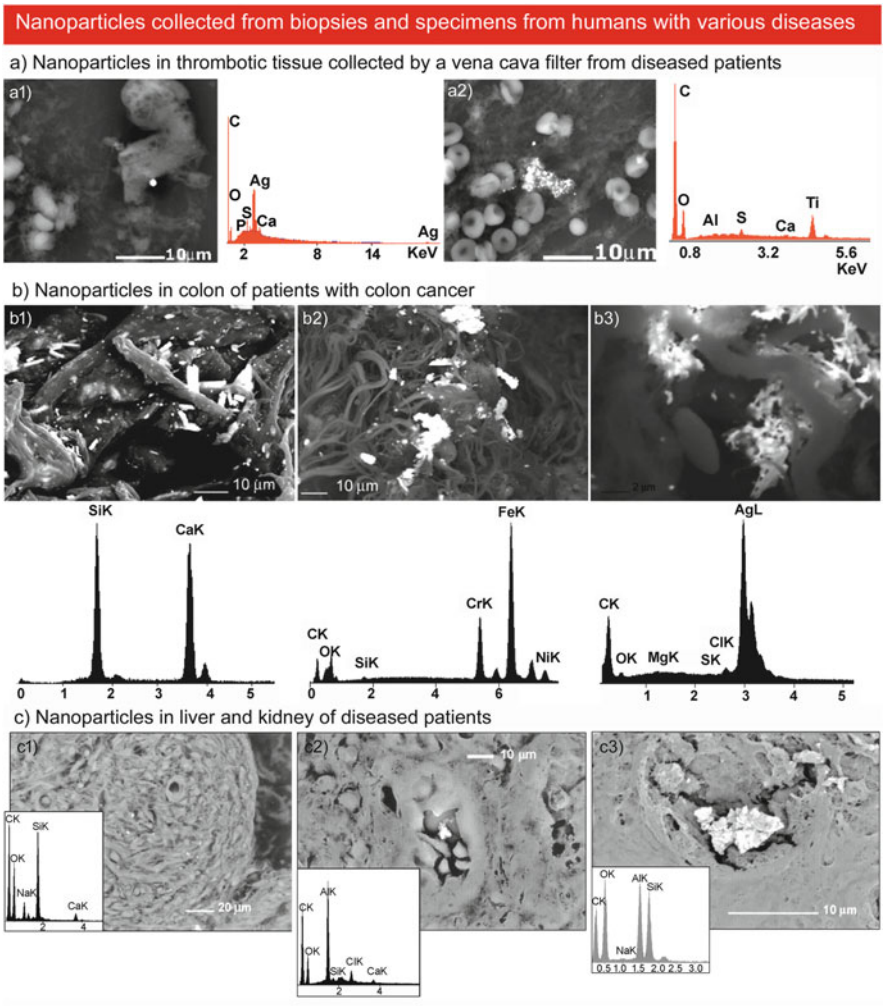

Fig. 1.9 Scanning electron microscope (SEM) images of nanoparticles observed in the blood, colon, liver, and kidney biopsies of patients with various diseases together with their EDS spectra indicating their compositions. (**A**) Nanoparticles in thrombotic tissues collected from diseased patients by using a vena cava filter; (a1) SEM image shows thrombus containing nanoparticle with the composition of Ag, S, and O; (a2) SEM image of red blood cells with a cluster of nanoparticles having the composition: Ti, O, and. Images (a1) and (a2) are reprinted from Gatti A. M. & Montanari S., Journal of Biomedical Materials Research Part B-Applied Biomaterials 77B (2006) 307, with permission from John Wiley & Sons, Inc. (Gatti and Montanari 2006). (**B**) SEM images showing nanoparticles with different compositions in the colon of patients with various diseases. Upper side shows the electron microscopy image and bottom the EDS spectrum indicating the composition of the nanoparticles; (b1) nanoparticles of calcium and silicon in the colon of a patient with adenocarcinoma; (b2) nanoparticles of stainless steel (Fe, Cr, Ni) in the colon of a patient with adenocarcinoma; (b3) nanoparticles of Ag in the colon of a patient with colon cancer. Images (b1), (b2), and (b3) are reprinted from Biomaterials, vol. 25, Gatti A. M., Biocompatibility of micro- and nano-particles in the colon. Part II., pp. 385–392, Copyright (2004), with permission from Elsevier (Gatti 2004). (**C**) SEM images of the liver and kidneys from diseased patients together with inset showing the EDS spectrum indicating the composition of nanoparticles;

1.7.5 Nanoparticles in the Central Nervous System

Increasing evidence show that nanoparticles can reach and accumulate in the brain and are associated to neurotoxicity (Cupaioli et al. 2014; Buzea et al. 2007; Song et al. 2015; Hillyer and Albrecht 2001; Wang et al. 2017; Heusinkveld et al. 2016; Maher et al. 2016). In vitro, in vivo, and epidemiological studies relate nanoparticle exposure to neuro-inflammation and neurodegenerative disease, nanoparticles being involved in oxidative stress, inflammation, and impaired activity of cellular organelles. It is believed that the accumulation of nanoparticles in the brain may accelerate the appearance of neurodegenerative diseases (Wang et al. 2017).

Animal Experiments In vivo experiments show that titania nanoparticle-exposed rodents suffer impaired ability of recognition, spatial memory, and learning (Song et al. 2015).

Occupational Exposure Manganese nanoparticles generated during welding and mining operations are associated with increased risk of neurological diseases in miners and welders (Buzea et al. 2007). For example, some welders develop Parkinson's disease in their mid-1940s, while the general population is affected by this disease at around 60 years of age.

Environmental Nanoparticle Pollution Environmental nanoparticles are linked to neurodegenerative disease, such as Alzheimer's disease, Parkinson's disease, and dementia (Calderon-Garciduenas et al. 2016a, b; Gonzalez-Maciel et al. 2017; Chin-Chan et al. 2015).

A recent study showed that pollution nanoparticles are able to translocate to the brain of adults and children living in a polluted environment, can enter cells and organelles, and produce neurotoxicity and cellular damage (Gonzalez-Maciel et al. 2017). Spherical incomplete combustion nanoparticles (29 nm size) have been observed in the neurons, endothelium, nasal, and olfactory epithelium of Mexico City residents that suffered accidental deaths. They were found at sites with abnormal mitochondria, vascular damage in the prefrontal white matter, and other disease pathologies. Samples from control residents living in less polluted environment had intact mitochondria usually with no nanoparticles, compared to those from Mexico City residents that had numerous abnormal mitochondria containing nanoparticles (Gonzalez-Maciel et al. 2017).

Children and adults residing in polluted environments show neuropathological traits of neurodegenerative disease, such as amyloid-beta diffuse plaques and tau

Fig. 1.9 (continued) (c1) liver section with giant-cell granuloma showing nanoparticles with composition of Si, Na, Al, Mg, Ca, O, and C; (c2) kidney granuloma with ceramic nanoparticles; (c3) kidney granuloma with an alumina particle. Images (c1), (c2), and (c3) are reprinted from Biomaterials, vol. 23, Gatti A. M. & Rivasi F., Biocompatibility of micro- and nanoparticles. Part I: in liver and kidney, pp. 2381–2387, Copyright (2002), with permission from Elsevier (Gatti and Rivasi 2002)

hyper-phosphorylation with pre-tangle disease (Calderon-Garciduenas et al. 2016a). Nanoparticles are present inside cells and organelles with abnormal pathologies of adults and children exposed to high concentrations of pollutant nanoparticles (residents of Mexico City) (Calderon-Garciduenas et al. 2016b; Gonzalez-Maciel et al. 2017).

A population-based cohort study of all Ontario adults between 2001 and 2012 found that living closer than 300 m from heavy traffic was associated with a higher incidence of dementia as opposed to those living further away than 300 m (Chen et al. 2017). In addition, dementia involved predominantly urban residents versus rural residents, with urban environments being known to have a higher concentration of particulate matter pollutants than rural ones.

Proof of nanoparticle internalization by human brain tissue is shown in Figs. 1.10a–b). Figure 1.10a shows nanoparticles of iron oxide, silica, and titania inside human cerebral endothelial cells (HCEC) (Kenzaoui et al. 2012).

Figure 1.10b shows nanoparticles in the prefrontal white matter of children living in Mexico City that were exposed to high concentrations of particulate pollution. Nanoparticles were internalized inside (b1) a red blood cell (RBC), (b2) mitochondria, (b3) and a degenerating myelinated axon (Calderon-Garciduenas et al. 2016b).

1.7.6 Nanoparticle Toxicity Following Maternal Exposure

Nanoparticles with different compositions and sizes can be transmitted from mother to offspring through the placental barrier or through milk (Muoth et al. 2016; Ema et al. 2016, 2017; Kulvietis et al. 2011; Melnik et al. 2013; Semmler-Behnke et al. 2014; Snyder et al. 2015; Wick et al. 2010; Yamashita et al. 2011). Rats exposed to titanium dioxide nanoparticle during gestation result in negative cardiovascular effects in progenies that last into adulthood (Hathaway et al. 2017). The potential mechanism of impaired functionality of the heart is believed to be related to mitochondrial dysfunction.

1.7.7 Nanoparticles in the Liver, Kidneys, and Other Organs

Systemically available nanoparticles larger than 6 nm locate mainly in the liver and spleen, and other reticular connective tissues (Lu and Gu 2017). Spleen localization is likely for nanoparticles with a diameter of 200–500 nm, comparable to the inter-endothelial slit. Liver fenestration size of ~100 nm allows accumulation of nanoparticles with smaller and comparable sizes, while the urinary system will eliminate those smaller than ~6 nm (Lu and Gu 2017; Landsiedel et al. 2012).

The long-term retention of nanoparticles in organs can be cytotoxic (Wang et al. 2013a). For example, 20 nm gold nanoparticles accumulate in the liver of rats and change the expression of gene expression involved in detoxification, lipid metabolism, and the cell cycle (Kermanizadeh et al. 2014). Silver nanoparticles with sizes of

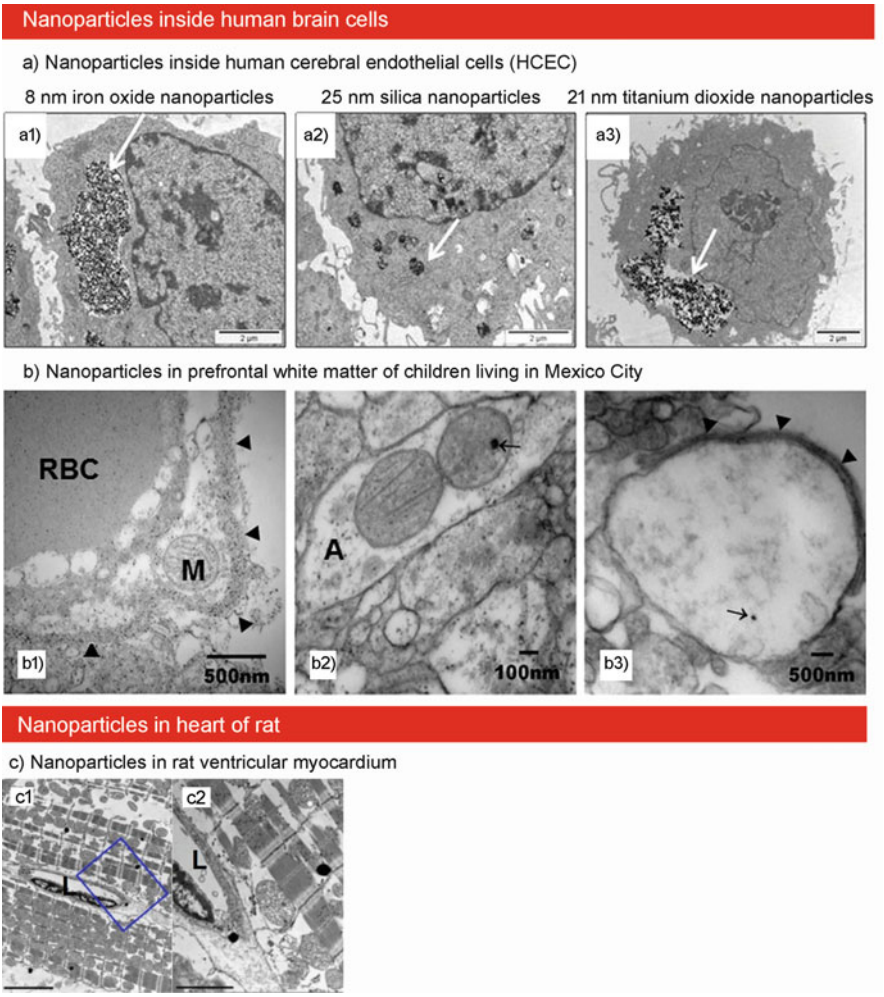

Fig. 1.10 Nanoparticles inside human brain cells. (**A**) Uptake of nanoparticles with various compositions by human cerebral endothelial cells (HCEC); (a1) 8 nm iron oxide, (a2) 25 nm silica, and (a3) 21 nm titanium dioxide nanoparticles. Reproduced from reference (Kenzaoui et al. 2012), courtesy of Portland Press. (**B**) Nanoparticles in the prefrontal white matter of children living in Mexico City and exposed to high concentrations of nanoparticulate pollution. (b1) Nanoparticles in a red blood cell (RBC), an endothelial cell mitochondria (M), and the basement membrane (arrowheads); (b2) one 30 nm diameter nanoparticle inside a mitochondria without cristae in a poorly preserved unmyelinated (short arrow); (b3) a nanoparticle (short arrow) inside a degenerating myelinated axon with remnants of myelin (arrowheads). Reprinted from Environmental Research, vol. 146, Calderon-Garciduenas L. et al., Prefrontal white matter pathology in air pollution exposed Mexico City young urbanites and their potential impact on neurovascular unit dysfunction and the development of Alzheimer's disease, pp. 404–417, Copyright (2016), with permission from Elsevier (Calderon-Garciduenas et al. 2016b). (**c**) Titanium dioxide nanoparticles in the rat ventricular myocardium after tracheal instillation. Nanoparticles are located in longitudinally oriented cardiomyocytes and in the wall of a vascular structure. Reprinted from (Savi et al. 2014) courtesy of Particle and Fibre Toxicology

20 nm can be found in the cytoplasm and nuclei of liver cells and upregulate pro-inflammatory genes (Kermanizadeh et al. 2014). Nanoparticles of copper and zinc oxide produce renal damage in mice (Wang et al. 2013a).

Nanoparticles of different materials have been found in the liver and kidneys of humans with different diseases (Gatti and Rivasi 2002). Some examples are illustrated in Fig. 1.9b–c where one can see nanoparticles in diseased tissue of the liver and kidneys (Gatti and Rivasi 2002).

Nanoparticles can be found in heart tissue as well. Titanium dioxide nanoparticles are internalized by heart cells following tracheal instillation of nanoparticles in rats (Savi et al. 2014). Figure 1.10c shows nanoparticles in the rat ventricular myocardium located in longitudinally oriented cardiomyocytes and in the wall of a vascular structure.

Nanoparticle exposure is also associated to diabetes, exacerbation of allergic diseases, and immune system disruption (Mannucci et al. 2015; Ilinskaya and Dobrovolskaia 2014).

A recent meta-analysis study found a positive association between particulate pollution and type 2 diabetes mellitus (He et al. 2017). In individuals suffering long-term exposure to particulate matter, for each 10 $\mu g/m^3$ increase in particulate concentration PM2.5, the risk of type 2 diabetes mellitus increases by 25% (He et al. 2017).

Nanoparticles with different compositions (Co, ZnO, TiO_2) are toxic to immune cells or immune system (Bregoli et al. 2009; Hanley et al. 2009; Andersson-Willman et al. 2012; Moon et al. 2011). When the immune system is deregulated, it can trigger the onset of cancer and autoimmune diseases (Ilinskaya and Dobrovolskaia 2014).

1.7.8 Toxicity of Nanoparticles with Various Compositions

In the following we will present information on the toxicity of nanoparticles with different compositions in humans and animals. Many of these nanoparticles are suggested to be beneficial agrichemicals.

1.7.8.1 Toxicity of Gold Nanoparticles

One might think that, just because bulk gold is chemically inert and biocompatible, gold nanoparticles should react very little and be biocompatible. Indeed, some gold nanoparticles can be chemically inert and have little or no toxicity depending on their size and surface functionalization. However, there is experimental evidence that indicates gold nanoparticles are toxic, the toxicity degree depending on their size and functionalization.

Gold Nanoparticle Magnetism The toxicity of gold nanoparticles might be related to the fact that when sufficiently small, gold in nanoform develops magnetic moments. Several materials at the nanoscale develop magnetic moments, while their bulk counterparts do not show magnetism (Pacheco and Buzea 2018). Gold in bulk form is diamagnetic—an external magnetic field will have a very weak effect

on it; after the removal of the field, the material will not show a magnetic moment. Decreasing the size of gold particles below 3 nm, they become ferromagnetic (Hori et al. 1999, 2004; Yamamoto et al. 2004; Maitra et al. 2011; Greget et al. 2012; Nealon et al. 2012). A similar phenomenon happens to platinum (Sakamoto et al. 2011) and palladium (Hori et al. 1999), these materials becoming magnetic in nanoform. Hence, gold nanoparticles smaller than 3 nm become magnetic, and their aggregation and chemical reactivity will differ from that of larger nanoparticles.

The magnetic behavior of nanoparticles can be modified by coating with various ligands (Krishna et al. 2014; Crespo et al. 2013). Gold nanoparticles of selected sizes can be made diamagnetic, paramagnetic, or ferromagnetic, just by changing surface ligand types (Krishna et al. 2014). In addition, gold surface functionalization can modify their electrical charge rendering them positively or negatively charged (Gerber et al. 2013; Cheng et al. 2013). The electromagnetic behavior of nanoparticles will influence their translocation and accumulation and hence their toxicity.

Accumulation Experiments demonstrated that intravenously administered gold nanoparticles accumulate in the liver, spleen, kidney, lung, brain, heart, thymus, skin, and testis (Johnston et al. 2010). For example, 8.5% of radiolabeled (1.4 nm size) gold nanoparticles are found in secondary targets, including the blood and liver of rats after 24 h of exposure (Semmler-Behnke et al. 2008). Gold nanoparticles administered via intravenous injection in pregnant rodents were detected in fetal tissue as soon as 2 h after exposure (Lin et al. 2015).

Mice injected intraperitoneally with gold nanoparticles with sizes 8–37 nm showed fatigue, loss of appetite, fur color changes, weight loss, camel-like back, and crooked spine; most of the mice died within 21 days (Chen et al. 2009). Gold nanoparticles with small size translocate from maternal blood into fetus as showed by experiments on rats (Semmler-Behnke et al. 2014).

Cytotoxicity The cytotoxicity to gold nanoparticles is cell specific and depends on their surface coating (Cheng et al. 2013; Schlinkert et al. 2015). Gold nanoparticles were found to be internalized by cells and, as a function of their surface functionalization, may locate in endosomes/lysosomes, mitochondria (Cheng et al. 2013), vacuoles (Khlebtsov and Dykman 2011), and nuclei (Ojea-Jimenez et al. 2012). In vivo cytotoxicity studies showed the presence of gold nanoparticles inside liver Kupffer cells and spleen macrophages accompanied by acute inflammation and apoptosis in the liver (Cho et al. 2009). Analysis of liver and spleen samples of rats exposed to gold nanoparticle via injection indicate gene expression changes in genes pertaining to detoxification, lipid metabolism, the cell cycle, defense response, and circadian rhythm (Balasubramanian et al. 2010).

Many experimental results suggest that in small enough concentrations, gold nanoparticles with sizes down to 3–5 nm are not toxic; however, smaller nanoparticles may be cytotoxic due to their irreversible binding to biomolecules such as DNA (Khlebtsov and Dykman 2011). This fact could be explained by the newly acquired magnetic behavior of very small gold nanoparticles (Pacheco and

Buzea 2018). Some in vitro genotoxicity studies indicate that gold nanoparticles may induce DNA strand break and chromosomal damage via oxidative stress in some mammalian cells (Li et al. 2011; Hadrup et al. 2015).

Charge-Dependent Cytotoxicity Cytotoxicity studies of gold with different surface properties on Cos-1 cells (kidney fibroblasts from the African monkey) indicate that cationic nanoparticles are several times more toxic than anionic ones (Khlebtsov and Dykman 2011). Study on other four cell lines (HeLa, Sk-Mel-28, L929, J774A1) shows that 1.4 nm nanoparticles cause cell necrosis 12 h after exposure, while 1.2 nm gold nanoparticles caused apoptosis (Khlebtsov and Dykman 2011).

1.7.8.2 Toxicity of Silver Nanoparticles

Silver nanoparticles are promoted as agrichemicals due to their broad-spectrum antimicrobial properties (Cox et al. 2016; Anjum et al. 2013; Jo et al. 2009; Lamsal et al. 2011a). However, silver in nanoform is found to be toxic to humans and animals.

Due to its antibacterial properties, silver is used in wound dressing (Marx and Barillo 2014). Sometimes overexposure of humans to silver from drugs or wound dressing leads to a condition called argyria, where the skin has a blue-gray discoloration, being accompanied by liver toxicity (Hadrup and Lam 2014; Christensen et al. 2010).

Accumulation Experiments on mice show that following silver nanoparticle inhalation, ingestion, and injection, they accumulate in the blood, stomach, liver, spleen, kidney, lung, brain, heart, and testis (Johnston et al. 2010; Gaillet and Rouanet 2015). Inhaled silver nanoparticles have a long residence time in the lung, about a third being still found in the lungs 2 months after exposure, as indicated by in vivo studies in rats (Anderson et al. 2015). Studies on animals showed that radioactive isotope-labeled silver nanoparticles with size of 35 nm can be passed through the placenta to fetuses and can be passed from mother to infants from breast milk (Melnik et al. 2013).

Toxicity Animal studies show that silver is toxic to animals resulting in immune system effects, enlarged heart, weight loss, pulmonary toxicity, changes in liver enzymes and blood biochemistry, and liver damage (Ahlberg et al. 2014; Gaillet and Rouanet 2015; Hadrup and Lam 2014; Kim et al. 2008). Silver nanoparticles accumulated in immune system organs are accompanied by damage in the liver, kidneys, thymus, and spleen, and possible genotoxicity due to chromosomal breakage (Wen et al. 2017). Experiments also indicated that silver nanoparticles might have a toxic effect on myocardial electrophysiology and induce lethal bradyarrhythmias in mice (Lin et al. 2017). They produce cardiac dysfunction and genotoxicity in chicken, heart malformation in fish, and thrombus formation in rats (Yu et al. 2016). A low concentration of silver nanoparticles with size of 45 nm produces vasoconstriction in isolated rat aortic rings, while a high concentration stimulates vasodilation (Rosas-Hernandez et al. 2009).

Cytotoxicity Silver nanoparticles enter cells and may localize in endosomes/lysosomes, mitochondria, and nuclei (Cheng et al. 2013). Once inside the cells and organelles, they interfere with their functions. Smaller Ag nanoparticles seem to be more toxic than larger nanoparticles (Avalos et al. 2014; Carlson et al. 2008). Experimental evidence indicate that human and animal exposure to silver nanoparticles is associated to oxidative stress, apoptosis, genotoxic effects, chromosome aberration, and DNA breaks (Ahlberg et al. 2014; Cheng et al. 2013; Hackenberg et al. 2011; Kim and Ryu 2013; Liu et al. 2015).

1.7.8.3 Toxicity of Titanium Dioxide Nanoparticles

Titanium dioxide nanoparticles are found to have some beneficial effect on selected plants (Zheng et al. 2005; Feizi et al. 2013). They are already widely used as additives in food and other consumer products; however there are studies that indicate they might be toxic (Song et al. 2015; Coccini et al. 2015; Buzea et al. 2007).

Accumulation Animal experiments in vivo demonstrate that 3 nm titania nanoparticles enter blood, cross the blood-brain barrier, and accumulate in the brain (Li et al. 2010; Moon et al. 2011). Fluorescently labeled titanium dioxide nanoparticles with size of 35 nm intravenously injected into pregnant mice crossed and distributed into the placenta, fetal liver, and brain (Yamashita et al. 2011).

Toxicity Animal models show that regardless of their way of internalization (instillation, inhalation, injection, or ingestion), titanium dioxide nanoparticles are toxic (Tortiglione 2014). Toxicity includes immune system effects, reduced sperm production, neurobehavior alteration, abnormal fetal brain development, smaller fetuses, fetal deformities, and mortality. Titanium dioxide nanoparticles promote arrhythmia in rats as a result of a direct interaction with cardiac tissue (Savi et al. 2014). Just one single dose of nanoparticles results in higher cardiac conduction velocity and tissue excitability, increasing the probability of arrhythmias. Titania nanoparticles accumulate in heart tissue of rodents and are associated with cardiac damage and dysfunction, myocarditis, vascular dysfunction, arrhythmia, and inflammatory responses (Yu et al. 2016).

Cytotoxicity Titanium dioxide nanoparticles are cytotoxic and/or genotoxic in various human cell lines (Karlsson et al. 2008; Coccini et al. 2015; Gurr et al. 2005; Yu et al. 2016).

1.7.8.4 Toxicity of Zinc Oxide Nanoparticles

Zinc oxide nanoparticles are known for their antibacterial properties (Saliani et al. 2015; Seil and Webster 2012). Despite being widely used in cosmetics, recent studies show that ZnO are toxic (Roy et al. 2015; Vandebriel and De Jong 2012). They lead to DNA and mitochondrial damage, decreased cell viability, chromosome aberration, and oxidative lesions and upregulate genes controlling apoptosis (Roy et al. 2015; Karlsson et al. 2008). Inhalation of Zn nanoparticles in rats results in

their translocation to the liver and was found to produce liver and lung tissue damage (Vandebriel and De Jong 2012). Zn nanoparticles were also found to produce cardiac inflammation, DNA damage, and apoptosis in mice and rats (Yu et al. 2016).

1.7.8.5 Toxicity of Copper Oxide Nanoparticles

Experiments on human and animal cell lines demonstrate that copper oxide nanoparticles are cytotoxic, neurotoxic, and genotoxic and generate oxidative stress in many cell types (Karlsson et al. 2008; Magaye et al. 2012). Copper nanoparticles degrade DNA via generation of oxygen species. In vivo experiments on mice indicate that copper oxide nanoparticles translocate to the liver, kidneys, and spleen and produce inflammation in these organs. Copper smelter workers exposed to copper dusts or fumes have an increased risk of cancer (Magaye et al. 2012).

1.7.8.6 Toxicity of Cerium Oxide Nanoparticles

Cerium oxide nanoparticles are special in the sense that can have either a beneficial or a toxic effect on mammalian cells depending on cerium oxidation state and oxygen vacancies. The preparation method seems to have an essential role in dictating their toxicity (Gagnon and Fromm 2015; Kumar et al. 2014). Synthesis at lower temperature usually results in reduced toxicity ceria, with a higher number of oxygen vacancies and hence a more beneficial antioxidant effect (Gagnon and Fromm 2015). In addition to synthesis, the storage conditions, aging, and oxidation state influence ceria nanoparticle properties (Kumar et al. 2014). Cerium oxide nanoparticles can be cytotoxic, most likely as a result of reactive oxygen species, and lead to apoptosis in different cell lines (Gagnon and Fromm 2015; Mittal and Pandey 2014). Some CeO_2 nanoparticles with size smaller than 20 nm can have beneficial properties: protection of cells against irradiation, inhibition of oxidative stress, and prevention of inflammation (Gagnon and Fromm 2015; Niu et al. 2011).

1.7.8.7 Iron Oxide, Cobalt, and Nickel Nanoparticle Toxicity

Nanoparticles made of Fe, Ni, and Co are ferromagnetic. Magnetic nanoparticles are chemically unstable over long periods of time, oxidizing easily in air (Rao et al. 2015). Magnetism makes nanoparticles more prone to aggregate. As learned from their applications for in vivo imaging, there is always a concern of their aggregation in organs that may lead to inflammation and immunological responses (Markides et al. 2012). Intravenously administered ultrasmall superparamagnetic iron oxide nanoparticles (USPION) promote the formation of blood clots, cardiac oxidative stress, and DNA damage in mice (Nemmar et al. 2016). Injected magnetite nanoparticles with size of 10 nm were found to accumulate in the liver and spleen of rats (Ruiz et al. 2016).

Cobalt exhibits extreme toxicity in large amounts, and cobalt long-term exposure is associated to health effects related to the thyroid gland, lungs, skin, and immune system (Simonsen et al. 2012). Cobalt and nickel compounds are carcinogenic; their inhalation and dermal exposure lead to skin allergies, lung fibrosis, and cancer (Magaye et al. 2012). Nickel nanoparticles elicit severe cytotoxicity producing oxidative stress, genotoxicity, and cell death (Magaye et al. 2012).

1.7.8.8 Toxicity of Silicon and Silica Nanoparticles

Silicon and silicon dioxide (silica) nanoparticles have been found to produce cardiovascular disorders: cerebrovascular toxicity, coagulation disorders, and endothelium dysfunction in rodents (Yu et al. 2016). They are cytotoxic and genotoxic to a range of human cell types, such as human umbilical vein endothelial cells, epithelial cells, microvascular endothelial cells, platelets, and aortic vessel cells (Yu et al. 2016).

1.7.8.9 Toxicity of Carbon-Based Nanoparticles

Carbon-based nanoparticles include carbon black, fullerenes C60 and C70, single-walled carbon nanotubes, SWCNTs, and multiple-walled carbon nanotubes MWCNTs. Sometimes SWCNTs and MWCNTs are referred to as simply "carbon nanotubes," CNTs.

Carbon black particles are a by-product of automobile exhaust and were found to be toxic to humans and animals. Carbon black nanoparticles were detected in the urine of 289 children at an average of 98.2×10^5 particles/ml (Saenen et al. 2017). Children living close to a major road (<160 m) had a higher amount of urinary particles (Saenen et al. 2017). Carbon black and CNTs were found to produce cardiac and endothelial dysfunction, vasorelaxation, thrombus formation, placenta vessel damage, and thrombus formation in rodents (Yu et al. 2016). They produce cytotoxicity and genotoxicity in a wide range of cell types, such as human umbilical vein endothelial cells, blood cells, smooth muscle cells, human dermal microvascular endothelial cell, and human aortic endothelial cells, to name a few (Yu et al. 2016).

A review of CNT toxicity and exposure concludes that CNTs lead to oxidative stress and inflammation, resulting to fibrosis and granulomas with possible genotoxic and carcinogenic effects (Aschberger et al. 2010). Figure 1.11a shows the persistence of MWCNT in mice lungs. These nanoparticles can be found in lungs and diaphragm of mice 17 months following inhalation exposure and promote lung adenocarcinoma (Sargent et al. 2014). Due to their morphological similarities, MWCNTs are suspected to be as toxic as asbestos (Stella 2011). A comparison between CNTs and asbestos can be seen in Fig. 1.1e–f (Murr and Soto 2004).

MWCNTs are shown to be teratogenic in mice, resulting in deformity of limbs and fusion of vertebrae and ribs (Fujitani et al. 2012; Ema et al. 2016). Figure 1.11b shows fetal external and skeletal malformations in mice administered with MWCNTs. The mice show deformity of the forelimbs, short or absent tail, and fusion of the vertebrae and ribs (Ema et al. 2016).

Consequently, the use of CNTs in agriculture is not justified taking into account their adverse effects on humans and animals, as well as environment overload.

1.7.9 Comparative Toxicity of Nanoparticles with Various Compositions

Comparative toxicity studies indicate that some nanoparticles are more toxic than others. For example, metallic nanoparticles are inherently toxic due to their

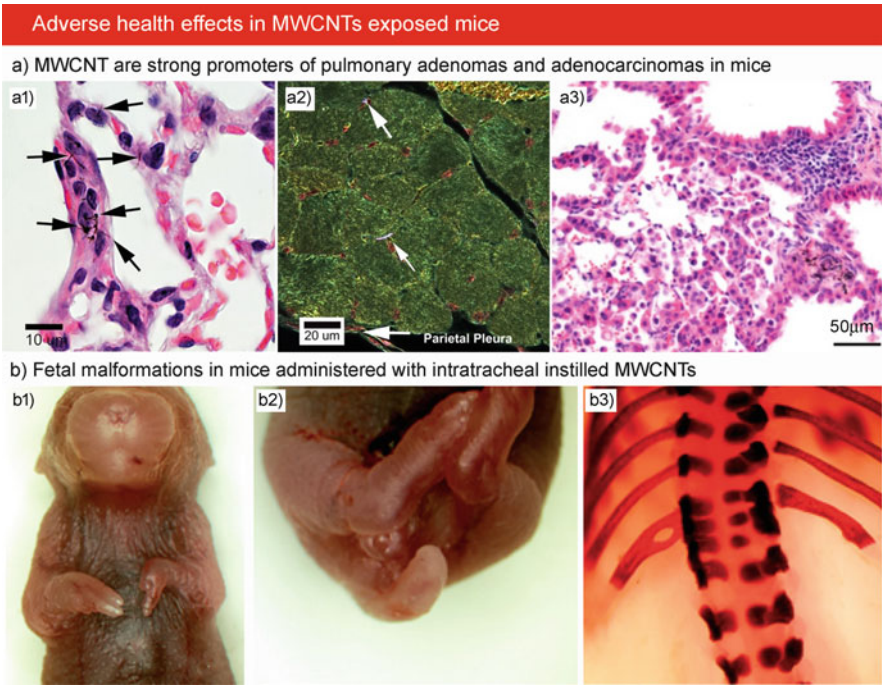

Fig. 1.11 Examples of adverse health effects in mice exposed to MWCNTs. (**A**) Light and enhanced dark-field imaging of MWCNT in lungs and diaphragm of mice exposed with MWCNTs 17 months following inhalation exposure. (a1) MWCNTs (black fibers) can be observed in the alveolar interstitium; (a2) enhanced dark-field imaging shows MWCNT (upper two arrows) in the diaphragm. MWCNTs are bright white; nuclei, brown-to-orange; muscle cells, green; and red blood cells, yellow. The lower arrow indicated the parietal pleural border; (a3) image showing a focal adenomatous hyperplasia in a mouse following the inhalation of MWCNT. Images (a1–a3) are reproduced from Sargent L. M. et al. 2014, Promotion of lung adenocarcinoma following inhalation exposure to multi-walled carbon nanotubes. Particle and Fibre Toxicology, 11, 18 (Sargent et al. 2014). (**B**) Fetal external and skeletal malformations in mice administered with intratracheal instilled MWCNTs at 4 mg/kg on GD 9. Malformations include (b1) reduction deformity of the forelimbs, (b2) short or absent tail, and (b3) fusion of the vertebrae and ribs. (Courtesy of Dr. T. Fujitani, Tokyo Metropolitan Institute of Public Health, Japan, Fujitani et al. (2012). Reproduced from Reproductive and developmental toxicity of carbon-based nanomaterials: A literature review, Ema M. et al., Nanotoxicology vol. 10 (2016) 391–412, reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com) (Ema et al. 2016)

composition, such as metal dust and welding fumes (cobalt, nickel, cadmium, zinc, manganese) (Buzea et al. 2007). Even though some materials are not considered toxic in bulk, in nanoparticle form they cause cancer in animals, as in the case of titanium dioxide (Borm et al. 2004). The toxicity of nanoparticles is also cell specific, as can be seen below.

Table 1.3 illustrates comparative toxicity of nanoparticles with various compositions on murine macrophage cells (Soto et al. 2005). The scale for the

Table 1.3 Nanoparticle comparative cytotoxicity

Material	Mean aggregate size (μm)	Particle size and (mean particle size)	RCI at 5 μg/ml	RCI at 10 μg/ml
Silver Ag	1	3–100 nm (30 nm)	1.5	0.8
Silver Ag	0.4	5–65 nm (30 nm)	1.8	0.1
Alumina Al_2O_3	0.7	4–115 nm (50 nm)	0.7	0.4
Iron oxide Fe_2O_3	0.7	5–140 nm (50 nm)	0.9	0.1
Zirconia ZrO_2	0.7	7–120 nm (20 nm)	0.7	0.6
Titanium dioxide TiO_2	0.8	5–100 nm (40 nm)	0.4	0.2
Chrysotile asbestos $Mg_3Si_2O_5(OH)_4$	0.5–15	15–40 nm diameter (20 nm); 15 μm length	1.0	1.0
Carbon black powder	0.5	2–50 nm (20 nm)	0.8	0.6
Single-wall carbon nanotubes SWCNTs	10	10–100 nm diameter	1.1	0.9
Multiple-walled carbon nanotubes MWCNTs	2	5–30 nm diameter (15 nm), 20 nm–1 μm length	0.9	0.8

Reprinted from Soto K. F. et al. 2005. Comparative in vitro cytotoxicity assessment of some manufactured nanoparticulate materials characterized by transmission electron microscopy. Journal of Nanoparticle Research, 7, 145–169, with permission from Springer (Soto et al. 2005)
RCI relative cytotoxicity index

comparison of nanoparticles toxicities is based on value "1" for asbestos, a known carcinogen. Nanoparticles with values smaller than "1" are less toxic than asbestos. At a concentration of 5 μg/ml, silver nanoparticles and SWCNTs are more toxic than asbestos. They are followed in decreasing toxicity order by MWCNTs and iron oxide, carbon black, zirconia and alumina, and titanium dioxide. At a concentration of 10 μg/ml, the materials show the following toxicity in decreasing order: SWCNTs, MWCNTs and silver, carbon black and zirconia, alumina, and titanium dioxide. It is interesting to note that the aggregation strongly modulates the cytotoxicity of silver.

In Fig. 1.12 is illustrated the comparative cytotoxicity of CuO, TiO_2, ZnO, $CuZnFe_2O_4$, Fe_2O_3, Fe_3O_4, C, and CNT nanoparticles in human lung epithelial cell line A549 (Karlsson et al. 2008). This study reveals that CuO nanoparticles show the highest level of toxicity, followed by ZnO, carbon nanotubes, $CuZnFe_2O_4$, and Fe_2O_3. Titania and Fe_3O_4 did not decrease cell viability; however they produced oxidative lesions.

The discrepancy between results on comparative cytotoxicity from different studies is likely due to the fact that the nanoparticles used in various experiments have different sizes, aggregations, and synthesis methods, which will result in different reactivity and interaction with cells and subcellular structures (Staszek et al. 2015). In addition, cytotoxicity is cell dependent, as we will see in the following.

Table 1.4 shows cellular responses of two types of cells (ht bronchial epithelial cells and RAW macrophages) subjected to TiO_2, SiO_2, and MWCNTs, having

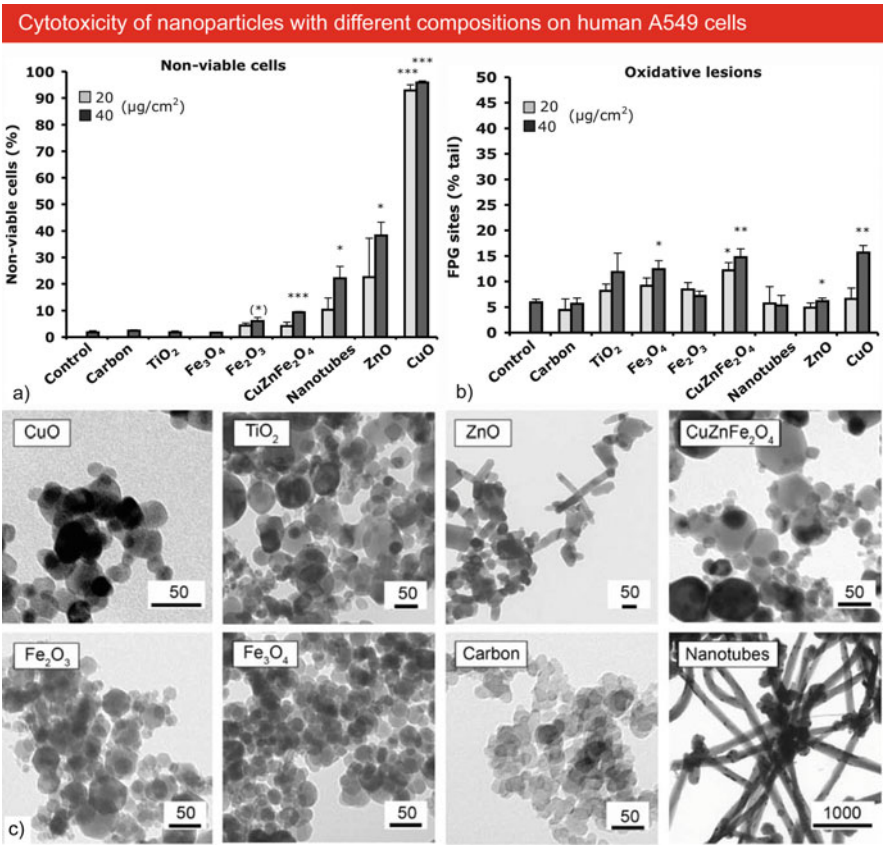

Fig. 1.12 (**a**) Cytotoxicity of various nanoparticles in cultures of human A549 cells (human adenocarcinomic alveolar basal epithelial cells) after exposure to 20 and 40 μg/cm^2 of nanoparticles. (**b**) Oxidative DNA lesions. (**c**) Transmission electron microscopy images of nanoparticles used in the experiment: CuO, TiO_2, ZnO, $CuZnFe_2O_4$, Fe_2O_3, Fe_3O_4, C, and CNTs. Reprinted with permission from Karlsson H. L. et al. 2008. Copper oxide nanoparticles are highly toxic: a comparison between metal oxide nanoparticles and carbon nanotubes. Chem Res Toxicol, 21, 1726–32. Copyright (2008) American Chemical Society 45 (Karlsson et al. 2008)

different sizes (Sohaebuddin et al. 2010). The response to nanoparticles is cell specific. For example, titania nanoparticles are more cytotoxic to macrophages than the ht bronchial epithelial cells, showing a higher apoptosis rate. In general, macrophages are more prone to cytotoxicity than fibroblasts and epithelial cells as a response to nanoparticle exposure.

Other cytotoxicity studies on pulmonary cell lines show that Cu and Zn nanoparticles have the highest toxicity, followed by TiO_2, Al_2O_3, CeO_2, Ag, Ni, and ZrO_2 (Lanone et al. 2009).

Table 1.4 Cellular responses of two types of cells (ht bronchial epithelial cells and RAW macrophages) subjected to several nanomaterials (TiO_2, SiO_2, and MWCNTs with different sizes in nm)

Cell responses	hT bronchial epithelial cells					RAW macrophages				
			MWCNT					MWCNT		
	TiO_2	SiO_2	<8	20–30	>50	TiO_2	SiO_2	<8	20–30	>50
Cytotoxicity	+	++	++	+	–	+++	+++	++	++	+++
ROS	–	+	+	–	–	+	+	+	–	+
LMD	–	–	–	–	+	–	–	–	–	+
MMP	–	+	++	–	–	–	+	+	–	+
Caspase	–	++	++ +	–	–	–	–	–	–	–
Apoptosis	–	+++	++	–	–	+++	+++	+	+	++
Necrosis	–	–	–	–	–	–	–	–	–	–

ROS reactive oxygen species, *LMD* lysosomal membrane destabilization, *MMP* mitochondrial membrane potential. The symbols "+" and "−" denote toxicity or its absence. "+" means a significant increase in the intracellular event, while "−" means that the material did not induce a toxic effect. "++" and "+++" signify twice and three times the response. Reproduced from (Sohaebuddin et al. 2010) under a Created-Commons CC-By license

1.8 Beneficial or Detrimental Effect of Nanoparticles?

Some nanoparticles are promoted as agrichemical for selected beneficial effects on some plants. While they show benefits for some plants, they are phytotoxic to others. If used in agriculture, nanoparticles will become ubiquitous in the soil, atmosphere, and water and will be available for uptake in other plant species for which they are phytotoxic. Last but not least, most nanoparticles are shown to be associated to many diseases in humans and animals. The environmental overload with agricultural nanoparticles together with the consumption of plants containing nanoparticles will pose a serious health risk to humans and animals. For example, silver, which is increasingly used in agriculture, can be more cytotoxic than asbestos. Another example is carbon in the form of nanotubes. Carbon nanotubes have morphologies very similar to asbestos and show similar toxicities in animal cells.

Here below we give the most important arguments explaining why nanoparticles should not be used in agriculture:

- Most studies of beneficial effects of nanoparticles were carried out on first-generation plants. The benefits shown in first-generation plants might not be present in second-generation plants, as in the case of ceria nanoparticles on tomato plants.
- The use of agrichemical nanoparticles as plant growth regulators will result in their environmental accumulation in soil and water. Due to their small size, it is very likely they will become airborne.

- Nanoparticle benefits are found to be plant species specific. Some nanoparticles show benefits for one plant, while they are phytotoxic for another plant type. Agrichemical nanoparticles cannot be confined to a specific location, becoming airborne and bioavailable for other plants that might suffer phytotoxic effects as a result of exposure.
- The accumulation of nanoparticles in soil will make a higher concentration of nanoparticles available to plants for uptake. In many cases a higher concentration of nanoparticles has been shown to have detrimental effects compared to the lower concentrations that might show beneficial effects.
- Edible plants have been shown to uptake and accumulate nanoparticles. The possible toxic effect on humans from nanoparticles within edible plants poses serious concerns.
- The use of nanoparticles can adversely affect soil microbiota, creating an imbalance in the bacterial diversity.
- Last but not least, most nanoparticles are shown to have toxic effects on humans and animals, leading to a plethora of diseases, ranging from respiratory, cardiovascular, and neurodegenerative diseases to various cancers. Agricultural nanoparticles can become available to humans via ingestion of edible plants that contain nanoparticles, via environmental exposure with nano-agrichemicals from atmosphere, soil, and water.

We should ask ourselves: are the beneficial effects of nanoparticles in some plants enough to warrant their use in agriculture with possible catastrophic consequences for humans, animals, and other plants?

Figure 1.13 shows a schematic of adverse effects of nanoparticles in humans, animals, and plants. There is overwhelming evidence demonstrating that nanoparticles with different composition are associated with health effects in humans and animals, such as arteriosclerosis, high blood pressure, blood clots, stroke, arrhythmia, heart disease, heart attack, respiratory diseases, neurodegenerative diseases, reproductive system diseases, and various cancers. Nanoparticle toxicity in plants relate to growth inhibition, physiological and biochemical traits, and toxicity at genetic level.

It is likely that many authors working in the agricultural field are not aware of the current knowledge on nanoparticle toxicity to humans and animals and are conducting experiments expected to improve plant yield and promote their growth. We hope that this chapter has shed some light on the most stringent problems related to nanoparticles use in agriculture and will help scientists decide whether or not to pursue research in different avenues of nano-agrichemicals.

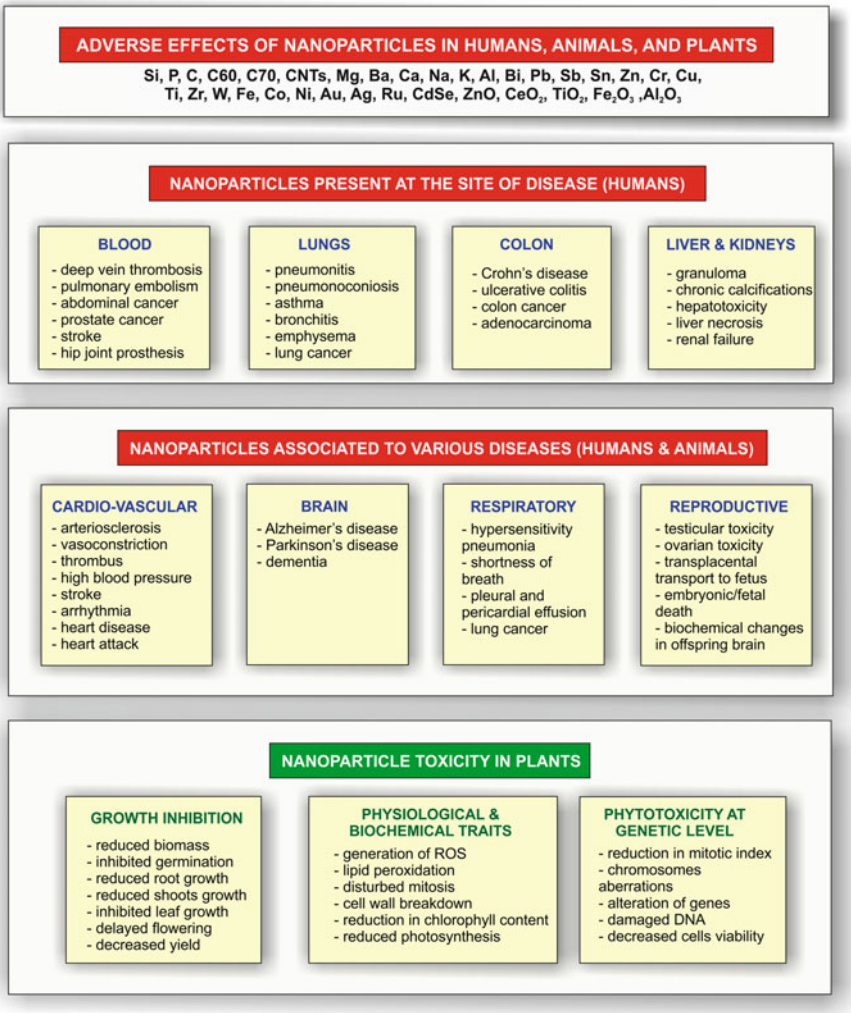

Fig. 1.13 Schematics of adverse effects of nanoparticles in humans, animals, and plants. Nanoparticles with different compositions shown in the upper part were found to localize in humans at the site of various diseases. Several health effects in humans and animals are associated to exposure to nanoparticles. Nanoparticle toxicity in plants relate to growth inhibition, physiological and biochemical traits, and toxicity at genetic level

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