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Silver Nanoparticles (AgNP) in the Environment: a Review of Potential Risks on Human and Environmental Health

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Abstract Silver nanoparticles (AgNP) are one of the most marketable nanomaterials worldwide. Their increasing production and their market insertion will deliver AgNP to the environment, exacerbating their human and environmental impacts. This review discusses the main techniques to synthesize AgNP, their properties, applications, and the cutting-edge knowledge on the effects of AgNP on human and environmental health. Through an identification of papers reporting AgNP until the beginning of 2016 in "ISI Web of Science," and running different combinations of keywords or search strings, we identified six toxicological factors with a clear hazard potential to workers and consumers. A grading system is proposed to rank and evaluate toxicological properties of AgNP, which can be useful in supplying assistance on the classification of the priorities and concerns in the regulatory and standardization policies of the occupational health and safety issues on nanomaterials.

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1 Introduction

Today, nanotechnologies serve as a strategic point in the scientific and technological development and innovation in all countries (OECD 2013). The incorporation of nanoparticles (NP) in the productive sectors is due to their scale (1 nm = 10^{-9} m), which provides higher surface area to volume ratio as well as to their novelty properties including: (i) *physical*, such as superconductivity (Shi et al. 2012; Iijima 2002), superparamagnetism (Vatta et al. 2009), ultrahardness (Lamni et al. 2005), and tribological increase to the thermal resistance (Miyake et al. 2013); (ii) *chemical*, rising optical performance (Kelly et al. 2003), high resistance to corrosion (Hamdy and Butt 2007), and photocatalytic capacity as semiconductor (Tong et al. 2012; Evanoff and Chumanov 2005); and (iii) *biological*, by its antimicrobial properties (Chen and Chiang 2008), antimicrobial coatings (Singh and Nalwa 2011), as well as soil or water remediation (Bodzek and Konieczny 2011; Zhang 2003).

An inventory of nanotechnology-based consumer products found that more than 1827 products containing or using nanomaterials (NM) were introduced on the market during the last years (Consumer Products Inventory 2015). In the USA, main investor on nanotechnology area (Harper 2011; Clunan and Rodine-

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Hardy 2014), it represented an increasing of 80 % since the last update in 2010 (Vance et al. 2015). This increasing production involves a significant investment by the government and industrial sectors in the creation, development, and manufacture of NM (OECD 2013), which turns, in less than 15 years a situation where there were virtually no NM around us, to be surrounded by a variety of products containing them (Ali et al. 2014; Rai et al. 2009; Consumer Products Inventory 2015; Roco et al. 2011). NM have been done with different types of chemical elements like copper (Cu), zinc (Zn), gold (Au), titanium (Ti), and silver (Ag), among others (Schabes-Retchkiman et al. 2006; Thakkar et al. 2010).

It is well known that 320 t silver nanoparticles (AgNP) per year are produced due to their fungicides and antibacterial properties. AgNP are used in a wide variety of processes and manufactured products, such as coatings, textiles, food, electronics, biomedical, and pharmaceutical industries (Konopka et al. 2009), i.e., AgNP are one of the most commercially used NM due to their effective properties against bacteria, viruses, and other microorganisms (Nowack et al. 2011; Piao et al. 2011; Avalos et al. 2013; Gong et al. 2007). AgNP have found their major applications in three main sectors: (i) *Biomedical*, through coatings or integrated into surgical instruments, prostheses, contraceptives, and dressings to prevent bacterial growth (Chen and Schluesener 2008; Lee et al. 2007; Shenava et al. 2015), (ii) *Alimentary*, extending food preservation and assembling packages containing them, due to their fungistatic effects that decelerate the growth of pathogenic microorganisms (Kumari and Yadav 2014), and (iii) *Textiles*, specifically in the manufacture of clothing, that potentialize ion activity generating anti-odor and anti-bacterial effects (Chen and Chiang 2008; Rai et al. 2009; Yu et al. 2013).

Although AgNP are widely used worldwide by their innovative and promising properties, the fate and impacts of these NP have not been fully studied. There exists a serious concern that AgNP could migrate to the environment and therefore into humans. In addition, many products that employ NP are not labeled to alert consumers about the potential risk, eliminating the right to choose or avoid using these products. The lack of both government surveillance and regulation in this new technology is further compounded by the lack of data and appropriate safety tests, reinforcing the potential negative effects that could occur on health and the environment. Denmark nanodatabase inventory (Nanodatabase 2015) and Johnston et al. (2010) has shown that the main exposure routes of AgNP are dermal, respiratory, and oral. The AgNP over-exposure can result in harmful risks, causing permanent bluish-gray discoloration of the skin (argyria) or the eyes (argyrosis) (Drake and Hazelwood 2005), but AgNP can also damage the epithelial cells (Stoehr et al. 2011) and interfere with DNA replication (Asharani et al. 2009). Furthermore, van der Zande et al. (2012) found, in an experiment performed to test the AgNP toxicity in rats, that AgNP may be deposited first in the gastro-intestinal tissues followed by the liver, spleen, testicles, kidney, brain, and lungs. In order to prevent and minimize these adverse effects into humans, it becomes imperative to find out the impact that involves the synthesis, use, and distribution of AgNP into the environment.

In earlier studies, Marambio-Jones and Hoek (2010) published a review of the antibacterial effects of AgNP, including proposed mechanisms and possible toxicity to higher organisms. In addition, Reidy et al. (2013) provided a critical assessment of AgNP toxicity and gave a set of pointers and guidelines for experimental design of future studies to assess the environmental and biological impact of AgNP. However, there is still a gap of knowledge about (i) which mechanisms of synthesis increase the toxicity of AgNP, (ii) how their mechanisms of synthesis, their properties, and their applications are correlated, and (iii) a risk-benefit analysis for all AgNP applications and their eventual restriction when clear evidences of the benefits of AgNP cannot be demonstrated. Hence, the objectives of the present critical review were as follows: (i) to discuss the main mechanisms of synthesis of AgNP, (ii) to determinate the correlation among mechanisms of AgNP synthesis, their properties, their applications, and their potential adverse effects to human and environmental health.

2 Methodology

In this review, we exhaustively cover all the studies reporting AgNP until the beginning of 2016. Purely methodological discussions were not considered. A summary of the mechanisms of AgNP synthesis, and the properties, applications, and potential adverse effects to human an environmental health is given in Table 1 and Fig. 1.

Table 1 Summary of AgNP mechanisms of synthesis, properties, applications, and potential toxic effects

Synthesis	Properties	Applications	Toxicity
Chemical			
Chemical reduction Photochemical Electrochemical Micro emulsion/reverse micelle	Antifungal effect, destroy fungi membrane integrity against deserving in dental and deodorant applications.	In medical field used for surgical instruments, prostheses, catheters, medical wounds.	Exposure metal nanoparticles to human lung epithelial cells could increase ROS, which can lead to oxidative stress and cellular damage.
Physical			
Thermal decomposition Electrical arc discharge Laser ablation Ionization Microwave Irradiation Evaporation/condensation. Ultrasonic	Antibacterial properties used in medical, food and textile fields. In addition, these are used as antiviral to prevent HIV-1 and inhibit the virus entry.	Also in water treatments and filtration to eliminate microorganisms.	Cell morphology changes, cytotoxicity, and immunological responses may affect fertility.
Biological			
Biological reduction (Green chemistry) using plants, fungi, and bacteria Via reducing or capping agent such as polysaccharides, polyphenols, polyoxometalate, or tollens	High electromagnetic interaction, electrical capacitance, electrochemical stability, catalytic activity, and non linear optical behavior.	In addition, these are used for textiles/clothing, home appliances, food preservation and packaging, paints, cosmetics, and electronics.	Reduce mitochondrial function and lactate dehydrogenase (LDH) leakage.

The increasing number of studies that have investigated the main mechanisms of AgNP synthesis, their properties, applications, and potential adverse effects to human and environmental health are indicated in Fig. 1. At the beginning, the search terms and/or the search string were tested and refined through several rounds of paper identification, running the full search term in "Scopus" and "Web of Science." At the end, all data employed were derived from "Web of Science" using different combinations of keywords or search strings (Table 2) because a growing number of papers have been published using the keywords "nano*" and "silver" as search parameters in the "title" field.

In addition, we have developed a proposal for ranking AgNP toxicity according to some scientific papers published during the last years in reputable high-impact factor journals (Tables 3, 4, and 5).

3 AgNP Synthesis

AgNP can be synthesized by several routes and methods in order to obtain certain characteristics such as size, shape, and agglomeration (Panáček et al. 2006). However, it is well known that physical and chemical approaches are the two main routes, but it is also well known that each process has advantages and disadvantages, sharing common issues such as cost, scalability, particle size, and size of distribution (Tran et al. 2013). Physical and chemical methods have been widely used, but their high requirement of energy and high price, in addition to the toxic reducing agents remnants and wasteful purifications with high cytotoxic residuals (Mandal et al. 2006), have been forced the development of NM through green chemistry, which is more eco-friendly, simple, economic, and viable alternative to

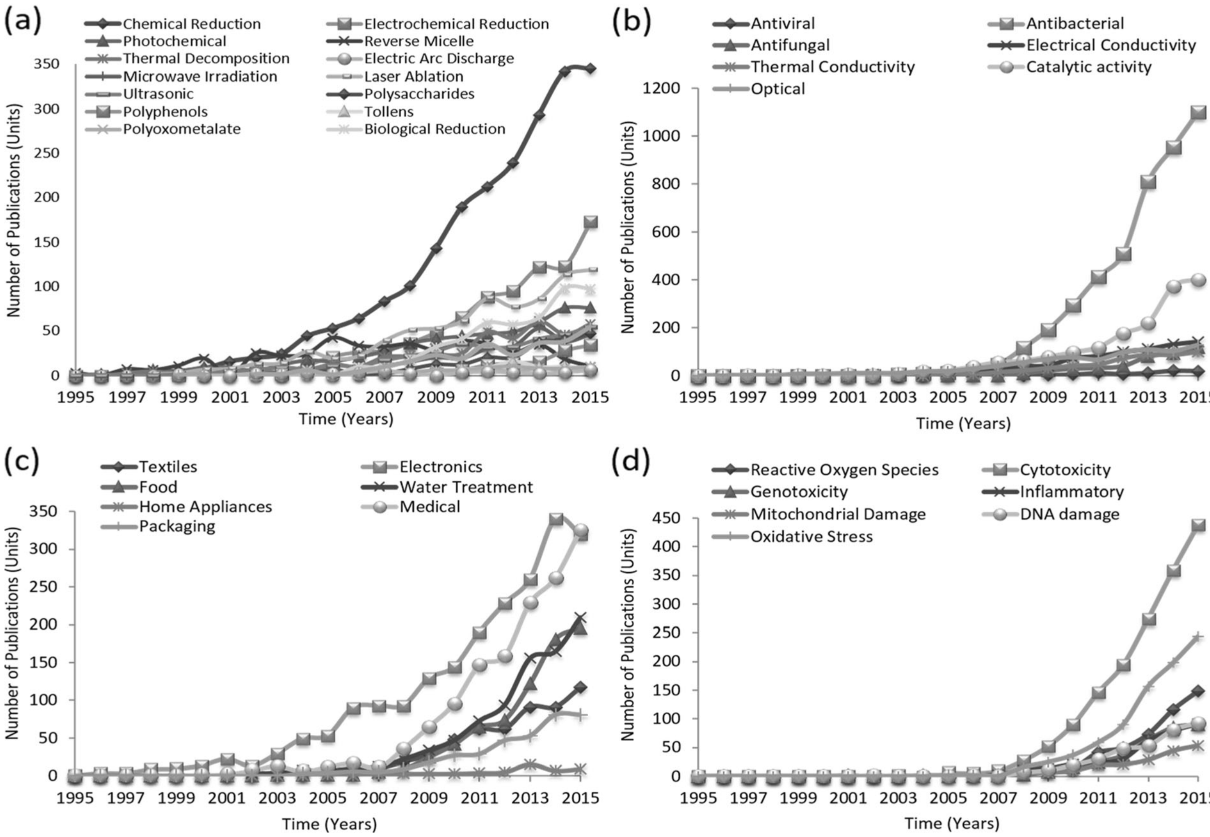

Fig. 1 Publications frequency on the mechanisms of synthesis (**a**), properties (**b**), applications (**c**), and potential toxicological effects (**d**) of AgNP (databases collected from "ISI Web of Science," up to January 19, 2016)

obtain AgNP, employing natural-reducing agents such as polysaccharides, plant extracts, and microorganisms such as bacteria, fungus, and yeast (Mandal et al. 2006; Balaji et al. 2009; Solgi 2014). It would be desirable that before the NP were brought to everyday products and/or used in food, medicine, cosmetics, or their packaging, toxicity tests were conducted in order to determine the possible harm to living beings and the environment. If these NP cause severe damage to the environment and/or their inhabitants, its production, use, and release into the environment should be forbidden (Fig. 2).

3.1 Physical Synthesis

This approach utilizes the physical energies, e.g., evaporation/condensation, inert gas condensation, co-condensation, ultraviolet irradiation, laser ablation, thermal decomposition, arc discharge, sonodecomposition, or radiolysis to obtain AgNP. Commonly, evaporation/condensation method is the most used worldwide; it occupies a tube furnace at atmospheric pressure, to raise the environmental temperature around the material until a thermal stability, consuming large quantities of space, time, and energy (Jung et al. 2006). Therefore, the cutting-edge knowledge has been used to develop innovative physical methods in order to create greener AgNP. Baker et al. (2005) synthesized AgNP by gas condensation and co-condensation techniques, which consists in the evaporation of a Ag solution into a carrier gas with the subsequent cooling for nucleation and growth of NP, this methods differs in the media where the condensation of AgNP takes place and are capable to produce several amounts of particles. Irradiation (via microwave, ultraviolet, ionization, or laser ablation) in a Ag solution is another technique to elaborate NP without the use of chemical agents, and the advantages of using this techniques is that particle size is controlled by the duration of the irradiation, number of shots, wavelength of beam, fluency, and liquid medium (Hwang et al. 2000; Link et al. 2000; Tsuji et al. 2003). Thermal-decomposition method develops AgNP in powder form, reacting $AgNO_3$ with sodium oleate in

Table 2 Frequency of occurrence terms searched, using "silver and nanoparticles" plus different combinations of keywords in the "Topic" field tag. Data collected from "ISI Web of Science" database at January, 2016

Combinations of keywords or search strings	Number of publications	Percentage of AgNP publications*
Synthesis	11,105	27.90
Application	9586	24.08
Reduction	8404	21.12
Antibacterial	4462	11.21
Toxic	4451	11.18
Environment	4177	10.49
Antimicrobial	3137	7.88
Exposure	2889	7.26
Human	2112	5.31
Degradation	1467	3.69
Nanotechnology	1365	3.43
Oxidative stress	831	2.09
Damage	812	2.04
Diseases	727	1.83
Safety	409	1.03
Consumer products	371	0.93
Inflammatory	330	0.83
Benefit	327	0.82
Adverse effects	291	0.73
Remediation	117	0.29

a water solution at high temperature (Lee and Kang 2004). Arc-discharge method reported by Tien et al. (2008) is another form of physical synthesize without adding surfactants, by submerging Ag wires in deionized water and applying an electrical current, using electrodes, and causing Ag atom surface to evaporate and condense back into aqueous AgNP. In addition, sonodecomposition method involves a sonochemical reduction, in an argon-hydrogen atmosphere, ultrasonic waves induce cavitation in the silver nitrate solution generating hydrogen radicals during the sonication process (Salkar et al. 1999). Another manner to synthesize AgNP is though radiolysis, where aqueous solution of Ag metal salt is exposed to Gamma rays, adding a OH radical scavenger with polyvinyl alcohol (PVA) to prevent oxidation, obtaining AgNP in an easy and no contaminating process (Temgire and Joshi 2004).

Physical methodologies enable to synthesize large quantities of AgNP with uniform distribution, high purity, desired size, and minimal or no use of chemicals, without releasing toxic residuals or contaminants that may affect human and environmental health. However, because no capping agents are used, agglomeration usually is the main challenge. In addition, these techniques require high power consumption as well as expensive and complex equipments which increase the operating cost, while time taken for AgNP manufacture is also a great challenge for nanotechnologists.

3.2 Chemical Synthesis

Chemical approach is the most typical process to synthesize colloidal dispersions of AgNP in water, organic, or inorganic solvents, due to its low cost and high stability (Ge et al. 2014). This process involves three main components: (i) metal precursors, (ii) reducing agents, and (iii) stabilizing/capping agents. It comprises photochemical, electrochemical, and chemical reduction techniques (Murray et al. 2005; Maretti et al. 2009). Photochemical synthesis can produce AgNP using a variety of photoinduced or photocatalythic techniques, basically a Ag salt is photo-reduced with a polymer or a citrate, irradiated by different light sources, e.g., ultraviolet (UV), resulting in a cleaner and simple manner of synthesizing AgNP

Table 3 Manuscripts from which information was taken in order to define the proposed system for ranking AgNP toxicological impacts

Evaluated factor	Brief description	Main conclusion	Reference
Size	They suggest a critical size of 70 nm for AgNP. Particles smaller than 40 nm shows skin penetrations and potential hazard.	Bigger particles shows to be less toxic and hazard compare with smaller particles.	Filon et al. 2015
	The average diameter of AgNP used in this study was about 5.0+/−1.0 nn with a spherical shape.	AgNP of 5 nm induce oxidative stress resulting from the generation of ROS, which in turn damaged the DNA, leading to apoptosis.	Awasthi et al. 2013
	Using 15, 30, and 55 nm AgNP, they found that 15 nm particles cause an increasing of ROS levels compare with the other sizes.	Size-dependent toxicity was produced by AgNP, and a predominant mechanism of toxicity was found to be largely mediated through oxidative stress.	Carlson et al. 2008
	They found inhibition to nitrifying organisms correlated with AgNP less than 5 nm in suspension.	Inhibition correlated with the fraction of AgNP less than 5 nm, but not with others particles sizes (10, 15, 20 nm), suggesting that smaller size NP could be more toxic.	Choi and Hu 2008
Shape	Truncated triangular silver nanoplates with a {111} lattice plane as the basal plane displayed the strongest biocidal action, compared with spherical and rod-shaped NP and with Ag^{+}.	AgNP showed shape-dependent permeation through skin; the permeation increased with respect to time.	Tak et al. 2015
	Cube particles or nanowires used in this study show less toxicity than spherical particles.	Spherical particles show to be more toxic than other shapes like wires or cubes.	Gorka et al. 2015
	Spherical nanoparticles show greater toxicity with fibroblast cells compare with nanorods.	Nanorod shape show to be less toxic compare with spherical particles.	Favi et al. 2015
	High reactivity was found in truncated triangular nanoplates, in comparison to other particles that contain fewer than {111} facets, like spherical or rod-shaped particles.	AgNP with the same surface areas but with different shapes may also have different effective surface areas in terms of active facets.	Pal et al. 2007
Superficial Charge	Positive charge produces greater cell proliferation, cell death, membrane disintegration and DNA damage.	Positive charge NP may produce severe cytotoxic, genotoxic and mutagenic effects.	Huk et al. 2015
	The more negative citrate-AgNP was the least toxic, whereas the positively charged BPEI-AgNP were the most toxic.	Surface charge is one of the most important factors that have to be taken into consideration when evaluating the toxicity of AgNP in the environment.	El Badawy et al. 2010
	In most experimental scenarios, positively charged NP are more toxic than negatively charged ones, which besides other effects can be attributed to enhanced cellular internalization of positively charged NP.	Larger NP are typically internalized at slower rates than smaller ones, this suggests that agglomerated NP, which have bigger size than individually dispersed NP, should be internalized less than individual NP.	Abdelmonem et al. 2015
Concentration	Surface charge of particles affects agglomeration/aggregation rates and particle stability.	Elevated concentration results in higher aggregation rates and stability of aggregate size in comparison with lower concentrations.	Tourinho et al. 2012
	According to the Derjaguin–Landau–Verwey–Overbeek theory, the aggregation is induced by screening the surface charge and depends upon attractive van der Waals forces and repulsive electrostatic forces.	Particle size and aggregation propensity are important for defining the toxicological effects of any material.	Tripathy et al. 2014
	NP aggregation rate in a fibrinogen solution depended on particle surface type.	Particle size, surface charge, and aggregation behavior significantly changed in the presence of fibrinogen.	Kendall et al. 2011
	Studied in vitro mouse spermatogonial stem cell line, and conclude that cytotoxicity in the mitochondrial function and membrane leakage increases, as the concentration of NP increases as well.	Demonstrate a concentration-dependent toxicity for all types of particles, being AgNP the most toxically.	Braydich-Stolle et al. 2005
Stability	Stabilized AgNP solutions proved to be fairly stable for a period up to 1 year, keeping the solutions at		Pinto et al. 2010

Table 3 (continued)

Evaluated factor	Brief description	Main conclusion	Reference
	4 °C greatly reduced the rate of changes of the particles in terms of their size and shape.	Changes in size distribution and morphology were related to the storage conditions as well as for environmental variations.	
	Colloidal stability is a function of many factors including the type of capping agent, the surrounding environmental conditions, such as pH, ionic strength, and the background electrolyte composition.	Phase transformations significantly affect the stability of AgNP and consequently their bioavailability and toxicity.	El Badawy et al. 2010
	The surface properties of NP are one of the most important factors that govern their stability and mobility as colloidal suspensions or their aggregation into larger particles and deposition in aquatic systems.	The stability of the colloidal suspension becomes an important requirement to determine the toxic behavior in aquatic organisms.	Navarro et al. 2008
Suggest toxicity	Zebrafish were exposed to AgNP solution, detecting that cellular alterations including disruption of hepatic cell cords and apoptotic changes were observed in the liver tissues.	Suggested that oxidative stress and apoptosis are associated with AgNP toxicity in the liver of adult zebrafish.	Choi et al. 2010
	Evaluated the toxic effects of metal NP using in vitro rat liver derived cell line (BRL 3A), showing that mitochondrial function decreased significantly in cells exposed to AgNP at 5–50 μg/ml.	Suggested that cytotoxicity of Ag (15, 100 nm) in the liver cells is likely to be mediated through oxidative stress.	Hussain et al. 2005
	Showed genotoxicity of starch-coated AgNP in human lung fibroblast (IMR-90) and glioblastoma (U251) cells.	AgNP reduce ATP content, causing mitochondrial damage and increasing production of ROS, which originate DNA damage and chromosomal abnormalities.	Asharani et al. 2009
	Shows in vivo oral toxicity of rats, with (56 nm) AgNP and conclude that, exposure to more than 125 mg/kg may result in liver damage.	The target organ for the AgNP is the liver, with a no observable adverse effect level of 30 mg/kg and lowest observable adverse effect level of 125 mg/kg.	Kim et al. 2010

(Sato-Berrú et al. 2009). In the electrochemical reduction, $AgNO_3$ in aqueous solution is reduced with a polymer conceiving AgNP in a range of 3–20 nm (Zhu et al. 2001), while particle size and homogeneity can be controlled adjusting electrolysis parameters and the composition of electrolytic solution. Finally, the chemical reduction is the most common synthesis method, by the reduction of a Ag salt dissolved in water with a reducing compound such as sodium borohydride ($NaBH_4$), sodium citrate ($Na_3C_6H_5O_7$), glucose ($C_6H_{12}O_6$), hydrazine (N_2H_4), hydrazine hydrate, ascorbate ($C_6H_7NaO_6$), ethylene glycol ($C_2H_6O_2$), N-dimethylformamide (DMF), hydrogen, dextrose, or UV light (Panáček et al. 2006; Gulrajani et al. 2008; Pillai and Kamat 2004). In this technique, silver ion (Ag^+) receives an electron from the reducing agent, returning from a positive valence to a zero-valent state (Ag^0). Then, to stabilize and avoid agglomeration and oxidation, a capping agent like surfactants, chitosan, oleylamine, gluconic acid, cellulose or polymers, as poly N-vinyl-2pyrrolidone (PVP), polyethylene glycol (PEG), polymethacrylicacid (PMAA), and polymethylmethacrylate (PMMA) are added (Pillai and Kamat 2004; Bai et al. 2007). AgNP can also be synthesized by micro-emulsion, in this technique, reduction reaction takes place in water droplets, covered by surfactant molecules, as particles enlarge, the surfactant molecules get adsorbed to the surfaces, stopping further growth and preventing clustering. This method produces uniform and size controllable AgNP, nevertheless highly organic solvents are employed and stability dispersion is only obtained at low concentrations.

Chemical approaches can easily change or modify reducing and capping agents to achieve desired characteristics as size distribution, shape, and dispersion rate. However, the remnants of this hazardous chemicals like sodium borohydride or hydrazine are highly reactive, non-biodegradable, and potentially detrimental to the environment. In addition, some of these chemicals

Table 4 Proposed system for ranking AgNP toxicological impacts

Factor	Score
A. Size (nm)	
< 20	20
20–80	15
> 80	10
B. Shape	
Triangular particles	20
Spherical particles	15
Wires particles	10
Cube particles	5
Others	5
C. Superficial charge	
Positive	15
Negative	5
Neutral	0
D. Concentration (mg/L)	
Low < 20	15
Medium 20–40	10
High > 40	5
E. Stability	
Low	10
Medium	5
High	0
F. Suggest toxicity	
Positive	20
Possible	10
Negative	0

might infect the AgNP surface making them inappropriate for certain biomedical applications.

3.3 Biological Synthesis

Polysaccharides, polyphenols, tollens, polyoxometalate, and biological reduction have decreased the use of hazardous chemicals and cytotoxic residuals through the development of new green chemistry methods (Sharma et al. 2009; Iravani and Zolfaghari 2013). Sintubin et al. (2009) stated that extracts produced by living organisms like bacteria, fungi, yeasts, or plants are substituting the reducing and capping agent components in a usual chemical reduction. This extracts used for biological reduction includes amino acids, proteins, vitamins, and polysaccharides (Sharma et al. 2009), as well as plant and leaf extracts. Some extracts from ginkgo (*Ginkgo biloba* L.), platanus (*Platanus orientalis* L.), magnolia (*Magnolia kobus* DC.), persimmon (*Diospyros kaki* Thunb.), geranium (*Pelargonium graveolens* L'Hér), Pine (*Pinus densiflora* Siebold & Zucc.), lemongrass (*Cymbopogon flexuosus* Nees ex Steud, J.F. Watson), neem (*Azadirachta indica* A.Juss.), amla (*Phyllanthus emblica* L.), aloe (*Aloe vera* L.), and camphorwood (*Cinnamomum camphora* L.) are also used as reducing or capping agents (Shankar et al. 2003; Song and Kim 2009; Syed et al. 2013). In addition, several bacteria, such as *Bacillus licheniformis*, *K. pneumonia*, *Pseudomonas stutzeri*, *Lactobacillus*, fungi such as *Verticillium*, *Fusarium oxysporum*, *Aspergillus flavus*, *Fusarium accuminatum*, *Humicola sp*., *Penicillium fellutanum*, *Alternaria alternata*, and yeast like *MKY3* (Mukherjee et al. 2001; Mandal et al. 2006; Vigneshwaran et al. 2007; Kalishwaralal et al. 2008; Gajbhiye et al. 2009; Kathiresan et al. 2009; Syed et al. 2013), are also known as carriers or producers of reducing or capping agents.

Methods used in biological synthesis in order to produce AgNP are more economical, simpler, and more feasible than chemical methods, with the additional advantage of that biological synthesis use natural products avoiding toxic agents and cytotoxic residuals. Nevertheless, the main disadvantages of using the biological synthesis are the impact on bacteria and fungi when these are used as biological reductors. Marambio-Jones and Hoek (2010) suggested that resistance may be fairly widespread during interactions among microbes and AgNP. However, Chaloupka et al. (2010) showed potential contamination with AgNP in medical applications when NP were synthesized inside bacteria during biological synthesis, and consequently, plant extracts are earning popularity due to their antioxidant and antimicrobial properties (Mighri et al. 2010; Vilas et al. 2014).

Biological nanosynthesis has been well established as a green method for the greener development of nanotechnology. However, the fundamental understanding of the biological nanosynthesis mechanisms and

Table 5 Ranking of AgNP classes according to total factor score

Total factor score	AgNP class	Possible effect
86–100	I	Acute
71–85	II	Severe
56–70	III	Medium
41–55	IV	Unobtrusive
>41	V	Slight

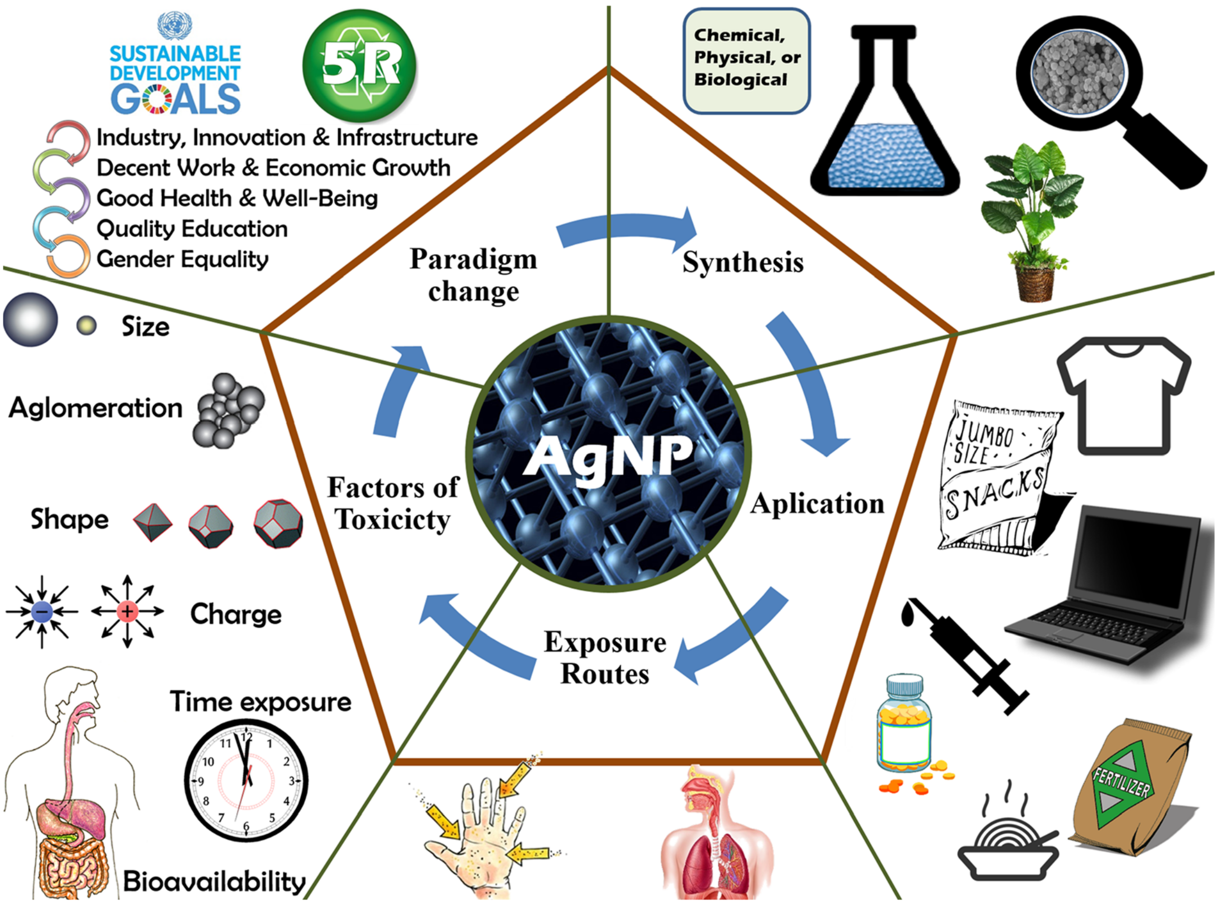

Fig. 2 Synthesis, application, exposition route, factors of toxicology, and paradigm changes related with the AgNP production and use

implementing of complete green methods to fabricate technologically important AgNP should be further promoted worldwide in order to shape a sustainable development. In addition, the wide distribution of sizes, the biological time reaction that usually is slow, and the low volume of AgNP obtained are the main obstacles hindering the acceptance of this technique worldwide.

4 Potential Exposure Pathways

Since the last century, nanotechnology has been growing exponentially because it is used in a wide range of applications and commercial products worldwide. However, there exists a lack of information concerning about human and environmental exposure to AgNP and their potential risks. For AgNP case, this exposure can be principally through dermal contact in textiles, ingested in food, or inhaled in air (Johnston et al. 2010), but recently genital route is increasing due to hygiene products (Chen and Schluesener 2008).

4.1 Oral Route

The ingestion of AgNP is tightly related to gastrointestinal tract contact, and their mobility and bioavailability through the ingestion pathway will depend, in part, on properties such as particle size and the surface chemistry that will influence their physical and chemical reactivity during transit (Mwilu et al. 2013; Luoma 2008). The toxicity of AgNP in any ecosystem is considerably affected in extent by colloidal stability (El Badawy et al. 2010). Colloidal stability is, in turn, influenced by capping agents and environmental surroundings such as ionic strength, pH, and electrolyte composition of the suspending media (El Badawy et al. 2011). According to this, the highly acidic environment of the human stomach likely influence colloidal stability of ingested NP, i.e., when a NP is into a human stomach, this NP might convert it to its ionic form (Luoma 2008), moving from the intestine to the bloodstream, with harmful consequences, including argyria (Drake and Hazelwood 2005), intestinal ulcers (Wadhera and Fung 2005), and liver damage. Inside the liver, macrophages contain in reticuloendothelial system are responsible of eliminating AgNP from blood circulation (Buzea et al. 2007). van der Zande et al. (2012) showed that AgNP can deposit on the kidneys, lungs, testicles, and brain.

Additionally, oral administration is a relevant route of exposure because of the use of AgNP in products related to food and food containing NM, which are being widely used in consumer goods increasing the human and environmental contact. Once into the body, AgNP can translocate to the blood, bone marrow, spleen, lymph nodes, liver, kidneys, brain, stomach, lungs, and small intestine, being the liver and spleen the target tissues, causing several negative effects such as argyria, intestinal ulcers, lung inflammation, and liver damage. These toxic effects of NP are directly related to the particle size, surface chemistry, particle stability, and dose administration. So, the consideration of these characteristics into future occupational and environmental risk assessments will be really relevant in order to decrease the risk of AgNP to the human and environmental health.

4.2 Respiratory Route

The respiratory system is the main entrance pathway for ultra fine particles, including AgNP, it may enter the tract due to inhalation of dust, aerosol, powders, steam, or fumes containing them, causing lung function changes, inducing inflammatory responses, such as inflammatory cell infiltration and chronic alveolar inflammation (Sung et al. 2009). Takenaka et al. (2001) showed that AgNP can accumulate in nasal cavities, alveolar region of lungs, and pulmonary lymph nodes, which activate alveolar macrophages and the release of reactive oxygen species (ROS), inducing an inflammatory response (Kim et al. 2009; Sung et al. 2009). This particle agglomeration can be eliminated by different ways, as lymphatic and mucociliary system, or by the dissolution of NP, which can result in the incorporation into the bloodstream (Takenaka et al. 2001). AgNP can also be deposited in the liver, kidneys, heart, olfactory bulb, and brain, but the presence in the olfactory bulb and brain, suggests that particles distributed through blood, can also be distributed through the nervous system (Sung et al. 2009).

The accumulation after inhaled AgNP in the human body can situate in the lungs, causing surface radicals and ROS, which are toxic to alveolar surfaces, due to their catalytic activity which derives on irritation in the respiratory tract; to trace the toxicity processes, distribution dynamic, and definition of the mechanisms of the adverse effects observed, more information is required. Further studies, to understand the toxicity of AgNP to prevent and reduce the human and environmental risk is necessary, provide reliable reference data for risk assessment estimates.

4.3 Dermal Route

The use of AgNP in textiles, cosmetics, and biomedical applications leads a direct contact through skin. The Denmark Nanodatabase (Nanodatabase 2015) shows more than 1600 dermal exposure products. The main function of the skin is to provide protection to the underlying organs, but the use of products that contain nano-sized particles like sunscreens with titanium dioxide (TiO_2) shows transdermal penetration of particles through the human epidermis and even reach dermis (Lademann et al. 1999), while Tinkle et al. (2003) stated that particles in the skin can be phagocytized by Langerhans cells could possibly generate perturbations of the immune system. Additionally, epidermal keratinocytes was capable of phagocytizing NP causing inflammatory responses (Monteiro-Riviere et al. 2005), as irritation and interference with dermal micro-flora can also be potential issues. Kim et al. (2004) also showed particles injected intradermally in the lymph nodes can systematically spread to other organs.

Due to their antibacterial properties, AgNP are extensively used in textiles, cosmetics, medical products, and surgical prosthesis, which are directly in contact with skin, but there is still a lack of information about their capability to permeate or penetrate the skin; more data on NP dermal absorption and their potential risk through the cutaneous route is necessary for consumers that can be constantly exposed to AgNP, to develop adequate models to evaluate the possibility of transdermal penetration and comprise the toxicological assessments.

5 Size, Surface Area, Shape, and Size Distribution Effects of AgNP

AgNP are used for different applications like catalysts, sensors, antibacterial, or electronics, but their potential use and effects depend in large degree on their size, surface area, shape, and size distribution properties (Vilchis-Nestor et al. 2008).

For example, the antibacterial activity of AgNP is closely related to their size and surface area, as smaller the particle is, the higher antibacterial activity has, the reason is that as decreasing the particle size, it increases the surface area allowing a higher contact with the bacterial cells; therefore, it will have more interaction than bigger particles (Morones et al. 2005). Thus, smaller particles with larger surface area can promote the dissolution of materials and lead to the release of Ag^+, which are potentially toxic, but also their shape plays an important role in the efficacy of NP; Pal et al. (2007) founded that truncated triangular AgNP with a content of 1 μg of Ag presented bacterial inhibition, while for spherical shape it needed 12.5 μg of Ag and rod shapes will require between 50 and 100 μg of AgNP content; therefore, NP with different shapes have distinctive effects on bacterial cells.

In other case, catalytic activity is dependent also on their shape, size, and size distribution. All the NP have a common trend to form aggregates and agglomerates (Yao et al. 2002), the first ones comprise two or more particles tightly bound together by rigid chemical bonding resulting from sintering or cementation, while agglomerates are collections of aggregates, loosely held together at point-to-point contact by weak electromagnetic forces, van der Waals forces, mechanical friction, and interlocking (Particle Sciences 2009). The form AgNP gets into and distributes in the organism, which also affects their toxicity, as the structure increases at size, and the surface area decreases; therefore, the toxicity will be less (Zook et al. 2011). Thus, control over size, shape, surface area, and size distribution is extremely important. This control is often achieved by modifying the synthesis methods, reducing and capping agents. (He et al. 2004).

The different and unique effects of AgNP are dependent of the size, surface area, shape, and distribution; they enhance the particle reactivity and efficiency, generating different arrangements available for photochemical, biochemical, physicochemical, or redox interactions with cells. To prevent noxious behaviors, appropriate synthesis and characterization methods are essential to comprehend, determine, and control the stabilization, agglomeration, and application influence of AgNP.

6 AgNP Toxicity and Their Potential Adverse Effects to Human and Environmental Health

AgNP may get into the human body through the skin, respiratory, gastrointestinal, and genital tract. Thereby, they may have toxic and harmful effects on a short-/long-term exposure in humans and environment, due to oxidative and inflammatory effects (Choi et al. 2010), which generates genotoxicity and cytotoxicity (Asharani et al. 2009; Kim et al. 2009; Krzyżewska et al. 2016).

Braydich-Stolle et al. (2005) studied in vitro toxicity of AgNP on a mouse spermatogonial stem cell line, concluding that cytotoxicity in the mitochondrial function and membrane leakage increases, as the concentration of AgNP increases as well. In addition, Hussain et al. (2005) observed the toxicity in different AgNP size of rat liver cells (BRL 3A) and found that after 24 h exposure, glutathione (GSH) level and mitochondrial cell function decreases exhibiting cellular contraction, irregular size, and atypical shape. Furthermore, ROS level increases, which suggest that generation of ROS and oxidative stress can be the two main mechanisms of cytotoxicity in the liver cells. Usually ROS are natural by-products of regular cellular metabolism of oxygen, and these can be discarded by cell's radical-scavenging activities but, a suddenly increase of ROS is above the capability of antioxidant defenses, triggering oxidative stress due excess of ROS (Luoma 2008; Marambio-Jones and Hoek 2010). Besides, Asharani et al. (2009) showed the genotoxicity of starch-coated AgNP in human lung fibroblast (IMR-90) and glioblastoma (U251) cells, inferring that AgNP reduce ATP content in cell, cause mitochondrial damage, and increase production of ROS which originate DNA damage and chromosomal abnormalities. In this context, Kim et al. (2010) demonstrated in vivo oral toxicity of rats; with (56 nm) AgNP over 90 days, concluding that exposure to more than 125 mg/kg may result in liver damage. Moreover, Hsin et al. (2008) evaluated AgNP cytotoxicity by inducing apoptosis in NIH3T3 fibroblast cells and determined that AgNP acts through ROS and c-Jun N-terminal Kinases (JNK) to induce apoptosis via the mitochondrial pathway.

These studies suggest that AgNP cytotoxicity and genotoxicity depends on size, concentration, and time exposure, which mainly promote the induction of ROS, reduction of GSH, and mitochondrial inhibition, leading into oxidative stress, DNA damage, apoptosis, and necrosis. In addition, it may produce reproductive failure and developmental malformation. The above biological mechanisms might be related to biological and environmental alterations, such as surface oxidation by O_2 or thiol compounds, as well as for lighting conditions, interactions with lipid molecules, nucleic acids, and other proteins in media, which lead the releasing of Ag^+, and consequently, the interaction with other molecules is increased (Johnston et al. 2010; Reidy et al. 2013; Yu et al. 2013). AgNP can be in contact with membrane proteins, activating signal pathways, which can drive to an inhibition of the cell proliferation (Braydich-Stolle et al. 2010). It also may introduce the cell by endocytosis, causing mitochondrial malfunction, producing ROS harmful to proteins and nucleic acids (Carlson et al. 2008; Choi and Hu 2008; Asharani et al. 2009; Bressan et al. 2013). Oxidative stress, as explained before, takes place when ROS exceeds the capability of the cellular antioxidant defense system. This depletes glutathione and protein-bound sulfhydryl groups and enhanced lipid peroxidation and DNA damage, and sulfhydryl homeostasis occurs by oxidative damage (Stohs and Bagchi 1995; Piao et al. 2011; Awasthi et al. 2013). An important toxicity mechanism for AgNP is the influence of the ionic and nanoform of Ag with sulfur macromolecules such as proteins, due to the strong affinity of Ag for sulfur (Hsin et al. 2008; Rai et al. 2009; Mcshan et al. 2014).

Asharani et al. (2009) and Bressan et al. (2013) observed that as AgNP accumulate outside the mitochondria, it causes damage and disturbance in the respiratory chain, resulting in ROS generation and oxidative stress, suggesting that the disruption of the mitochondrial respiratory chain increases ROS production and interrupts the ATP synthesis, which causes DNA damage. Additionally, Hsin et al. (2008) and Cheng et al. (2013) studied the AgNP toxicity mechanism in NIH3T3 fibroblasts, finding that AgNP acts through ROS and C-Jun N-terminal kinase, inducing apoptosis via the mitochondrial pathway.

An updated research was published recently in order to provide a comprehensive review of the behavior of nanosilver in multiple mammals, which might be found in Wen et al. (2016). Additionally, various toxicity mechanisms of nanosilver have been proposed during the last years, but the full mechanisms have not been determined yet. Nevertheless, before getting a definite conclusion to determine the real impact of the NP on the human and environment heath, further in vivo studies are recommended (Fernández-Luqueño et al. 2014).

AgNP toxicity is influenced by different factors as their physical and chemical properties, like size, shape, surface, distribution, solubility, and stability that affect the cell surface causing malfunctions and aberrations, such as by the environmental conditions including pH, organic matter, light, or salinity, which could increase or decrease the toxicity (Johnston et al. 2010; Reidy et al. 2013). To deduct the transformation, behavior, and fate of AgNP in complex environmental conditions, further research in source, transport cytotoxicity, and genotoxicity are required to understand the complete process involved in the mechanisms of toxicity to prevent compromise human health as well as the environment.

The characteristics of AgNP may result in toxicological actions related to their nanoscale, which may have implications on their toxicological limits and eventual regulations. Actually, there is a regulatory gap between the technological innovations and the regulatory safeguards in order to look after the environment, i.e., a regulatory oversight to ensure the appropriate identification, evaluation, and disposal of AgNP is indispensable.

A regulatory framework for nanomaterial risk assessment, based on their toxicological properties was developed according to recent toxicological studies (Table 4). The first step to determinate the toxicological impact of any AgNP is to determinate the score for each factor according to Table 4. After that, it is necessary to determine the total factor score and compare it with the ranking shown in Table 5. The properties that we identified could give some tentative steps towards defining a new regulatory approach on which this technology may operate. These properties should not be viewed as the unique factors to be considered in a safety regulation of NM. Regardless of the regulatory approach that is applied, there exists an obligation between regulators and the regulated community to ensure that a material is properly evaluated in order to determine whether it poses a risk to human or environmental health. This evaluation should be based not only on the intrinsic hazard potential of the materials but also on the consideration of exposure potential during manufacturing, use, and disposal.

7 AgNP Applications

In recent years, AgNP have gained great interest due to their conductivity, chemical stability, catalytic, and antibacterial activity, inter alia. AgNP represents one of the most profitable materials in the industry, with a wide range of products worldwide, basically due to their antimicrobial activity, which is their mainly used characteristic on different applications, such as water treatments, water filters, sprays, detergents, refrigerators, washing machines, paints, cosmetics, and electronics (Gong et al. 2007; Jain and Pradeep 2005; Kumar et al. 2008; Gupta and Silver 1998). Nevertheless, AgNP are especially developed in technological and medical devices and supplies, food industry, and textile area.

7.1 Technological and Medical Devices and Supplies

The purpose to use AgNP in this area is to prevent bacterial infections and reduce inflammation. They are used in wound dressings, contraceptive devices, bone cements, female hygiene, dental fillings, surgical instruments, catheters, bandages, sutures and prosthesis, compose, or coat with AgNP to prevent bacterial growth (Silver et al. 2006; Furno et al. 2004; Singh and Nalwa 2011). In addition, these are used for treatment of diseases that requires sustained drug delivery in blood or specific tissue. Biosensors are another AgNP application, due to their plasmonic properties; they can effectively detect numerous illnesses and disorders in human body including cancer (Zhou et al. 2011). These properties are also useful for bio-imaging as they can be used to monitor dynamic reactions (Sotiriou et al. 2011). Also AgNP have been applied for the impregnation or coating of different surgical materials in different areas as dental instruments and composites, Ahn et al. (2009) shows the use of AgNP in orthodontic adhesives increasing its strength and its resistance to bacteria. Furthermore, Roe et al. (2008) and Furno et al. (2004) use AgNP to developed polyurethane catheters with an antibacterial coated preventing bacterial infections and complications. Surgical masks (Li et al. 2006), cardiovascular heart valves (Grunkemeier et al. 2006), and bone cements used in artificial replacements (Alt et al. 2004) and dressings commonly employ to treat wounds, burns, and ulcers are other medical applications used in the prevention and treatment of bacterial infections with AgNP (Duran et al. 2007; Chaloupka et al. 2010).

AgNP found in medical applications their major desired field, due to its antibacterial, anti-inflammatory, antifungal, and antiviral effects is considered hugely effective and useful against infections, diseases, accelerating healing, and reducing inflammation, situating as the preferred candidate for use in different treatments and therapies with a growing trend in the future years.

7.2 Food Industry

In this field, AgNP are mainly used in food storage, water purification, and agriculture, by improving and prolonging nourishment preservation, through a biodegradable coating, with fungistatic effects, slowing the growth of pathogenic fungi (Rhim et al. 2013) and extending their shelf-life (Duncan 2011). Also, developing “smart packaging” designed to detect changes in the food produce by microbes or spoiling gases before it becomes contaminated, as well as for changes in environmental conditions for self-repair holes or leaks (Silvestre et al. 2011).

AgNP are also used to encapsulate and control the delivery of nutrients, flavors, or fragrances (Huang et al. 2009), as well as for powerful pesticide, herbicides, fertilizers, and other agrichemicals developed to improve the efficiency of growing crops (Nair et al. 2010). Also Das et al. (2012) used AgNP for water treatment, obtaining potable water free from pathogens and pesticides in one step process.

The application of AgNP in the food industry will have a deep impact on several products. As a powerful bactericide, it can be used in food storage, packaging, and processing, such as storage containers. Nevertheless, for a complete developing of food packaging, there are different issues to take into account, the most significant are the safety concerns due to the possible migration of AgNP from the packaging material into food, and their consequential toxicological effects, as well as the proper labeling of products containing AgNP to give the consumer the right to choose whether to avoid these products or not.

7.3 Textile Area

On this category, AgNP have been applied in the manufacture of clothing, underwear, socks, and footwear with fibers and yarns incorporated. Antimicrobial textiles amended with AgNP potentiate ion activity, conferring antibacterial and anti-odor effect (Chen and Chiang 2008; Yeo et al. 2003). Besides these, AgNP in textile fibers control the release of antibacterial agents in order to extend the biocidal activity even after multiple washing cycles (Gao and Cranston 2008). Duran et al. (2007) show that cotton fabrics incorporated with AgNP displayed a significant antibacterial activity against *S. aureus*, concluding that incorporation in cloths, provide sterile properties. Additionally, Xue et al. (2012) modifies fibers coated by AgNP with hexadecyltrimethoxysilane obtaining superhydrophobic cotton textiles, obtaining other properties, such as electrical conductivity, antistatic properties, and UV-protection.

Nano-textiles coated with AgNP have a great commercial potential in a wide variety of products like bed lining, medicinal bandages, shoes, socks, and underwear. The coated fabrics can also be used in domestic cleaning appliances or house furniture like couches and living rooms. Furthermore, the materials involved in the preparation are cheap, non-toxic, and commonly available, expecting to become multifunctional materials. However, it is important to consider further investigation in the release of AgNP into the environment though water after several washing cycles and final disposal of products.

8 Future Developments and Challenges

Currently AgNP are used in numerous commercial applications, but due their previously described properties, AgNP recently research has revealed novel developments focusing principally in cancer treatments, wound healings, tissues remodeling, and repairing (Nagase et al. 2006). Also Sriram et al. (2010) described the efficacy of AgNP as antitumor agent using Dalton's lymphoma ascites (DLA) cell lines, concluding that AgNP possess antitumor properties without adverse effects and as a cost-effective alternative in the treatment of cancer and angiogenesis-related disorders. Additionally, Jeyaraj et al. (2013) shows cytotoxic effects against breast cancer (MCF-7) cell lines observing that the AgNP induces DNA damage through the generation of reactive oxygen species, suggesting that AgNP will help to find alternative chemotherapeutic agent.

Also AgNP are being used to inhabit HIV-1 replication. Elechiguerra et al. (2005) found that in vitro AgNP interact with the virus and inhibit its ability to attached cells, as well, for hepatitis B virus (Lu et al. 2008) and herpes treatments (Baram-Pinto et al. 2009).

Despite the success of promising developments with nanoparticles, AgNP face various challenges related to their use in several consumer products, because the adequate final disposal and the released quantities into the environment are unknown. In that sense, Benn and Westerhoff (2008) studied the release of AgNP from commercial socks into water and they found that socks leached as much as 650 mg AgNP with an average size from 10 to 500 nm, concluding that WWTP could treat higher concentration of silver wastewater, but limiting their biosolids disposal as agricultural fertilizer. In other research, Benn et al. (2010) tested the release of AgNP from several home products contains a maximum of 270,000 μg Ag/g product^{-1}, after submitting to a 1-h wash with tap water to assess the potential release of Ag into aqueous environmental matrices such as wastewater, surface water, and saliva, they found that Ag released in quantities up to 45 μg Ag/g product^{-1}, in size fractions of ±100 nm, concluding that the release of AgNP via aquatic media indicates a clear potential exposure to sewage and WWTP. In addition, Sussman et al. (2015) also investigate the release of AgNP from medical devices in aqueous media, using three wound dressing products and two catheters finding after extract assays that one out of five devices released significantly more AgNP than the others, raising the concern of potential risk assessment.

Additionally, Quadros and Marr (2011) investigated the inhalation exposure emitted by airborne particles from anti-odor spray, throat spray, and surface disinfectant, detecting that products can be emitted into 0.24–56 ng of Ag and can rise up to 70 ng by constant use on a modeling exposure, with an average range of 1–2.5 μm, inferring that AgNP emitted by aerosols per spray action may deposit in the respiratory tract. Furthermore, another research by Quadros et al. (2013) assessed the potential for children's exposure to AgNP during the use of plush toys, fabric products, breast milk storage bags, sippy cups, cleaning products, humidifiers, and humidifier accessories, by measuring the release of ionic and particulate Ag from products into water, orange juice, milk formula, synthetic saliva, sweat, and urine. They concluded that fabrics, plush toys, and cleaning products were most likely to release Ag, also in liquid media sweat and urine yielded the highest amount of Ag release, up to 38 % of the silver mass in products; this research shows the potential of AgNP in dermal and respiratory exposure on consumers. Hence, exhaustive investigations on the potential risks and exposure paths of consumer products containing AgNP are indispensable to understand and minimize the impact on human and environmental health.

The exploitation of AgNP in many commercial products and applications are continuously increasing because their antibacterial, antiviral, antifungal, and anti-inflammatory properties give them immense possibilities of development in order to increase the social welfare worldwide. However, if the nanoparticle demand increases, it would be proper to design a cleaner and safer way to produce, use, and dispose the products containing AgNP.

9 Conclusions

In conclusion, AgNP offers a bunch of opportunities for developing innovative products with applications in biomedicine, pharmaceuticals, food processing and storage, as well as electronics, home appliances and textiles, which can bring important benefits to industry and consumers. However, negative effects caused by exposure, use and final disposure of products using AgNP, may include DNA damage, gene perturbation and metabolic changes, which toxicity varies depending on size, shape, size distribution, exposure, and concentration in the environment.

Due to its surface area and energy reactivity, once in the environment, AgNP may suffer different transformations such as oxidation, agglomeration, sedimentation, or reduction that modifies their behavior, and even with the recent synthesizing and characterization techniques, it is still complicate tracking in the environment, compromising the generation of real and reliable data. Even more, the complexity of the environment turns extremely difficult to determine a position on its toxicity, because depending on its conditions is how AgNP will behave. Proper investigation in use and fate of AgNP on a complex environment is crucial to design appropriate methods to forecast the real mechanisms of impact on human health and natural environment.

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