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Antibacterial Silver

Silver as Antibacterial Agent: Ion, Nanoparticle, and Metal

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Dedicated to Professor Günter Schmid on the occasion of his 75th birthday

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The antibacterial action of silver is utilized in numerous consumer products and medical devices. Metallic silver, silver salts, and also silver nanoparticles are used for this purpose. The state of research on the effect of silver on bacteria, cells, and higher organisms is summarized. It can be concluded that the therapeutic window for silver is narrower than often assumed. However, the risks for humans and the environment are probably limited.

From the Contents

1. Introduction

Silver metal has been used by mankind for about 7000 years. Its use in coins and cutlery is due to the corrosion resistance of the noble metal, but also to its antibacterial effect. By slow corrosion, silver ions are continuously released. Herodot has already mentioned the antibacterial action of silver,[1] and since the 19th century, this was related to silver ions.[2,3] With many bacterial strains today being resistant against antibiotics, silver is used in many cases for disinfection, as coatings as well as in ionic or nanoparticulate form. It has also found application in many consumer products outside of the medical sector, for example, in textiles or sprays to prevent bad odors from sweat.[4–7] It is also increasingly used in cosmetics,[8] and it has also been proposed in medical implants and instruments for the prevention of infection.[1,9]

Herein, we discuss the use of silver in its different forms of application as metal, salt, and nanoparticle from a chemical viewpoint. We review literature data on its interaction with biological systems (from single-celled organisms over cell culture to whole organisms), and close with a critical assessment of the current knowledge.

2. History of Silver as an Antibacterial Agent

Alexander has summarized the medical applications of silver.[1] It was first mentioned by Herodot that Persians used silver containers for the transport of water. In ancient times, silver was used by the Greeks, the Romans, the Egyptians, and others for the conservation of water and food.[1] It has also been used for a long time for the prevention of infection of burnt skin.[10,11] In the first half of the 20th century (until the introduction of antibiotics), silver was used in large extent as aqueous colloidal dispersion for oral consumption (also for the prevention of infection). In some cases, this led to argyria, that is, to the incorporation of silver into the skin and into other tissues. Alexander has reported that the "blue blood" of noblemen was possibly due to blue–gray silver deposits in the skin, which were caused by the frequent use of silver cutlery.[1] No cases of argyria were reported in the medical literature until the 18th century.[1] Starting around 1900, there were cases where the uptake of large amounts of silver, both intravenously and orally, led to spasms, gastrointestinal disorders, and even to death.[1] The application of silver nitrate solution for the therapy of eye infections was very common in the 20th century, and also to prevent eye infections in newborn babies (so-called Credé's eye prophylaxis, which was legally mandatory in Germany until 1992). However, it was objected that too large amounts of silver nitrate may lead to corneal damage.[3] Even today, installations are sold to produce aqueous colloidal silver at home for daily consumption; a habit which is prominent to some extent in non-conventional medicine.

3. Silver as Metal

As a noble metal ($E^0 = +0.80$ V), silver is not attacked by water or acids. However, silver metal continuously releases small amounts of ions, which act antibacterially at the metal surface. As oxidizing agent, dissolved oxygen (O_2) in particular comes into play ($E^0 = +1.23$ V), whereby the oxidation can be enhanced by complexation of the released silver ions by inorganic ions or organic molecules. A similar process is used in the oxidation of metallic gold by oxygen from air in the presence of cyanide as complexing agent: The cyanide leaching process. The antibacterial effect is also known for copper in weaker form. Glover et al. have recently reported that macroscopic metal objects continuously release silver nanoparticles and copper nanoparticles, a remarkable observation.[12]

Coatings of silver on other substrates (typically stainless steel) are often preferred to pure silver objects owing to the comparably high price of silver, for example, in the case of medical instruments. Silver can be deposited electrolyti-

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cally,[13] by electrophoretic deposition of silver nanoparticles,[14,15] by coating with silver nanoparticle-loaded polymers,[16] or by physical sputter processes.[13,17] It should be noted that the contact of metallic silver with less noble metals leads to a corrosion element that promotes the corrosion of the less noble metal. Metallic silver is used in alloys, for example for coins, in jewelry, and in dental alloys (also as silver amalgam). Some permanent implants are coated with silver, for example, the so-called mega-endoprostheses that are implanted after the removal of bone tumors. In a long-term study, Hardes et al. observed a reduction of the infection rate with no adverse effects.[18,19] In contrast, artificial heart valves that contained silver sutures led to local inflammations that were ascribed to released silver.[20]

4. Silver Salts

The application of silver metal as bactericidal agent requires the oxidation to the Ag^+ ion, which is a slow process under normal conditions and leads to low effective silver concentrations. Therefore, silver salts were used since the first century BC for disinfection.[1] A prominent example is silver nitrate that was applied in medicine as early as 69 BC.[1] As "lunar caustic" (Latin: *Lapis infernalis*), it was used since the middle ages in solid form to treat inflammations and warts.[10] The high solubility of silver nitrate leads to a high local silver concentration, which kills bacteria and damages the surrounding tissue as well.

Sparingly soluble salts, such as silver halides and silver sulfide, lead to a slower release of silver. Here, the solubility decreases in the series $AgCl > AgBr > AgI > Ag_2S$ in accordance with the solubility product. For instance, silver chloride is applied in antibacterial sprays and as antibacterial additive to cleaning liquids. The solubility product is $1.7 \times 10^{-10}\ mol^2\,L^{-2}$, that is, the equilibrium concentration of silver is $1.4\ mg\,L^{-1}$ in pure water. Table 1 summarizes some equilibrium concentrations of silver in the presence of chloride ions.

The solubility product of silver sulfide is $5.5 \times 10^{-51}\ mol^3\,L^{-3}$. Owing to the protolysis of sulfide to HS^- and H_2S, the solubility strongly depends on the pH value, that is, silver sulfide is much better soluble at low pH. In saltwater, the presence of different ions leads to a complex equilibrium of various species and complexes (especially chloro and hydrogen sulfide complexes).[22,23] Besides, humic acids[24] and proteins[25] can bind silver ions. This prevents a prediction of the solubility and requires suitable experiments to measure the silver concentration. In biological media such as blood, the same problem arises.

Table 1: Some equilibrium concentrations of silver ions in the presence of chloride (computed from the solubility product of AgCl).

Medium	Equilibrium concentration of Ag^+
freshwater; $c(Cl^-) = 0.03$–0.3 mM	0.06–$0.6\ mg\,L^{-1}$
blood plasma; $c(Cl^-) = 95$–110 mM	$0.18\ \mu g\,L^{-1}$
seawater (ocean); $c(Cl^-) = 540$ mM	$34\ ng\,L^{-1}$
seawater (European coastal waters)[21]	1–$20\ ng\,L^{-1}$ (experimentally determined range)

Silver sulfadiazine is the silver salt of an organic molecule. It is remarkable that it sulfadiazine is a sulfonamide, which itself has antibacterial properties, that is, a form of combination drug arises. Zeolites can be loaded with silver ions and silver nanoparticles, causing a slow release system of silver ions.[26–29] To treat wounds and burns, silver is added to bandages[30–33] and also applied as silver sulfadiazine cream or as silver nitrate.[34–36]

The state of silver in solution determines its biological effect. We found a considerable decrease of the toxicity of silver towards cells when serum albumin was present, which we ascribed to the binding of silver to the protein.[37] It was also shown that dissolved organic compounds considerably decrease the toxicity of silver towards *Daphnia Magna*.[24] Note that sparingly soluble silver salts such as AgCl can also be present in colloidally dispersed form, therefore they should also be able to penetrate the cell membrane (for example by endocytosis).

5. Silver Nanoparticles

Nanoparticulate (colloidal) silver has also been known for about 120 years.[4] Typically, the synthesis occurs by reduction of soluble silver salts with reduction agents such as citrate, glucose, ethylene glycol, or sodium borohydride. The reduction can be carried out in water as well as in organic solvents. The addition of stabilizing compounds, which prevent growth

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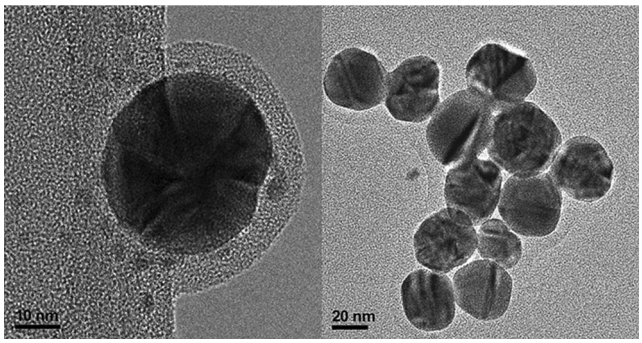

Figure 1. High-resolution transmission electron micrographs of stabilized silver nanoparticles. Left: Silver nanoparticles after reduction with citrate, stabilized with poly(*N*-vinylpyrrolidone) (PVP); right: Silver nanoparticles after reduction with citrate and without further functionalization. The domain structure (twinning) of the nanocrystals is clearly visible for all particles (taken from Ref. [37] with permission).

Figure 2. Some noble-metal-containing cosmetics and a sports sock with silver coating.

and aggregation of the formed silver nanoparticles, plays a decisive role. Figure 1 shows typical transmission electron microscopic images of silver nanoparticles.

Practically, the reproducible synthesis of silver nanoparticles in the laboratory is more difficult than expected.[38] This can be related to the initially formed nuclei of metallic silver, which develop into different morphologies and crystal sizes when the reaction conditions (concentrations, reduction agent, temperature, presence of additives) are changed.[38,39] Many different kinds of silver nanoparticles have been described in the literature.[40] Besides spherical particles, bipyramids,[41] discs,[42] rods,[39,43–46] cubes,[47–50] prisms,[51,52] rings,[53] platelets,[54] triangular prisms,[55] and octahedra[49] were found, depending on the reaction conditions. Xia reviewed nucleation and growth in the case of silver nanoparticles[38] and pointed out that even small impurities in the silver nitrate used (such as photolytically formed silver clusters) can influence the nature of the products.[38,56] Additives can constrain the growth of distinct crystal faces by preferential adsorption;[47–49] if polymers are used for functionalization, the nature of the product sometimes depends on the batch of the polymer (from our own unpublished experience). It is also noteworthy that the particle morphology is sometimes not stable over time. For example, a photoinduced transformation of spherical particles to prisms was reported.[57] Frequently, the synthesized silver nanoparticles tend to aggregate after a few hours or days if the colloidal stabilization is insufficient. Good stabilizers are polymers such as poly(*N*-vinylpyrrolidone) (PVP) and substituted phosphane ligands.[37]

Physical syntheses of silver nanoparticles are typically carried out in the gas phase.[58] Such silver nanoparticles are not surface-functionalized, and typically not redispersable in water, but are highly agglomerated. Laser ablation from metallic silver in liquids has been developed into an attractive way to prepare colloidal silver dispersions.[59,60] Flame synthesis is another method to prepare silver nanoparticles from the gas phase.[61,62]

"Nanosilver" has gained some popularity in consumer products. For example, refrigerators, mobile phones, clothes, plasters, toothbrushes, and cosmetics are equipped with silver to obtain an antibacterial effect (Figure 2). Installations for the preparation of colloidal silver at home are available by which silver nanoparticles are created by electric pulses in water. The motivation is always the antibacterial action of silver, which combats even germs that are resistant against antibiotics. It is noteworthy that other noble metals, such as gold or platinum, are also added to cosmetics despite the fact that a biological effect is unlikely. We have measured the noble metal contents in some cosmetics by atomic absorption spectroscopy (AAS) and found that the concentrations of silver covered a range of more than three orders of magnitude (Table 2). This raises the question about the medical evidence for the choice of these silver concentrations. In these cases the border line between cosmetics and a drug is not sharp, if an antibacterial effect should be accomplished by a high silver concentration. Provided that the purity is given, metallic silver is approved for use in cosmetics in the European Union, but there is no explicit statement regarding nanoparticulate silver in this legal regulation. However, the regulation explicitly points out the necessity for a thorough characterization of nanoproducts.[63]

Table 2: Noble metal concentration in some cosmetics, determined by atomic absorption spectroscopy after chemical pulping. The content of platinum was below the detection limit of 15 ppm.

Sample	Noble metal concentration [ppm]	Packaging size [mL]	Noble metal per package [mg]
Silver toothpaste	0.1	75	0.0075
Silver shower gel	2.7	200	0.54
Silver hand cream	2700	75	202.5
Silver deodorant (roller)	950	50 mL	47.5 mg
Gold night cream	2.4	50 mL	0.12 mg
Platinum anti-wrinkle cream	<15	50 mL	<0.75 mg

Silver-containing textiles are advertised on account of their antibacterial effect and the corresponding reduction of bad odors after sweating.[64–67] Concerns have been raised about the release of silver after repeated washing into sewage treatment plants and further into the environment.[68,69] Geranio et al. found silver concentrations between 8 and 21 600 ppm in silver-containing textiles, with silver as metallic nanoparticles and as silver chloride nanoparticles.[68] Wiechers and Musee discussed the fate of nanoparticles in the environment after use and developed parameters for risk assessment. They concluded that after all, silver is less problematic in the environment than TiO_2.[8]

Owing to its antibacterial effect, nanoparticulate silver is also used to coat medical instruments and products,[9,15,16,70,71] for example, for venal catheters,[14,72] urinary catheters,[73] drainage catheters,[74,75] wound and burn bandages, scalpels and needles.[15] It is remarkable that Bayston did not find an antibacterial effect in vitro of silver-containing neurosurgical catheters.[76]

Silver-coated medical devices must cause a sufficiently high and long-lasting silver ion concentration in their vicinity to have the desired antibacterial effect. However, a negative impact on human cells surrounding the device must be avoided.[35,36,77] This can be achieved by the application of a thin silver-containing polymer layer.[71,78,79] Agarwal et al. used the layer-by-layer technique[80] to immobilize silver nanoparticles in a thin polymer layer on the surface. This polymeric layer showed an antibacterial effect in vitro, but no cytotoxicity.[78,79] Cao et al. have coated titanium with silver nanoparticles by silver plasma immersion ion implantation and observed that such silver-containing surfaces inhibited bacterial growth and stimulated the proliferation of eukaryotic cells at the same time.[77] Silver nanoparticles were released from calcium phosphate ceramics, induced by bacteria, as described by Loher et al.[61]

Nanoparticles release ions unless they consist of fully insoluble compounds.[81,82] Consequently, silver is released from nanoparticles by slow oxidation (Figure 3). The release kinetics depend on the size of the nanoparticles, their surface functionalization, the temperature, and the composition of the surrounding medium.[83–89] If dissolved molecular oxygen is completely absent, there is almost no dissolution of silver nanoparticles.[90,91] The release of silver ions can also be regulated in an elegant way by mixing nanoparticles of more and less noble metals in a polymer in the sense of a local corrosion element.[92] In summary, silver nanoparticles can be considered as depot for silver ions. However, Sotiriou et al. have postulated that the antibacterial effect of silver nanoparticles depends on their size. Larger nanoparticles (> 10 nm) release less silver ions and may have an antibacterial effect in direct contact with bacteria.[62,93] This is in contrast to the recent studies by Xiu et al., who excluded a "nano effect".[91] Sometimes an application of silver nanoparticles as drug carriers and for imaging is proposed; on account of the comparably high cytotoxicity of silver this is only reasonable if an uncontrolled release of silver ions can be prevented by a tight surface functionalization.[94–98]

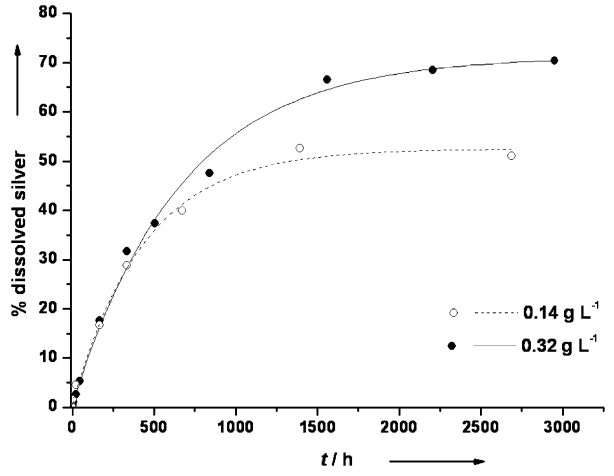

Figure 3. Release of silver ions from citrate-stabilized silver nanoparticles at 37 °C at two different silver concentrations (modified from [83]).

6. The Biological Action of Silver

The literature on the biological effect of silver is vast. A search with the keywords "silver and toxi*" gave more than 4300 entries in the Web of Science. A narrowing to "silver and toxi* and nano*" still gave more than 800 entries, with strongly increasing tendency. Tolaymat has published a bibliometric analysis of this area in 2010.[99] In the following, we present the state of the literature in a condensed form.

A silver cation is a soft Lewis acid that has an affinity to sulfur, but also to nitrogen. Thereby, it has many possibilities to disturb biochemical processes. Besides the formation of sparingly soluble silver salts (AgCl, Ag_2S), the adverse effect of silver ions is due to interactions with thiol and amino groups of proteins, with nucleic acids, and with cell membranes.[3,7,100–103] The formation of reactive oxygen species (ROS) was also observed,[104–110] but excluded in other cases.[90,111,112] It seems as if the formation of reactive oxygen species in the presence of silver depends on the involved cell type.[111,112] Thus, as there are different possibilities for silver to distract biological processes, a general statement about the origin of the toxic action of silver is not possible.

In general, cells readily take up nanoparticles.[82,113–120] Eucaryotic, non-phagocytising cells take up silver nanoparticles by endocytosis and macropinocytosis.[112,121] By a combination of focused ion beam (FIB), scanning electron microscopy, and energy dispersive X-ray spectroscopy, silver nanoparticles were visualized directly inside a cell.[121] Alternative methods to trace nanoparticles in cells are confocal laser scanning microscopy (CLSM) for fluorescing particles[120,122] and fluorescence microscopy,[123] surface enhanced Raman spectroscopy (SERS),[124] and transmission electron microscopy.[96] Like all nanoparticles, silver nanoparticles are rapidly coated by a shell ("corona") of proteins if brought into a biological medium.[125–131] This corona clearly influences the interaction with cells.[113,132]

Metallic silver, silver nanoparticles, and sparingly soluble silver salts release silver ions when they come in contact with water. These silver ions are the biochemically active agent.[7]

It must be stressed that these silver ions will react to sparingly soluble salts, which precipitate or remain in colloidal dispersion and will also undergo complexation with proteins and other biomolecules if they are released in "real" media. Such an environment is any biological environment, like blood, cell culture medium, or "impure" water found in the environment; chloride will lead to the precipitation of AgCl (see Table 1). Thus, the ion-release curves that are typically measured in pure water cannot be easily transferred to more complex (biological) environments.[85,86] Nature and concentration of the silver species that are present in such media are mostly unknown. In a fundamental study was recently shown that a specific "nano effect" can be excluded for silver. Silver nanoparticles were prepared and stored under anaerobic conditions. The effect on bacteria (*E. coli*) was also studied under exclusion of oxygen. The toxicity was clearly correlated to the amount of released silver ions. Nanoparticles (5 and 11 nm diameter) alone were not toxic up to 200 $mg\,L^{-1}$.[91]

Typical results of the action of silver on single-celled organisms are comprised in Table 3. Although the results are not strictly comparable owing to different experimental conditions and different silver species, it can be concluded that the toxic concentrations and inhibitory concentrations are in the range of 0.1 to 20 $mg\,L^{-1}$. In a remarkable work, Hwang et al. showed that *L. pneumophila* and *P. aeruginosa* are rapidly killed at a silver concentration of 0.1 $mg\,L^{-1}$, but survive easily as endosymbionts in amoeba.[133] The viable but nonculturable state (VBNC) which can be assumed by bacteria upon external stress (like an incubation with heavy metal ions), can easily be mistaken with a killing.[134,135] This was recently demonstrated by Flemming et al. for copper ions.[136] Sheng et al. showed that silver nanoparticles are toxic for planktonic bacteria, but that the same bacteria are almost insensitive towards silver if present as biofilm.[137] This illustrates the problems when transferring the results of in vitro cell culture experiments to practical situations.

Table 4 shows the effect of silver on eukaryotic cells in vitro. The toxic concentrations are around 1–10 $mg\,L^{-1}$ for silver ions and 10–100 $mg\,L^{-1}$ for silver nanoparticles. Silver ions can also interact with the surface of viruses and cause their inactivation.[138,139]

Table 5 shows the effect of silver on higher organisms. The lethal concentrations are in the range of a few $mg\,L^{-1}$ for land-living organisms and in the range of a few $g\,L^{-1}$ for sea-living organisms. It must be stressed that concentrations only make sense for sea-living organisms. For land-living organisms, it is more reasonable to give lethal doses (LD50) in mg per kg body weight. For metallic silver, such a number would not be reasonable because a macroscopic piece of silver (like a swallowed coin) would only be marginally dissolved in the gastrointestinal system. For colloidally dispersed metallic silver, this will likely change, because silver nanoparticles release silver ions upon immersion in water. Owing to the higher specific surface, this occurs faster than for macroscopic silver objects. For mice, the LD50 value is of the order of 50–100 $mg\,kg^{-1}$ for soluble silver salts.[180] The WHO gives a no observed adverse effect level (NOAEL) for humans with 10 g silver over the whole lifetime, which corresponds to a maximum silver concentration in tap water of 0.1 $mg\,L^{-1}$.[180] The tap water regulation act (*Trinkwasserverordnung*) in Germany permits 0.01 mg silver L^{-1}.

It is not possible to extract a clear trend in the toxicity of silver nanoparticles as a function of particle size from Tables 3–5. This is due to the variation of the nanoparticles used with respect to functionalization and charge and also to the variation of the biological systems used. However, there are studies of the effect of silver nanoparticles with different size with all other conditions being identical. These indicate that normalized to the same amount of silver, smaller silver nanoparticles have a higher toxicity than larger silver nanoparticles or silver microparticles.[105,146,151,153,171] Even more difficult are statements about the relationship between particle morphology and biological effect; only very few studies have been published with this respect.[181] Besides the release of silver ions, the kinetics of cellular uptake will play an important role, and the agglomeration in biological media will also influence the bioavailability.[37,82,113,114]

A high dose of silver leads to argyria.[1,182] Bowden et al. have reported on a clinical case where argyria occurred after a few months of eating a silver-containing food supplement.[183] Plack et al. have reported the argyria of a patient who was used to chew photographic films after he gave up smoking. It is remarkable that the sparingly soluble silver halides from the photographic film were so easily mobilized in the gastrointestinal tract.[184] The year-long application of a nose spray that contained protein-bound silver also led to argyria, as Stammberger reported.[185] Negative effects on silver on the reproductive system and on the embyonal delevoplent were found at a concentration of 10 $mg\,L^{-1}$.[150,162,168,186]

The mobility of nanoparticles in the body is difficult to investigate. Fundamental results were obtained with radioactively labeled nanoparticles, which showed the distribution in the body in vivo after exposition.[187–192] Alternatively, nanoparticles can be detected by elemental analysis (for example by AAS or ICP-MS) in tissues after exposition or injection.[193] The distribution in the bloodstream must be taken into account, as well as the accumulation in different tissues and organs and the final excretion. Lankveld et al. have modeled the biodistribution in a rat model in vivo, based on experimental data.[193] The aspects discussed below on the pathways of silver in the environment (precipitation, complexation, dissolution, adsorptive binding to surfaces) apply to biological systems as well, but locally different cellular effects like endocytosis lead to an even more complex situation. In biological environments, silver ions precipitate as silver chloride or form complexes with biomolecules. Silver nanoparticles will form a protein corona and change their properties, sometimes leading to agglomerates and precipitation. In this context, Teeguarden discussed the aspects of particle dosimetry in vitro.[114]

A fundamental concern in the medical application is definitely the development of bacterial resistance against silver. This was discussed in the literature as early as in the 1970s.[194–196] This topic was extensively studied by Simon Silver (*Nomen est Omen*). He showed that the resistance against silver in *Salmonella* is coded by pMG101 plas-

Table 3: The biological effect of silver on single-celled organisms (bacteria, fungi, and algae).[a]

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
Bacillus subtilis ATCC 6633	Ag nanoparticles	6.5–43.8 nm	not reported	$MIC_{90} = 6.25\ mg\,L^{-1}$; $MBC_{99.9} = 12.5\ mg\,L^{-1}$	[140]
Bacillus subtilis	Ag nanoparticles	10 nm	citrate	no growth inhibition at $50\ mg\,L^{-1}$; EC_{50} (CFU assay) $> 10\ mg\,L^{-1}$; EC_{50} (LTP assay; 0 h) = 0.01-1.41 $mg\,L^{-1}$; EC_{50} (LTP assay; 1 h) = 0.06-0.09 $mg\,L^{-1}$; EC_{50} (LTP assay; 2 and 3 h) $< 0.025\ mg\,L^{-1}$	[141]
Bacillus subtilis	Ag_2S nanoparticles	9 ± 3.5 nm	unfunctionalized	not toxic at $150\ mg\,L^{-1}$	[142]
Chlamydomonas reinhardtii	Ag nanoparticles	25 ± 13 nm	carbonate	EC_{50} (1 h) = $0.36\ mg\,L^{-1}$; EC_{50} (5 h) = $0.089\ mg\,L^{-1}$	[143]
Candida albicans I	Ag^+	–	–	$MIC = 0.42\ mg\,L^{-1}$	[144]
Candida albicans I	Ag nanoparticles	not reported	unfunctionalized	$MIC = 0.42\ mg\,L^{-1}$	[144]
Candida albicans I	Ag nanoparticles	25 nm	PVP	$MIC = 0.1\ mg\,L^{-1}$	[144]
Candida albicans II	Ag^+	–	–	$MIC = 0.42\ mg\,L^{-1}$	[144]
Candida albicans II	Ag nanoparticles	not reported	unfunctionalized	$MIC = 0.21\ mg\,L^{-1}$	[144]
Candida albicans II	Ag nanoparticles	25 nm	PVP	$MIC = 0.21\ mg\,L^{-1}$	[144]
Candida parapsilosis	Ag^+	–	–	$MIC = 1.69\ mg\,L^{-1}$	[144]
Candida parapsilosis	Ag nanoparticles	not reported	unfunctionalized	$MIC = 1.69\ mg\,L^{-1}$	[144]
Candida parapsilosis	Ag nanoparticles	25 nm	PVP	$MIC = 0.84\ mg\,L^{-1}$	[144]
Candida tropicalis	Ag^+	–	–	$MIC = 0.84\ mg\,L^{-1}$	[144]
Candida tropicalis	Ag nanoparticles	not reported	unfunctionalized	$MIC = 0.84\ mg\,L^{-1}$	[144]
Candida tropicalis	Ag nanoparticles	25 nm	PVP	$MIC = 0.42\ mg\,L^{-1}$	[144]
Escherichia coli PHL628-gfp	Ag^+	–	–	$0.5\ mg\,L^{-1}$ inhibits bacterial growth by 100%	[102]
Escherichia coli ATCC 117	Ag nanoparticles	6.5-43.8 nm	not reported	$MIC_{90} = 6.25\ mg\,L^{-1}$; $MBC_{99.9} = 12.5\ mg\,L^{-1}$	[140]
Escherichia coli DH5α	Ag^+	–	–	$MIC = 3.5\ mg\,L^{-1}$ for 10^3 cells; MBC = 3.5-5 $mg\,L^{-1}$ at cultivation in LB medium; $MIC = 0.5–1\ mg\,L^{-1}$ for 10^3 cells; MBC = 0.5–1.25 $mg\,L^{-1}$ at cultivation in RPMI/FCS	[145]
Escherichia coli DH5α	Ag nanoparticles	75 ± 20 nm	PVP	$MBC = 12.5–20\ mg\,L^{-1}$ for 10^3 cells at cultivation in RPMI/FCS	[145]
Escherichia coli	Ag nanoparticles	7 nm	gallic acid	$MIC = 6.25\ mg\,L^{-1}$	[146]
Escherichia coli	Ag_2S nanoparticles	9 ± 3.5 nm	unfunctionalized	not toxic at $150\ mg\,L^{-1}$	[142]
Escherichia coli	Ag nanoparticles	10 nm	citrate	30 and $50\ mg\,L^{-1}$ inhibit bacterial growth; EC_{50} (CFU assay) = 3.2–4.2 $mg\,L^{-1}$; EC_{50} (LTP assay. 0 h) $> 0.25\ mg\,L^{-1}$; EC_{50} (LTP assay; 1 h) = 0.06-0.09 $mg\,L^{-1}$; EC_{50} (LTP assay; 2 and 3 h) $< 0.025\ mg\,L^{-1}$	[141]
Escherichia coli PHL628-gfp	Ag nanoparticles	14–16 nm	PVA	$0.5\ mg\,L^{-1}$ inhibits bacterial growth by 55 ± 8%	[102]
Escherichia coli	Ag nanoparticles	29 nm	gallic acid	$MIC = 13.02\ mg\,L^{-1}$	[146]
Escherichia coli	Ag nanoparticles	89 nm	gallic acid	$MIC = 11.79\ mg\,L^{-1}$	[146]
Escherichia coli PHL628-gfp	AgCl nanoparticles	250 nm	unfunctionalized	$0.5\ mg\,L^{-1}$ inhibits bacterial growth by 66 ± 6%	[102]
Klebsiella aerogenes ATCC 1950	Ag nanoparticles	6.5–43.8 nm	not reported	$MIC_{90} = 6.25\ mg\,L^{-1}$; $MBC_{99.9} = 12.5\ mg\,L^{-1}$	[140]
Legionella pneumophila ATCC 33152	Ag^+	–	–	complete inactivation at $0.1\ mg\,L^{-1}$; survival after 7 days at $0.1\ mg\,L^{-1}$ as endosymbiont in *A. polyphage*	[133]
Proteus vulgaris NCIB 4157	Ag nanoparticles	6.5–43.8 nm	not reported	$MIC_{90} = 6.25\ mg\,L^{-1}$; $MBC_{99.9} = 12.5\ mg\,L^{-1}$	[140]
Pseudomonas aeruginosa ATCC 9027	Ag nanoparticles	6.5–43.8 nm	not reported	$MIC_{90} = 6.25\ mg\,L^{-1}$; $MBC_{99.9} = 12.5\ mg\,L^{-1}$	[140]
Pseudomonas aeruginosa ATCC 10145	Ag^+	–	–	complete inactivation at $0.1\ mg\,L^{-1}$; survival after 7 days at $0.1\ mg\,L^{-1}$ as endosymbiont in *A. polyphage*	[133]
Salmonella abony NCTC 6017	Ag nanoparticles	6.5–43.8 nm	not reported	$MIC_{90} = 6.25\ mg\,L^{-1}$; $MBC_{99.9} = 12.5\ mg\,L^{-1}$	[140]
Salmonella typhimurium ATCC 23564	Ag nanoparticles	6.5–43.8 nm	not reported	$MIC_{90} = 6.25\ mg\,L^{-1}$; $MBC_{99.9} = 12.5\ mg\,L^{-1}$	[140]

Table 3: (Continued)

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
nitrifying bacteria	Ag^+	–	–	1 mg L^{-1} inhibits respiratory activity by 42 ± 7%	[102]
nitrifying bacteria	Ag nanoparticles	14–16 nm	PVA	1 mg L^{-1} inhibits respiratory activity by 86 ± 3%	[102]
nitrifying bacteria	AgCl nanoparticles	250 nm	unfunctionalized	1 mg L^{-1} inhibits respiratory activity by 46 ± 4%	[102]
Shewanella oneidensis	Ag_2S nanoparticles	9 ± 3.5 nm	unfunctionalized	not toxic at 150 mg L^{-1}	[142]
Staphylococcus aureus	Ag^+	–	–	MIC = 2.5 mg L^{-1} for 10^3 cells; MBC = 5 mg L^{-1} at cultivation in LB medium MIC = 0.5 mg L^{-1} for 10^3 cells; MBC = 1.25 mg L^{-1} at cultivation in RPMI/FCS	[145]
Staphylococcus aureus ATCC 6538	Ag nanoparticles	6.5–43.8 nm	not reported	MIC_{90} = 12.5 mg L^{-1}	[140]
Staphylococcus aureus	Ag nanoparticles	7 nm	gallic acid	MIC = 7.5 mg L^{-1}	[146]
Staphylococcus aureus	Ag nanoparticles	29 nm	gallic acid	MIC = 16.67 mg L^{-1}	[146]
Staphylococcus aureus	Ag nanoparticles	75 ± 20 nm	PVP	MBC = 20 mg L^{-1} for 10^3 cells at cultivation in RPMI/FCS	[145]
Staphylococcus aureus	Ag nanoparticles	89 nm	gallic acid	MIC = 33.71 mg L^{-1}	[146]
Staphylococcus epidermidis ATCC 12228	Ag nanoparticles	6.5–43.8 nm	not reported	MIC_{90} = 6.25 mg L^{-1}; $MBC_{99.9}$ = 12.5 mg L^{-1}	[140]

[a] Inhibitory and lethal concentrations are of the order of 0.1–20 mg L^{-1}. If the particle morphology is not explicitly stated, particles with either spherical or unspecified morphology were applied. CFU = colony forming units, EC_{50} = half maximal effective concentration, FCS = fetal calf serum, LB = lysogeny broth (bacterial culture medium), MIC = minimum inhibitory concentration, MBC = minimum bactericidal concentration, RPMI = RPMI-1640 (cell culture medium).

Table 4: The biological effect of silver on eucarytoic cells in vitro.[a]

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
alveolar epithelial cells A549 (adenocarcinome, human)	Ag^+	–	–	mitochondrial function was reduced at 4–10 mg L^{-1}	[110]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag^+	–	–	after 24 h, the cell morphology was changed at 3.24 mg L^{-1}	[147]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag nanoparticles	30–50 nm	PVP	mitochondrial function was reduced at 10–20 mg L^{-1}; necrosis/apoptosis at 2.5–15 mg L^{-1}	[110]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag nanoparticles	79 ± 1 nm	unfunctionalized	toxic at 15 and 30 mg L^{-1}	[148]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag nanoparticles	82 ± 1 nm	glucose	increase of the vitality at 7.5 and 15 mg L^{-1} (1^{st}–3^{rd} day); toxic at 7.5 and 15 mg L^{-1} (after 4 days); toxic at 30 mg L^{-1} (after 2 days)	[148]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag nanoparticles	88 ± 1 nm	lactose	increase of the vitality at 7.5 mg L^{-1} (1^{st}–3^{rd} day); toxic at 7.5 mg L^{-1} (after 4 days); toxic at 15 and 30 mg L^{-1} (after 2 days); increase of the vitality at 15 mg L^{-1} (after 3 days); toxic at 15 mg L^{-1} (after 4 days)	[148]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag nanoparticles	94 ± 1 nm	oligonucleotide	increase of the vitality at 7.5 and 15 mg L^{-1} (1^{st}–3^{rd} day); toxic at 7.5 and 15 mg mL^{-1} (after 4 days); toxic at 30 mg L^{-1} (after 4 days)	[148]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag nanoparticles	95 ± 1 nm	glucose and oligonucleotide	toxic at 7.5. 15 and 30 mg L^{-1} (after 4 days)	[148]
alveolar epithelial cells A549 (adenocarcinome, human)	Ag nanoparticles	99 ± 1 nm	lactose and oligonucleotide	toxic at 7.5. 15 and 30 mg L^{-1} (after 4 days)	[148]
astrocytes (Wistar rat)	Ag nanoparticles	75 ± 20 nm	PVP	increase of the amount of metallothioneins after 4 h incubation over 168 h at 10.8 mg L^{-1}	[149]
embryonal testicular carcinoma cells NTERA-2 (human)	Ag nanoparticles	20 nm	BSA	metabolism reduced by 50% at 100 mg L^{-1}; up to 20% necrotic cells at 12.5 mg L^{-1}	[150]
embryonal testicular carcinoma cells NTERA-2 (human)	Ag nanoparticles	200 nm	BSA	metabolism reduced by 50% at 100 mg L^{-1}; up to 20% necrotic cells at 12.5 mg L^{-1}	[150]

Table 4: (Continued)

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
embryonal stem cells D3 (mouse)	Ag nanoparticles	20 nm	not reported	EC_{20} (WST test) = 21 mg L^{-1}; EC_{20} (LDH assay) = 3 mg L^{-1}	[151]
embryonal stem cells D3 (mouse)	Ag nanoparticles	80 nm	not reported	EC_{20} (WST test) = 31 mg L^{-1}; EC_{20} (LDH assay) = 33 mg L^{-1}	[151]
embryonal stem cells D3 (mouse)	Ag nanoparticles	113 nm	not reported	EC_{20} (WST test) = 29 mg L^{-1}; EC_{20} (LDH assay) = 43 mg L^{-1}	[151]
epithelial cells HeLa S3 (human)	Ag^+	–	–	cytotoxic at 12 mg L^{-1}; IC_{50} at 17 mg L^{-1}	[152]
epithelial cells HeLa S3 (human)	Ag nanoparticles	2–5 nm	not reported	cytotoxic at 80–120 mg L^{-1}; IC_{50} at 92 mg L^{-1}	[152]
epithelial cells HeLa (human)	Ag nanoparticles	8.6 ± 3.2 nm	not reported	cell viability ca. 70% at 10 mg L^{-1} after 72 h	[153]
epithelial cells HeLa (human)	Ag nanoparticles	46 ± 8 nm	not reported	cell viability ca. 70% at 10 mg L^{-1} after 24 h cell viability ca. 70% at 10 mg L^{-1} after 48 h cell viability ca. 60% at 10 mg L^{-1} after 72 h	[153]
epithelial cells HeLa (human)	Ag nanoparticles	75 ± 26 nm	not reported	cell viability ca. 70% at 10 mg L^{-1} after 24 h cell viability ca. 80% at 10 mg L^{-1} after 48 h cell viability ca. 50% at 10 mg L^{-1} after 72 h	[153]
fibroblasts L929 (mouse)	Ag nanoparticles	20 nm	not reported	EC_{20} (WST test) = 2.8 mg L^{-1}; EC_{20} (LDH assay) = 0.2 mg L^{-1}	[151]
fibroblasts L929 (mouse)	Ag nanoparticles	79 ± 1 nm	unfunctionalized	toxic at 15 and 30 mg L^{-1}	[148]
fibroblasts L929 (mouse)	Ag nanoparticles	80 nm	not reported	EC_{20} (WST test) = 17 mg L^{-1}; EC_{20} (LDH assay) = 5.2 mg L^{-1}	[151]
fibroblasts L929 (mouse)	Ag nanoparticles	82 ± 1 nm	glucose	increase of the viability at 7.5, 15 and 30 mg L^{-1} (1^{st}–2^{nd} day); toxic at 30 mg L^{-1} (after 3 days)	[148]
fibroblasts L929 (mouse)	Ag nanoparticles	88 ± 1 nm	lactose	increase of the viability at 7.5, 15 and 30 mg L^{-1} (1^{st}–2^{nd} day); toxic at 30 mg L^{-1} (after 3 days)	[148]
fibroblasts L929 (mouse)	Ag nanoparticles	94 ± 1 nm	oligonucleotide	increase of the viability at 7.5, 15 and 30 mg L^{-1} (1^{st}–2^{nd} day); toxic at 30 mg L^{-1} (after 2 days)	[148]
fibroblasts L929 (mouse)	Ag nanoparticles	95 ± 1 nm	glucose and oligonucleotide	increase of the viability at 7.5, 15 and 30 mg L^{-1} (1^{st}–2^{nd} day); toxic at 30 mg L^{-1} (after 2 days)	[148]
fibroblasts L929 (mouse)	Ag nanoparticles	99 ± 1 nm	lactose and oligonucleotide	increase of the viability at 7.5, 15 and 30 mg L^{-1} (1^{st}–2^{nd} day); toxic at 30 mg L^{-1} (after 2 days)	[148]
fibroblasts L929 (mouse)	Ag nanoparticles	113 nm	not reported	EC_{20} (WST test) = 12 mg L^{-1} EC_{20} (LDH assay) = 2.4 mg L^{-1}	[151]
hepatocellular carcinoma cells Hep G2 (human)	Ag nanoparticles	6.5–43.8 nm	not reported	IC_{50} = 251 mg L^{-1}	[140]
hepatocellular carcinoma cells C3A (human)	Ag nanoparticles	35 nm	unfunctionalized	cytotoxicity ca. 90% at ≥100 mg L^{-1}	[154]
hepatocellular carcinoma cells C3A (human)	Ag microparticle	0.6–1.6 μm	unfunctionalized	cytotoxicity ca. 90% at ≥500 mg L^{-1}	[154]
hepatocytes (primary, fish)	Ag nanoparticles	35 nm	unfunctionalized	cytotoxicity ca. 30% at ≥800 mg L^{-1}	[154]
hepatocytes (primary, fish)	Ag nanoparticles	0.6–1.6 μm	unfunctionalized	cytotoxicity ca. 20% at ≥1000 mg L^{-1}	[154]
testicular cells (primary, C57BL6 mouse)	Ag nanoparticles	20 nm	BSA	metabolism reduced by 50% at 10 mg L^{-1}	[150]
testicular cells (primary, C57BL6 mouse)	Ag nanoparticles	200 nm	BSA	metabolism reduced by 50% at 10 mg L^{-1}	[150]
gill cells RW-T1 (fish)	Ag nanoparticles	10 nm	PVP	cytotoxicity ca. 40% at 25 mg L^{-1}	[155]
gill cells RW-T1 (fish)	Ag nanoparticles	20 nm	PVP	cytotoxicity ca. 20% at 25 mg L^{-1}	[155]
gill cells RW-T1 (fish)	Ag nanoparticles	40 nm	PVP	not toxic at 25 mg L^{-1}	[155]
gill cells RW-T1 (fish)	Ag nanoplatelets	32 nm	PVP	cytotoxicity ca. 50% at 12.5 mg L^{-1}; ca. 70% at 25 mg L^{-1}	[155]
gill cells RW-T1 (fish)	Ag nanorods	65 nm × 20 μm	PVP	not toxic at 25 mg L^{-1}	[155]
lung epithelial cells C 10 (mouse)	Ag_2S nanoparticles	9 ± 3.5 nm	not reported	not toxic at 150 mg mL^{-1}	[142]

Table 4: (Continued)

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
lung cells HLF (human)	Ag nanoparticles	25 nm	PVP	toxic at 62.5 mg L^{-1}	[156]
lung cells HLF (human)	Ag nanoparticles	35 nm	PVP	toxic at 62.5 mg L^{-1}	[156]
lung cells HLF (human)	Ag nanoparticles	45 nm	PVP	toxic at 62.5 mg L^{-1}	[156]
lung cells HLF (human)	Ag nanoparticles	60 nm	PVP	toxic at 125 mg L^{-1}	[156]
lung cells HLF (human)	Ag nanoparticles	70 nm	PVP	toxic at 125 mg L^{-1}	[156]
macrophages U937 (human)	Ag nanoparticles	4 nm	PVP	cell viability 36% at 3.12 mg L^{-1}	[157]
macrophages U937 (human)	Ag nanoparticles	5 nm	PVP	cell viability 50% at 6.25 mg L^{-1}; 0% at $\geq$12.5 mg L^{-1}	[158]
macrophages U937 (human)	Ag nanoparticles	20 nm	PVP	cell viability 6% at 25 mg L^{-1}	[157]
macrophages U937 (human)	Ag nanoparticles	100 nm	PVP	cell viability 100% at 25 mg L^{-1}	[158]
macrophages THP-1 (human)	Ag nanoparticles	20 nm	peptide	IC_{50} (24 h) = 110 mg L^{-1} IC_{50} (48 h) = 18 mg L^{-1}	[159]
macrophages THP-1 (human)	Ag nanoparticles	40 nm	peptide	IC_{50} (24 h) = 140 mg L^{-1} IC_{50} (48 h) = 30 mg L^{-1}	[159]
macrophages U937 (human)	Ag nanoparticles	70 nm	PVP	cell viability 100% at 50 mg L^{-1}	[157]
macrophages RAW264.7 (mouse)	Ag nanoparticles	55 nm × 278 nm	chitosan	cell viability 60% at 10 mg L^{-1}	[160]
mesenchymal stem cells (human)	Ag^+	–	–	toxic at 2.5 mg L^{-1}	[145, 161]
mesenchymal stem cells (human)	Ag nanoparticles	75 ± 20 nm	PVP	toxic at 50 mg L^{-1}	[145, 161]
monocytes (human)	Ag^+	–	–	toxic at 1 mg L^{-1}	[145]
monocytes (human)	Ag nanoparticles	75 ± 20 nm	PVP	toxic at 30 mg L^{-1}	[145]
adrenal medulla cells PC-12 (rat)	Ag nanoparticles	8.6 ± 3.2 nm	not reported	cell viability ca. 60% at 10 mg L^{-1} after 72 h	[153]
adrenal medulla cells PC-12 (rat)	Ag nanoparticles	46 ± 8 nm	not reported	cell viability ca. 60% at 10 mg L^{-1} after 72 h	[153]
adrenal medulla cells PC-12 (rat)	Ag nanoparticles	75 ± 26 nm	not reported	cell viability ca. 70% at 10 mg L^{-1} after 24 h cell viability ca. 30% at 10 mg L^{-1} after 48 h cell viability ca. 10% at 10 mg L^{-1} after 72 h	[153]
ovary cells CHO (Chinese hamster)	Ag nanoparticles	8.6 ± 3.2 nm	not reported	cell viability ca. 85% at 10 mg L^{-1} after 72 h	[153]
ovary cells CHO (Chinese hamster)	Ag nanoparticles	46 ± 8 nm	not reported	cell viability ca. 75% at 10 mg L^{-1} after 24 h cell viability ca. 70% at 10 mg L^{-1} after 48 h cell viability ca. 70% at 10 mg L^{-1} after 72 h	[153]
ovary cells CHO (Chinese hamster)	Ag nanoparticles	75 ± 26 nm	not reported	cell viability ca. 75% at 10 mg L^{-1} after 24 h cell viability ca. 80% at 10 mg L^{-1} after 48 h cell viability ca. 75% at 10 mg L^{-1} after 72 h	[153]
preosteoblasts MC3T3-E1 (mouse)	Ag nanoparticles	8.6 ± 3.2 nm	not reported	cell viability ca. 70% at 10 mg L^{-1} after 72 h	[153]
preosteoblasts MC3T3-E1 (mouse)	Ag nanoparticles	46 ± 8 nm	not reported	cell viability ca. 90% at 10 mg L^{-1} after 24 h cell viability ca. 80% at 10 mg L^{-1} after 48 h cell viability ca. 60% at 10 mg L^{-1} after 72 h	[153]
preosteoblasts MC3T3-E1 (mouse)	Ag nanoparticles	75 ± 26 nm	not reported	cell viability ca. 70% at 10 mg L^{-1} after 24 h cell viability ca. 30% at 10 mg L^{-1} after 48 h cell viability ca. 10% at 10 mg L^{-1} after 72 h	[153]
T-cells (human)	Ag^+	–	–	toxic at 1.5 mg L^{-1}	[145]
T-cells (human)	Ag nanoparticles	75 ± 20 nm	PVP	toxic at >50 mg L^{-1}	[111, 145]

[a] If the particle morphology is not explicitly stated, particles with either spherical or unspecified morphology were applied. BSA = bovine serum albumin, EC_{20} = effective concentration, IC_{50} = half maximal inhibitory concentration, LDH = lactate dehydrogenase, WST = water soluble tetrazolium.

Table 5: Biological effect of silver on multicellular organisms in vivo.[a]

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
Aedes aegypti (mosquito larvae)	Ag nanoparticles	3–21 nm	not reported	LC_{50} (II. larval instar) = 1.29 ± 0.09 mg L^{-1}; LC_{90} (II. larval instar) = 3.08 ± 0.21 mg L^{-1}; LC_{50} (III. larval instar) = 1.48 ± 0.09 mg L^{-1}; LC_{90} (III. larval instar) = 3.33 ± 0.22 mg L^{-1}; LC_{50} (IV. larval instar) = 1.58 ± 0.07 mg L^{-1}; LC_{90} (IV. larval instar) = 3.41 ± 1.23 mg L^{-1}	[162]
Anopheles stephensi (mosquito larvae)	Ag nanoparticles	3–21 nm	not reported	LC_{50} (II. larval instar) = 1.17 ± 0.09 mg L^{-1}; LC_{90} (II. larval instar) = 2.99 ± 0.21 mg L^{-1}; LC_{50} (III. larval instar) = 1.30 ± 0.09 mg L^{-1}; LC_{90} (III. larval instar) = 3.13 ± 0.21 mg L^{-1}; LC_{50} (IV. larval instar) = 1.41 ± 0.09 mg L^{-1}; LC_{90} (IV. larval instar) = 3.29 ± 1.22 mg L^{-1}	[162]
Capoeta fusca (fish)	Ag^+	–	–	LC_{50} = 0.014–0.013 mg L^{-1} (24-96 h)	[163]
Danio rerio (zebrafish)	Ag^+	–	–	LC_{50} = 28 μg L^{-1} (24 h) LC_{50} = 25 μg L^{-1} (48 h)	[164]
Danio rerio (zebrafish embryos)	Ag nanoparticles	10 nm	PVP	lethal for ca. 12% at 2.5 mg L^{-1}; for ca. 22% at 5 mg L^{-1}	[155]
Danio rerio (zebrafish embryos)	Ag nanoparticles	20 nm	PVP	lethal for ca. 16% at 2.5 mg L^{-1}; for ca. 17% at 5 mg L^{-1}	[155]
Danio rerio (zebrafish embryos)	Ag nanoplatelets	32 nm	PVP	lethal for ca. 34% at 2.5 mg L^{-1}; for ca. 42% at 5 mg L^{-1}	[155]
Danio rerio (zebrafish embryos)	Ag nanoparticles	40 nm	PVP	lethal for ca. 16% at 2.5 mg L^{-1} and 5 mg L^{-1}	[155]
Danio rerio (zebrafish embryos)	Ag nanoparticles	41.6 ± 9.1 nm	citrate	not toxic at ≤ 0.002 μg L^{-1}; lethal for 100% at ≥ 0.022 μg L^{-1}	[165]
Danio rerio (zebrafish embryos)	Ag nanowires	65 nm × 20 μm	PVP	lethal for ca. 7% at 5 mg L^{-1}	[155]
Danio rerio (zebrafish)	Ag nanoparticles	81 ± 2 nm	PVP	LC_{50} = 89 μg L^{-1} (24 h) LC_{50} = 84 μg L^{-1} (48 h)	[164]
Daphnia magna (crustacean)	Ag^+	–	–	LC_{50} = 0.4 ± 0.12 μg L^{-1} (24 h)	[166]
Daphnia magna (crustacean)	Ag^+	–	–	EC_{10} = 1.7 μg L^{-1} EC_{50} = 2.3 μg L^{-1} EC_{90} = 3.1 μg L^{-1}	[167]
Daphnia magna (crustacean)	Ag nanoparticles	5–25 nm	citrate	EC_{10} = 3 μg L^{-1} EC_{50} = 4 μg L^{-1} EC_{90} = 5 μg L^{-1}	[167]
Daphnia magna (crustacean)	Ag nanoparticles	16.6 nm	not reported	EC_{10} = 1.5 μg L^{-1} EC_{50} = 2 μg L^{-1} EC_{90} = 3 μg L^{-1}	[167]
Daphnia magna (crustacean)	Ag nanoparticles	20 nm	not reported	EC_{10} = 140 μg L^{-1} EC_{50} = 187 μg L^{-1} EC_{90} = 251 μg L^{-1}	[167]
Daphnia magna (crustacean)	Ag nanoparticles	35 nm	PVP	LC_{50} = 10.6 ± 5.2 μg L^{-1} (24 h)	[166]
Daphnia magna (crustacean)	Ag nanoparticles	36 nm	citrate	LC_{50} = 3–4 μg L^{-1}	[168]
Daphnia magna (crustacean)	Ag nanoparticles	40 nm	citrate	LC_{50} = 1.8 ± 0.96 μg L^{-1} (24 h)	[166]
Daphnia magna (crustacean)	Ag nanoparticles	52 nm	citrate	LC_{50} = 3–4 μg L^{-1}	[168]
Daphnia magna (crustacean)	Ag nanoparticles	66 nm	citrate	LC_{50} = 3–4 μg L^{-1}	[168]

Table 5: (Continued)

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
Daphnia magna (crustacean)	Ag nanoparticles	35 nm	unfunctionalized	acute toxicity (96 h): survival rate at 10 $\mu g L^{-1}$ $93.33 \pm 3.33\%$; survival rate at 100 $\mu g L^{-1}$ $43.33 \pm 23.33\%$; survival rate at 1 and 10 $mg L^{-1}$ $0 \pm 0\%$ chronic exposition (21 days): survival rate at 1 $\mu g L^{-1}$ 70%; survival rate at 5 $\mu g L^{-1}$ 100%; survival rate at 10 $\mu g L^{-1}$ 90%; survival rate at 50 $\mu g L^{-1}$ 80%	[154, 169]
Daphnia magna (crustacean)	Ag microparticles	0.6–1.6 μm	unfunctionalized	acute toxicity (96 h): survival rate at 10 $\mu g L^{-1}$ $96.67 \pm 3.33\%$; survival rate at 100 $\mu g L^{-1}$ $86.67 \pm 6.67\%$; survival rate at 1 $mg L^{-1}$ $20 \pm 20\%$ survival rate at 10 $mg L^{-1}$ $0 \pm 0\%$ chronic exposition (21 days): survival rate at 1 $\mu g L^{-1}$ 90%; survival rate at 5 $\mu g L^{-1}$ 80%; survival rate at 10 $\mu g L^{-1}$ 90%; survival rate at 50 $\mu g L^{-1}$ 90%	[154, 169]
Drosophila melanogaster (fruit fly)	Ag nanoparticles	29 ± 4 nm	maltose	acute toxicity at 20 $mg L^{-1}$; effect on fertility at 5 $mg L^{-1}$	[170]
Drosophila melanogaster (fruit fly eggs)	Ag nanoparticles	20–30 nm	not reported	$57 \pm 48\%$ of the eggs reached the adult stadium at 10 $mg L^{-1}$	[171]
Drosophila melanogaster (fruit fly eggs)	Ag nanoparticles	100 nm	not reported	$91 \pm 19\%$ of the eggs reached the adult stadium at 10 $mg L^{-1}$	[171]
Drosophila melanogaster (fruit fly eggs)	Ag nanoparticles	500–1200 nm	not reported	$94 \pm 52\%$ of the eggs reached the adult stadium at 10 $mg L^{-1}$	[171]
Hartley albino guinea pig	Ag nanoparticles	<100 nm	not reported	acute dermal toxicity (10 $mg mL^{-1}$): no change in the weight of organs and no macroscopic changes; histopathologic anomalies in skin, liver, and spleen; subchronic dermal toxicity (10 $mg mL^{-1}$, 5 times per week for 13 weeks): histopathologic anomalies in skin, liver, and spleen	[172]
Lytechinus variegatus (Echinoderm larvae)	Ag^+	–	–	$EC_{20} = 10.68$ $\mu g g^{-1}$ dw Ag in algae (corresponds to 3.88 $\mu g L^{-1}$ Ag in water) after 18 days feeding	[173]
Lolium multiflorum (Italian ryegrass)	Ag nanoparticles	6 ± 1.7 nm	gummi arabicum	increase of the concentration from 1 to 40 $mg L^{-1}$ led to a decrease in the root biomass from 18.6 ± 1.3 to 4.7 ± 0.7 mg. The inhibition was much stronger than in the case of Ag^+ ions with the same concentration.	[174]
Mouse (balb/c)	Ag microparticles	<20 μm	sodium hyaluronate	1.18 mg Ag were injected into the brain. After 9 months, neural inflammation and progressive tissue loss in the brain were observed.	[175]
Mouse C57Bl/6	Ag nanoparticles	5 ± 2 nm, 22 ± 4 nm	not reported	inhalation of 3.3 $mg m^{-3}$ Ag nanoparticles for 40 h induced minimal lung toxicity and inflammation.	[176]
Nereis diversicolor (ragworm)	Ag^+	–	–	1250 ng Ag^+ per worm for 10 days were given. The silver was bound by metallothioneins.	[177]
Nereis diversicolor (ragworm)	Ag nanoparticles	30 ± 5 nm	citrate	1250 ng Ag^+ per worm for 10 days were given. The particles were associated with the apical cell membrane, in endocytotic invaginations, and in endosomes.	[177]
Pimephales promelas (fish embryo)	Ag nanoparticles	35 nm	not reported	$LC_{50} = 9.4$ $mg L^{-1}$	[178]
Pimephales promelas (fish embryo)	Ag nanoparticles	≤ 100 nm	not reported	$LC_{50} = 10.6$ $mg L^{-1}$	[178]
Ulva lactuca (makroalga)	Ag^+	–	–	toxic at 2.5 $\mu g L^{-1}$	[179]

Table 5: (Continued)

Organism	Silver species	Particle diameter	Functionalization	Effect	Source
Ulva lactuca (makroalga)	Ag nanoparticles	100 nm	not reported	not toxic at 15 $\mu g\,L^{-1}$	[179]

[a] If the particle morphology is not explicitly stated, particles with either spherical or unspecified morphology were applied. $EC_{10/50/90}$ = effective concentration, $LC_{50/90}$ = inhibitory concentration.

mids.[100,197–199] Nagy et al. studied the upregulation of genes that cause resistance against antibiotics and silver in *E. coli* and in *S. aureus*.[28] Khan et al. found silver-resistant bacteria in sewage sludge.[200] Mechanistically, cells protect themselves by increasingly pumping out silver ions[197] and also by binding silver to suitable molecules like metallothioneins.[149] Quadros et al. has summarized the state of knowledge on silver nanoparticles in the form of aerosols. The number of consumer products based on silver-containing sprays is increasing, therefore the risk of inhalation must be critically assessed.[187,190,201]

There are some fundamental problems with the assessment of toxicological studies of silver and silver nanoparticles. For instance, not in all cases it is reported whether the prepared nanoparticles were purified after synthesis. It is likely that in many cases the whole reaction mixture was applied after corresponding dilution, that is, unreacted silver salt, polymers and citrate from the synthesis, counterions (like nitrate) will all be present. Furthermore, agglomeration of nanoparticles in the biological media is often neither studied nor investigated. Aggregation of nanoparticles is a typical process in more complex media in which the colloidal stability is decreased (for example by the presence of salts).[82] The particle size is often only measured by electron microscopy, a technique which does not provide information about the degree of dispersion in pure water, let alone in biological media. Different particle size analysis methods give different numerical data for the particle size distribution, therefore it is mandatory to apply more than one method to characterize nanoparticles.[202–208] In the presence of chloride and biomolecules in biologically relevant concentrations, the concentration of free Ag^+ should be very small (Table 1). This is a fundamental question because complexed silver cations cannot be easily distinguished or separated from hydrated silver cations, that is, Ag^+(aq). It is probably safe to assume that in reality, the denotation "dissolved silver" often comprises Ag^+(aq) together with complexed silver cations and colloidally stable, that is, not sedimenting silver salts, such as AgCl.

7. Silver in the Environment

The way of silver in the environment has been discussed in a number of review articles that summarize the current discussion, with sometimes distinctly different conclusions.[4,6,21,69,209–219] The range of opinions goes from "problematic" to "no problem at all" (see also Section 8).

Silver can be released into the environment both in ionic and nanoparticulate form by washing processes, for example, from textiles or cosmetics. It then ends up in sewage sludge and rivers. An agglomeration of primarily present or newly formed nanoparticles is likely.[82] Nowack et al. have modeled the silver flux in the environment and estimated the amount of released silver to 20 $t\,a^{-1}$ in the USA (Figure 4).[220] Ionic silver is immobilized to a large extent as sparingly soluble salt like AgCl or Ag_2S;[87,221–223] besides, a rapid aggregation occurs in the presence of higher salt concentrations (depending on the particle functionalization, if present).[224,225] Furthermore, binding to other colloidally dispersed organic matter such as humic acid plays an important role, so that only small amounts of dissolved silver remain. The majority of silver is

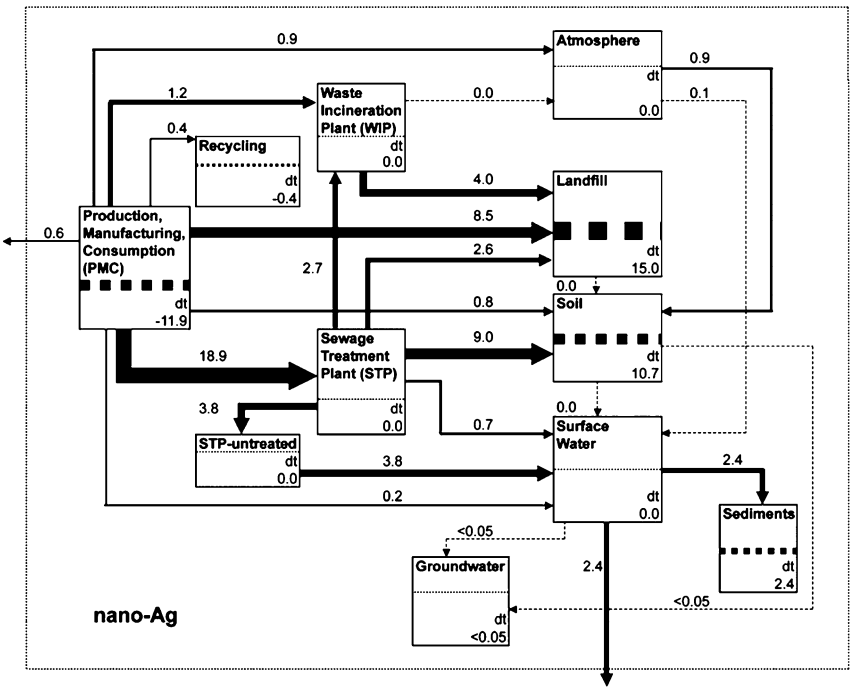

Figure 4. The pathways of silver in the environment (taken from Ref. [220] with permission). The figure shows the flux of synthetically prepared silver nanoparticles in tons of silver per year in the USA.

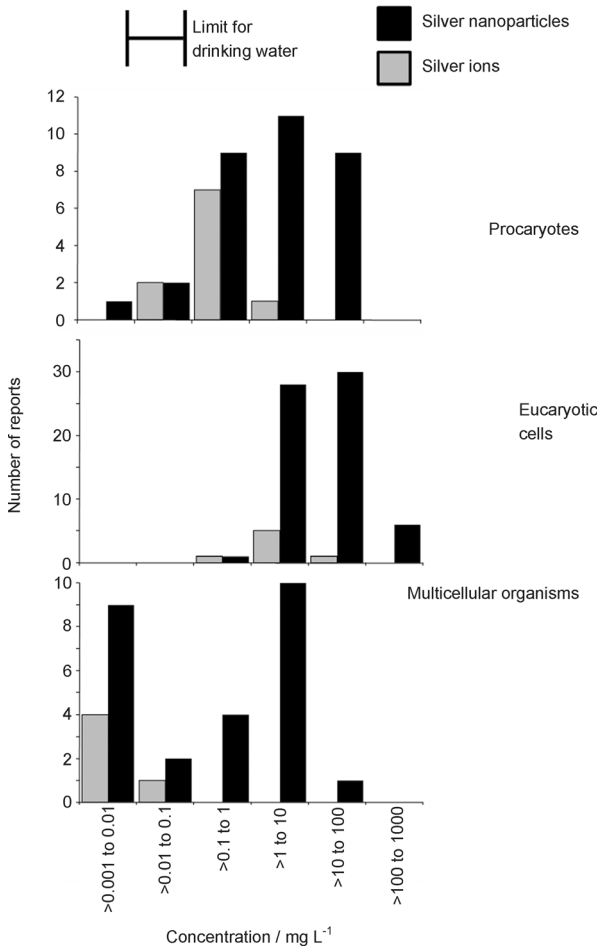

Figure 5. Compilation of the toxicological data for ionic silver and for silver nanoparticles. The data in Tables 3–5 were used, with the smallest concentration causing adverse effects. We did not distinguish between the different kinds of nanoparticles, but we included only nanoparticles of metallic silver, that is, no silver salt nanoparticles.

found in sewage sludge from where it may mobilized again after landfilling or combustion.[21,69,209,217,218,220]

8. Critical Assessment of Silver as an Antibacterial Agent

The current discussion in Europe and in the USA increasingly focuses on the risks of nanotechnology. Besides more or less diffuse fears, it is increasingly recognized that the interaction of nanoparticles with biological systems and the pathway of nanoparticles in the environment are not fully understood. This is mostly due to the fact that a "nanoparticle" is a complex object that shows many characteristic features that go beyond its chemical composition, among them particle size, particle size distribution, particle morphology, crystallinity, surface functionalization, and charge.[82,130,226–230] In the case of silver, the increasing application in consumer products leads to particularly anxiety and discussion (see for example Refs. [4,211,219,231,232]). In the USA, a petition was filed to the Environmental Protection Agency (EPA) in 2008 to label silver as a pesticide. It is evident that a package label "contains pesticides" would ruin the market for many silver-containing products, such as cosmetics. This has stimulated further studies on the properties of (silver) nanoparticles.[219] However, taking into account the decade-long experience in the application of colloidal silver, there is a large amount of potentially toxicologically relevant data (with few reported adverse effects), therefore an excessive fear of silver is probably not justified.[4]

In Figure 5, we have arranged the critical concentrations for silver and silver nanoparticles towards single-celled organisms, cells, and higher organisms (taken from Tables 3–5). The quality of the individual studies was not assessed. Despite the logarithmic scale it is evident that the effective range for different organisms is overlapping, and therefore the therapeutic window is rather small. It must be acknowledged that the literature data accumulated in Figure 5 do not comprise the whole published literature, but that the image is nevertheless rather consistent. This is corroborated by our recent comparative study on silver ions and silver nanoparticles with bacteria and eukaryotic cells in identical culture media.[145]

The question is open whether an increasing exposition with silver (for example in cosmetics) leads to resistance among bacteria, and whether benign bacteria on the skin or in the intestines will be influenced by small amounts of silver. Furthermore, the question of a selective enrichment of silver-tolerant or silver-resistant bacteria on silver-coated medical devices must be addressed. However, taken the published data it may be stated that the current application of silver, be it as ion, as metal, or as nanoparticle, does not constitute a major risk for humans.

9. Summary

On account of its bactericidal effect, silver has been used for many years in consumer products and medical products. Colloidal silver and silver nanoparticles are increasingly used, stimulated by its depot function for silver ions and its high specific surface area. Beyond these features, a specific "nano effect" cannot be derived from the present data. The literature on the biological aspects of silver is vast. A more detailed consideration shows that a range of characterization methods is necessary to correctly assess nanoparticle dispersions: even in pure water, let alone in complex biological or environmental media. Nanoparticles do change after transfer from pure water in biological media, for example by adsorption of biomolecules and agglomeration. After analyzing a multitude of singe studies, it can be concluded that the effect of silver towards bacteria is typically overestimated, and towards cells it is typically underestimated. Therefore, the application of silver in consumer products, cosmetics, and medical products should be critically assessed, also with a view on possible resistances of bacteria.

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