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Nano-silver – a review of available data and knowledge gaps in human and environmental risk assessment

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Abstract

Nano-silver is used in an increasing number of products. Some of the applications have resulted in the concern of governments and the public, since little is known about the potential risks of nano-silver. In this review, an inventory is made to identify knowledge gaps that have to be filled before risks for both man and the environment can be assessed as reliable as for 'non-nanosized' chemicals. It is hypothesized that the toxic effects of nano-silver are due to a combination of the specific properties of silver nanoparticles and the generation of ions from them. The main topic for future research is validation of our '0-hypothesis' that toxic effects of nano-silver are proportional to the activity of free silver ions released by the nanoparticles. Furthermore, it must be determined whether – or to what extent – nano-silver particles will enter the body. The outcomes of these tests will determine the requirements for further toxicity testing.

Keywords: *Nanotechnology, nanoparticle, silver, risk assessment, health, environment*

Introduction

Nanotechnology is an enabling technology that deals with structures ranging from approximately 1–100 nm in at least one dimension (British Standards Institute [BSI] 2007; Scientific Committee on Emerging and Newly Identified Health Risks [SCENIHR] 2008). The nanosize results in specific physicochemical characteristics that may differ from those of the bulk substance or particles of larger size. This effect is mainly attributed to high surface area to volume ratio, which potentially results in high reactivity. Because of these specific characteristics the use of substances in nanoform may have advantages over the use of bulk chemicals. Nanotechnology is rapidly expanding and is used in various areas, such as health care, consumer products like cosmetics, ICT, food and feed, environmental health, and agriculture (Roszek et al. 2005; Bouwmeester et al. 2007; Dekkers et al. 2007a; www.nanotechproject.org). It is therefore not surprising that many products containing engineered nanoparticles are already available for consumers.

One of the substances used in nanoformulation is silver (nano-silver). It has been used since ancient times for jewelry, utensils, monetary currency, dental alloy, photography, explosives, etc. (Chen and Schluesener 2008). Until the introduction of antibiotics, it was also used for its antiseptic activity, specifically in the management of open wounds and burns. Due to its antimicrobial properties, silver has also been incorporated in filters to purify drinking water and clean swimming pool water (Agency for Toxic Substances and Disease Registry [ATSDR] 1990, cited in World Health Organization [WHO] 2002). To generate nano-silver, metallic silver has been engineered into ultrafine particles by several methods, including spark discharging, electrochemical reduction, solution irradiation and cryochemical

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synthesis (Chen and Schluesener 2008). Nano-silver particles are mostly smaller than 100 nm and consist of about 20–15,000 silver atoms (Oberdörster et al. 2005a,b; Warheit et al. 2007, cited in Chen and Schluesener 2008). Nanoparticles, including nano-silver, may have different shapes, such as spheres, rods, cubes. In addition, nanostructures can be produced as tubes, wires, multifacets, or films. At the nanoscale, the silver particles exhibit deviating physico-chemical properties (like pH-dependent partitioning to solid and dissolved particulate matter) and biological activities compared with the regular metal (Lok et al. 2007; Pal et al. 2007). This is due to the higher surface area per mass, allowing a larger amount of atoms to interact with their surroundings.

Due to the properties of silver at the nanoscale, nano-silver is nowadays used in an increasing number of consumer and medical products. Because silver is a soft white lustrous element, an important use of silver nanoparticles is to give products a silver finish. Still, the remarkably strong antimicrobial activity is the major direction for development of nano-silver products. Of the more than 800 consumer products that contain nanomaterials, roughly 30% are claimed to contain silver particles. Examples are food packaging materials and food supplements, odor-resistant textiles, electronics and household appliances, cosmetics and medical devices, water disinfectants, and room sprays. Some of the applications of nano-silver have resulted in the concern of governments and discussions among the public. An example is the addition of silver nanoparticles to socks to kill the bacteria associated with foot odor. A recent study (Benn et al. 2008) revealed that the silver can easily leak into waste water during washing, thus potentially disrupting helpful bacteria used in waste-water treatment facilities, or endangering aquatic organisms in lakes and streams. Benn and colleagues found that some brands of socks lose nearly 100% of their silver content within four washings, while two other brands lost less than 1% over the same number of washings (Benn et al. 2008).

Nano-silver is also used in washing machines because of its antimicrobial activity (Vigneshwaran et al. 2007, cited in Chen and Schluesener 2008). Several Swedish Agencies, including the Swedish Environmental Protection Agency, have protested against this application because waste water may be contaminated with nano-silver. Recently, the United States Environmental Protection Agency (USEPA) has decided to regulate this specific form of nanotechnology. Silver-ion generating devices such as washing machines, with the declared aim to kill bacteria, will no longer be a simple washing device, but a pesticide. This notice is not an action to regulate nanotechnology; it is the silver's bactericidal effect rather than the size that led to the decision. In view of potential effects in aquatic ecosystems, new purification methods need to be developed to eliminate the nano-silver, which may increase costs for government. Also, farmers are concerned that the antimicrobial activity of nano-silver will affect the beneficial bacteria in soil, which are essential for the soil used for farming (Murata et al. 2005).

Despite the rapidly growing share of nanoproducts on the market, large knowledge gaps exist with regard to the possible risks of exposure to nanoparticles. For this reason, we searched the literature for information about toxic effects of nano-silver to man – when exposed via food, consumer products and medical products – or to the environment. Although worker exposure to nano-silver is beyond the scope of this review, toxicity to workers exposed during the production phase of the products is also included.

Because silver nanoparticles are indicated as one of the fastest growing products in the nanotechnology industry, a widespread exposure of man and the environment occurs (Chen and Schluesener 2008). All silver-containing nanomaterials are considered in this literature study (nanoparticles, nanowires, nanofilms, nanocoatings, etc.) and a comparison with the toxicological characteristics of regular silver is made as well. The aggregated information on nano-silver is used to detect gaps in the current state of knowledge. With this insight, topics for future research are formulated to reach the ultimate goal: The minimization of potential risks of nano-silver by collecting sufficient data to assess human health and environmental risks for every form and size of nano-silver.

Silver

Silver, background information

Silver is one of the basic elements that make up our planet. It is a rare but naturally occurring element, slightly harder than gold and very ductile and malleable. Pure silver has the highest electrical and thermal conductivity of all metals and has the lowest contact resistance (Nordberg and Gerhardsson 1988). It may be released into the air and water through natural processes such as the weathering of rocks or by human activities like processing of ores, cement manufacture and the burning of fossil fuel. Rain may wash silver out of soil into the groundwater. Silver can be present in four different oxidation states: Ag^0, Ag^+, Ag^{2+} and Ag^{3+}. The former two are the most abundant ones; the latter two are unstable in the aquatic environment (Smith and Carson 1977, cited in WHO 2002). The free silver

ion is Ag^+. In the environment, silver is found as a monovalent ion together with sulfide, bicarbonate or sulfate or more complex with chlorides and sulfates adsorbed onto particulate matter in the aqueous phase (ATSDR 1990, cited in WHO 2002). Metallic silver itself is insoluble in water, but metallic salts such as silver nitrate ($AgNO_3$) and silver chloride (AgCl) are soluble in water (WHO 2002). Silver at low concentrations in this phase exists as silver sulfhydrate (AgSH) or as HS-Ag-S-Ag-SG, a simple polymer. When silver is present in high concentrations in the aqueous phase, it is found as colloidal silver sulfide or polysulfide complexes.

The general population is exposed to silver primarily through the ingestion of drinking water and food. In former times, silver has already been used in a wide variety of applications. Ancient civilizations were aware of the bactericidal properties of silver (Hill and Pillsbury 1939). Metallic silver was used for surgical prosthesis and splints, fungicides, and coinage. Soluble silver compounds such as silver salts, have been used in treating mental illness, epilepsy, nicotine addiction, gastroenteritis, and infectious diseases, including syphilis and gonorrhea (Marshall and Schneider 1977; Shelley et al. 1987; Gulbranson et al. 2000). Some of the current uses of silver metal and silver compounds are listed in Table I.

In 2003, industrial applications, jewelry and silverware and the photographic industry were the largest consumers of silver (40, 31 and 22%, respectively: Gold Fields Mineral Services [GFMS] 2004). However, the rise of digital photography has resulted in an enormous reduction of silver emissions in the last four years. The widest and best known use of silver in medicine is in combination with sulfadiazine, where it becomes a topical antibacterial agent for the treatment of burns (Russell and Hugo 1994; Klasen 2000; Silver 2003; reviewed in Drake and Hazelwood 2005). Colloidal silver proteins were at one time commonly used to fight colds (Fung and Bowen 1996) and are once again gaining popularity as a dietary supplement for treating certain diseases such as allergy prophylaxis (Gulbranson et al. 2000; Silver 2003).

Table I. Various uses for silver and silver compounds.

Silver compounds	Silver and silver alloys
Photography	Jewelry
Batteries	Silverware
Bactericide	Electronic components
Catalysts	Heat sink
Medicinals	Solders
Lubrication	Brazing alloys
Cloud seeding	Superconductors
Window coating	Bactericide
Mirrors	Dental amalgams
Flower preservative	Bearings
Electroplating	Coinage/medals
Cosmetics	
Sanitation of swimming pools, hot tubs/spas, drinking water	

Silver, general toxicity

Since the most common forms of silver are elemental silver (0 oxidation state) and the monovalent silver ion, the majority of the toxicological data on silver concern these two chemical forms of the element. Despite the widespread use of silver and silver ions in industry and for medicinal purposes, only limited information on silver toxicity is available. Existing environmental and human studies seem to demonstrate that some forms of silver, especially those that release free silver ions (Ag^+), are more toxic than others. This leads us to formulate the following hypothesis:

> Toxic effects of silver substances are proportional to the rate of release of free silver ions from them.

Although acute toxicity of silver in the environment is dependent on the availability of free silver ions, investigations have shown that these concentrations of Ag^+ ions are too low to lead to toxicity (WHO 2002). Metallic silver appears to pose minimal risk to health, whereas soluble silver compounds are more readily absorbed and have the potential to produce adverse effects (Drake and Hazelwood 2005). The wide variety of uses of silver allows exposure through various routes of entry into the body. Ingestion is the primary route for entry for silver compounds and colloidal silver proteins (Silver 2003). Dietary intake of silver is estimated at 70–90 $\mu g.day^{-1}$. Inhalation of dusts or fumes containing silver occurs primarily in occupational settings, for example in industrial plants involved in silver chemical manufacturing (e.g., silver powder, silver nitrate, silver oxide, silver chloride, and silver cadmium powder), jewellery manufacturing, silver reclamation, and production of tableware (Drake and Hazelwood 2005). Also skin contact occurs in occupational settings (ATSDR 1990), as well as from the application of burns creams (Wan et al. 1991) and from contact with jewelry (Catsakis and Sulica 1978). Silver can also gain entry into the body through the use of acupuncture needles, catheters, dental amalgams or accidental puncture wounds (reviewed in Drake and Hazelwood 2005). The most common health effects associated with chronic exposure to silver are a permanent grey or blue grey discoloration of the skin (argyria), primarily in sun-exposed regions and eye (argyrosis) (ATSDR 1990;

Drake and Hazelwood 2005). Chronic symptoms from prolonged intake of low doses of silver salts are fatty degeneration of the liver and kidneys and changes in blood cells (Venugopal and Luckey 1978). Soluble silver compounds are also capable of accumulating in small amounts in brain and muscles following long-term exposure (Fung and Bowen 1996). Since silver in any form is not thought to be toxic to the immune, cardiovascular, nervous or reproductive systems (ATSDR 1990) and it is not considered to be carcinogenic (Furst and Schlauder 1978), the prevailing view is that except for argyria or argyrosis and some minor problems, silver is relatively non-toxic (Chen and Schluesener 2008).

Environmental aspects

Silver in the environment

Although silver is rare in the natural environment, concentrations may be elevated due to anthropogenic activities such as smelting, manufacture and disposal of photographic supplies, or coal combustion (WHO 2002). It also leaks into the aquatic environment via municipal and industrial water treatment plants, which receive liquid waste from the photographic industry, the largest producer of silver contamination (Smith and Carson 1977, cited in WHO 2002; Wen et al. 1997). From 1964–2000 the world production of silver went from 7.4–15.5 million kg (Silver Institute 2007). No numbers are available for more recent years, but uses of silver have changed significantly in the past decade. The rise of digital photography has resulted in an enormous reduction of the amount of film manufactured and processed annually, accompanied by a decrease in attendant silver emissions. This reduction (the photographic sector consumed 26% of the total silver demand in 1997) has been more than offset by the increased manufacture of electronic goods and the use of silver-containing conductive pastes and solders. Silver demand will likely continue to rise as silver finds new uses, particularly in the textiles, plastics, and medical industries, changing the pattern of silver emissions as these technologies and products diffuse through the global economy (Eckelman and Graedel 2007). About 25% of the silver production is lost to terrestrial and aquatic ecosystems (approximately 2/3 and 1/3, respectively) (Scow et al. 1981, cited in Purcell and Peters 1998). Smith and Carson (1977) found that 150,000 kg of silver enter the aquatic system every year from industry; as the world production of silver has almost doubled since; up until 2000 close to 300,000 kg of silver probably enter the aquatic system every year. In the 1980s levels up to 150 $mg.kg^{-1}$ have been found in the sediment of the Genesee River, USA. The highest silver concentration (38 $\mu g.l^{-1}$) in fresh water was detected in the Colorado River, not far from industry serving as an anthropogenic source (USEPA 1980). Ambient background concentrations of silver are 0.01 $\mu g.l^{-1}$ in pristine waters (WHO 2002). Even though elevated levels due to anthropogenic sources may seem high at first, only a small amount is actually bioavailable.

The most abundant form of silver in the open ocean is $AgCl_2$ (Bryan and Langston 1992). Silver easily adsorbs to ferric compounds, clay minerals, etc. Furthermore, sorption by manganese dioxide and precipitation with halides reduce the concentration of dissolved silver in the water phase, consequently increasing the concentration in the sediment compared to the water. Only under reducing conditions will the adsorbed silver in the sediment be released resulting in either metallic silver or silver sulfide, which are both insoluble in water (USEPA 1980). Silver thiolate complexes have been found in highly polluted waters. These complexes constantly exchange silver ions with each other and they also have the capability to transfer onto or off particulate matter and cells of organisms, besides the capability of forming silver sulfide (Bell and Kramer 1999, cited in WHO 2002). Under oxidizing conditions, silver is found as bromides, chlorides and iodides in fresh water and soils. Under reducing conditions, silver exists as free metal and silver sulfide (ATSDR 1990, cited in WHO 2002). With increasing salinity of marine waters, more silver-chloro complexes form (Luoma 1994).

Bioaccumulation of silver

Bioaccumulation of silver has been investigated in several studies. Sanders and Abbe (1987) found that just 2 μg of $silver.l^{-1}$ of water are enough for marine algae to accumulate significant amounts of silver (i.e. above the detection limit). Marine bivalve mollusks accumulate silver more strongly than algae and some mollusks can even accumulate silver from sediments. Oysters, gastrops and arthropods can all incorporate silver; the quantity in which this occurs depends on the biological availability of silver and age, size, sex, reproductive stage, general health and metabolism of the organism. Also, water temperature, salinity, dissolved oxygen, turbidity, and presence of other compounds may influence bioaccumulation (Presley et al. 1990). It was thought that silver accumulation results from the bioavailability of the free silver ion, but Reinfelder and Chang (1999) showed that AgCl was a factor contributing to an increase in silver uptake (Fortin and Campbell 2000).

Experiments with rainbow trout have shown that the uptake of silver takes place via a sodium-ion channel located on the branchial apical membrane (Bury and Wood 1999). Research with the same fish by Hogstrand et al. (1996) suggested that possible toxicity from silver accumulation in the liver was reduced by metallothionein, a protein that sequesters metals (WHO 2002).

Silver, environmental toxicity

The acute toxicity of silver is dependent on its chemical form and the availability of free silver ions. Research has shown that with an aqueous concentration of only 1–5 $\mu g.l^{-1}$ sensitive aquatic organisms and insects, trout and flounder can be killed (Bryan and Langston 1992; Wood et al. 1994). Furthermore, accumulation of silver in species exposed to a slightly lower concentration of silver has lead to adverse effects on growth (Eisler 1997). With respect to marine environments, investigations have shown that the concentrations of bioavailable free silver ions are too low to lead to toxicity (WHO 2002).

Toxicity of (nano-)silver in ecosystems

Even though silver is usually not available in concentrations high enough to pose a risk to human health and the environment, nano-silver has physical and surface properties which could pose a threat to human and environmental health (Lee et al. 2007). Especially the possibility of nano-silver providing a reservoir for toxic silver ions is of concern in this respect. The most relevant properties are summarized in Table II.

Because of the different physico-chemical properties and biological activities of nano-silver when compared with the regular metal, it cannot be excluded that the increased reactivity of nano-silver (because of the large surface area) leads to increased toxicity due to the activity of free silver ions released by the nanoparticles (see above hypothesis).

Recent research with zebra fish showed that single silver 12 nm nanoparticles affected early development of fish embryos (Lee et al. 2007). Silver nanoparticles have the potential to cause chromosomal aberrations and DNA damage and are capable of inducing proliferation arrest in cell lines of zebrafish (Asharani et al. 2007). More *in vitro* and *in vivo* toxicity studies in mammalian species have been performed recently with nano-silver showing that silver nanoparticles have the capability to enter cells and cause cellular damage (Hussain et al. 2005; Ji et al. 2007). Consequently, more research is needed on ecologically relevant species to investigate whether silver nanoparticles present a threat to environmental health in general.

It also has to be determined whether nano-silver that is present in various products is actually capable of reaching the aqueous and terrestrial environment. More specifically, how strong are the bonds between nano-silver and the product it is incorporated in and do these chemical properties change under certain circumstances leading to more/less release of nano-silver into the aqueous environment, on top of releases of nano-silver not incorporated in products? No toxicity data on nano-silver in soils were found.

Table II. Main characteristics influencing the fate and behavior of nanomaterials in living systems and the environment.

Size
Surface area
Surface chemistry
Water and lipid solubility
Organic carbon partition coefficient (K_{oc})
Vapor pressure (mainly important for liquids)
Coagulation or aggregation state
Chemical composition (including coatings and purity)

Conclusion environment

The effects of silver have been investigated for more than 30 years. Levels of silver in various aqueous environments have been determined, but free silver ion levels, mostly responsible for toxicity, rarely reached levels leading to adverse effects. Nano-silver, a relatively new and different type of silver with different chemical and physical properties, is applied in products which may easily reach the aqueous environment.

In vitro studies have demonstrated that nano-silver has effects on, among other things, reproduction and development and has an effect on DNA. Furthermore, nano-silver is incorporated in products such as water filters and washing machines; the presence of nano-silver in these products easily leads to a leakage into the aqueous environment and aqueous environmental species.

Overall, very little is known on the specific effects of nano-silver in the environment along all aspects of the causality chain from release from products → emissions → distribution in the environment (i.e., fate in the environment) → effects on biota. Therefore, it is currently impossible to reliably assess the environmental risks associated with the production and use of nano-silver.

An important research question is the validation of the 0-hypothesis of toxic effects being proportional to the activity of the free silver ions released by the nanoparticles. Apart from effect assessment in the aqueous environment, specifically more research is needed to investigate the effects of nano-silver in

terrestrial environments as no toxicity data for nano-silver in soils were found. Finally, release patterns and release kinetics of nano-silver from specific applications need to be investigated in more depth.

Properties and mode of action of nano-silver

Properties of nano-silver

Nano-silver has biological properties which are significant for consumer products, food technology (e.g., food processing equipment, packaging materials, food storage), textiles/fabrics (e.g., antimicrobial clothing), and medical applications (e.g., wound care products, implantable medical devices). In addition, nano-silver has unique optical and physical properties that are not present in bulk silver, and which are claimed to have great potential for medical applications (e.g., diagnostics, drug delivery, and imaging).

Antibacterial properties. Nano-silver is an effective killing agent against a broad spectrum of Gram-negative and Gram-positive bacteria (Burrell et al. 1999; Yin et al. 1999), including antibiotic-resistant strains (Wright et al. 1998; Percival et al. 2007). Gram-negative bacteria include genera such as *Acinetobacter*, *Escherichia*, *Pseudomonas*, *Salmonella*, and *Vibrio*. *Acinetobacter* species are associated with nosocomial infections, i.e., infections which are the result of treatment in a hospital or a healthcare service unit, but secondary to the patient's original condition. Gram-positive bacteria include many well-known genera such as *Bacillus*, *Clostridium*, *Enterococcus, Listeria*, *Staphylococcus*, and *Streptococcus*. Antibiotic-resistant bacteria include strains such as methicillin-resistant and vancomycin-resistant *Staphylococcus aureus*, and *Enterococcus faecium*. Recently, it has been shown that silver nanoparticles (diameter 5–32 nm, average diameter 22.5 nm) enhance the antibacterial activity of various antibiotics (Shahverdi et al. 2007). The antibacterial activities of penicillin G, amoxicillin, erythromycin, clindamycin, and vancomycin against *Staphylococcus aureus* and *Escherichia coli* were increased in the presence of silver nanoparticles.

Size-dependent (diameter 1–450 nm) antimicrobial activity of silver nanoparticles has been reported with Gram-negative bacteria (Baker et al. 2005; Morones et al. 2005; Panacek et al. 2006) and Gram-positive bacteria (Panacek et al. 2006). Small nanoparticles with a large surface area to volume ratio provide a more efficient means for antibacterial activity even at very low concentration. In addition to size and concentration, shape-dependent antimicrobial activity of silver nanoparticles has been shown with Gram-negative bacteria (Pal et al. 2007). Silver nanoparticles of different shapes (spherical, rod-shaped, truncated triangular nanoplates) were developed by synthetic routes. Truncated triangular silver nanoplates were found to display the strongest anti-bacterial activity. The top basal plane of truncated triangular silver nanoplates is a high-atom-density surface, i.e., a {111} facet. Generally, spherical silver nanoparticles (generally with cubooctohedral, multiple-twinned decahedral, or quasi-sperical morphology) have {100} facets along with a small percentage of {111} facets, whereas rod-shaped silver nanoparticles (e.g., pentagonal rods) have side surfaces with {100} facets and end with {111} facets (Wiley et al. 2005). It has been demonstrated that silver reactivity is favored by {111} facets (Hatchett and Henry 1996). Moreover, spherical silver nanoparticles with {111} facets attach directly to the bacterial surface of the cell membrane and are located inside bacteria (Morones et al. 2005). Thus, the strong anti-bacterial activity of truncated triangular silver nanoplates could be due to their large surface area to volume ratios and their crystallographic surface structures.

Antifungal properties. Nano-silver is an effective and a fast-acting fungicide against a broad spectrum of common fungi including genera such as *Aspergillus*, *Candida*, and *Saccharomyces* (Wright et al. 1999). Moreover, silver nanoparticles (diameter 13.5 ± 2.6 nm) are effective against yeast isolated from bovine mastitis (Kim et al. 2007).

Antiviral properties. Silver nanoparticles (diameter 5–20 nm, average diameter $\sim$10 nm) inhibit HIV-1 virus replication (Sun et al. 2005). An interesting observation was that gold nanoparticles (average diameter $\sim$10 nm) showed relatively low anti HIV-1 activity (6–20%) when compared to silver nanoparticles (98%). In addition, size-dependent antiviral activity of silver nanoparticles has been shown with HIV-1 virus (Elechiguerra et al. 2005). Interaction of silver nanoparticles with HIV-1 was exclusively within the range of 1–10 nm.

Anti-inflammatory properties. In animal models nano-silver alters the expression of matrix metallo-proteinases (proteolytic enzymes that are important in various inflammatory and repair processes) (Kirsner et al. 2001), suppresses the expression of tumor necrosis factor (TNF)-α, interleukin (IL)-12, and IL-1β, and induces apoptosis of inflammatory cells (Bhol and Schechter 2005, 2007). Moreover, silver nanoparticles (diameter 14 ± 9.8 nm) modulate cytokines involved in wound healing (Tian et al. 2007). The results indicate the possibility of

achieving a scarless wound healing even though further studies using other animal models are required to confirm this.

Diffusion through glycoprotein film. Surfaces of implanted devices immediately and rapidly become coated with patient-derived glycoproteins from tissue and blood plasma (Green et al. 1999). Once protein adhesion has occurred, proliferation leads to the development of a biofilm which is insusceptible to most therapeutic agents. In the case of impregnation of medical-grade silicone with silver nanoparticles (diameter 10–100 nm) there is both a depot effect and a diffusion pressure available to equilibrate the silver concentration and to push silver through the glycoprotein conditioning film (Furno et al. 2004). This unexpected finding has obvious clinical implications, because silver is known to have a high avidity to protein and the presence of a glycoprotein film has been assumed to inactivate any silver ions released (Schierholz et al. 1998).

Prevention of biofilm formation. Nano-silver inhibits the formation of biofilms (Percival et al. 2007). Biofilms are complex communities of surface-attached aggregates of microorganisms embedded in a self-secreted extracellular polysaccharide matrix. Biofilm forming bacteria act as efficient barriers against antimicrobial agents and the host immune system, resulting in a persistent colonization and/or infection at the site of the biofilm formation.

Surface plasmon resonance. Noble metal nanoparticles can be deposited onto a glass matrix and exhibit a very intense color, which is absent in bulk material as well as in individual atoms. Their origin is attributed to the collective oscillations or fluctuations in electron density with an interacting electromagnetic field. These resonances are also denoted as surface plasmons. These oscillations are very sensitive to adsorption of molecules to the metal surface. The plasmonic coupling of metal nanoparticles with light enhances a broad range of useful optical phenomena which have application potential in ultra-sensitive biomolecular detection and lab-on-a-chip sensors, e.g., Moores and Goettmann (2006). The effect of the size of silver nanoparticles on the surface plasmon resonance, i.e., plasmon band width and peak position, has been demonstrated (Thomas et al. 2008). Decreasing nanoparticle size (diameter <10 nm) is associated with a red-shift and broadening of the plasmon-related absorption peak. The impact of silver nanoparticle shape on plasmon surface resonance has been less studied.

Plasmonic heating. Plasmonic photo-activation of hollow polyelectrolyte-multilayer capsules incorporating silver nanoparticles and containing drug models has been demonstrated as proof-of-principle (Skirtach et al. 2004). Silver nanoparticles were remotely activated using laser irradiation, causing not only absorption of photons but also heat transfer from the nanoparticles to the surrounding polymer matrix. The local heating disrupts the polymer matrix and allows the encapsulated material/drug to leave the interior of the capsule. The concept of remote opening of polyelectrolyte-multilayer capsules incorporating silver nanoparticles (diameter $>$ 20 nm) has been demonstrated in living cells (Skirtach et al. 2006). Recently, it has been shown that duration of laser treatment to open polyelectrolyte-multilayer capsules is dependent on the size of silver nanoparticles (diameter 10–23 nm) (Radziuk et al. 2007).

Metal-enhanced fluorescence. Metallic nanostructures (size range 30–80 nm) alter the intrinsic spectral properties (i.e., emission intensity and photostability) of fluorophores. The proximity of silver nanostructures results in an increase in intensity of low-quantum-yield fluorophores. The effects of metallic surfaces include fluorophore quenching at short distance ($\sim$ 0–5 nm), spatial variation of the incident light filed ($\sim$ 0–15 nm), and changes in the radiative decay rate ($\sim$ 0–20 nm). Applications are in immunoassays and DNA/RNA detection, e.g., Aslan et al. (2005).

Potential problem of silver resistance. Remarkably, in light of the antibacterial properties of nano-silver, the feasibility of biosynthesis of silver nanoparticles using bacteria has been demonstrated (Klaus et al. 1999). Silver nanoparticles (size up to 200 nm) were synthesized using *Pseudomonas stutzeri* and found to be mostly located at the periplasmic area of the bacteria. Another silver-resistant bacteria used in the biosynthesis of silver nanoparticles (diameter 5–32 nm, average diameter 22.5 nm) is *Klebsiella pneumoniae* (Shahverdi et al. 2007). Fungi can also be used to biosynthesize silver nanoparticles. Intracellular silver nanoparticles (diameter 25 ± 12 nm) were produced in *Verticullium* fungal cells (Mukherjee et al. 2001) and extracellular silver nanoparticles (diameter 5–25 nm) using pathogenic filamentous fungi such as *Fusarium oxysporum* (Ahmad et al. 2003) and *Aspergillus fumigatus* (Bhainsa and D'Souza 2006). Recently, extracellular silver nanoparticles (diameter 13–18 nm) were biosynthesized using non-pathogenic fungus *Trichoderma asperellum* (Mukherjee et al. 2008). In addition to microbial organisms, plant extracts can be used in the

biosynthesis of metallic nanomaterial (Mohanpuria et al. 2008).

The widespread and increasing use of nano-silver within healthcare settings raises issues concerning bacterial and fungal silver resistance. Whether resistance is a threat in the clinical setting needs to be elucidated (Chopra 2007). Currently, standardization for silver antimicrobial testing methods is lacking. In part, this is due to the complex solubility issues affecting the bioavailability of silver.

Antibacterial mode of action

Bacteria have different membrane structures on which the general classification as Gram-positive and Gram-negative bacteria is based. Structural differences reside in the organization of the key component of the cell wall, peptidoglycan, which is located immediately outside the cytoplasmic membrane. The cell wall of Gram-positive bacteria contains a peptidoglycan layer of ~ 30 nm thick. Unlike the Gram-positive cell wall, the Gram-negative cell wall has only a thin peptidoglycan layer of $\sim$ 2–3 nm. In addition to the peptidoglycan layer, the Gram-negative cell wall also contains an additional outer membrane composed by phospholipids and lipopolysaccharides which face into the external environment.

Although the antimicrobial effect of silver ions has been studied extensively, the effects of nano-silver on bacteria and the bactericidal mechanism are only partially understood. Based on studies having shown that silver nanoparticles anchor to and penetrate the cell wall of Gram-negative bacteria (Sondi and Salopek-Sondi 2004; Morones et al. 2005), it is reasonable to suggest that the resultant structural change in the cell membrane could cause an increase in cell permeability, leading to an uncontrolled transport through the cytoplasmic membrane and ultimately cell death. It has also been proposed, that the antibacterial mechanism of silver nanoparticles is related to the formation of free radicals and subsequent free radical-induced membrane damage (Danilczuk et al. 2006; Kim et al. 2007). Very recently, Hwang and colleagues (2008) performed a study on stress-specific bioluminescent bacteria, based on which they propose a synergistic toxic effect of the silver nanoparticles and the silver ions that they produce. The ions move into the cells and lead to the production of reactive oxygen species. Furthermore, because of the membrane damage caused by the nanoparticles, the cells cannot effectively extrude the silver ions and limit their effect.

Based on the greater tendency of silver ions to strongly interact with thiol groups of vital enzymes and phosphorus-containing bases (Hatchett and White 1996) and on the presence of silver nanoparticles inside the cells (Morones et al. 2005), it is likely that further damage could be caused by interactions with compounds such as DNA. This interaction may prevent cell division and DNA replication from occurring, and also ultimately lead to cell death. However, no DNA damage was found by Hwang et al. (2008).

Recently, evidence has been obtained suggesting that silver nanoparticles may modulate the phosphotyrosine profile of putative bacterial peptides that could affect cellular signaling and therefore inhibit the growth of bacteria (Shrivastava et al. 2007).

Exposure to nano-silver

Human exposure – the inventory

To gain more insight in the human exposure to nano-silver an inventory has been made of products containing nano-silver. Three major product categories are respectively food, consumer products and medical products. An inventory of the probable worker exposure to nano-silver is beyond the scope of this review and is not included. For the inventory, information was obtained from different sources, varying from Google^{TM} using the terms nano-silver, food, consumer products and medical products in various combinations to different databases freely available on the internet. Most food and consumer products have been found via the database of the Nanotechnology project (www.nanotechproject.org) of the Woodrow Wilson International Centre for Scholars, the Nanotechnology Product Directory (www.nanoshop.com) and the nanoforum report on Nanotechnology in Consumer Products (Nanoforum 2006, www.nanoforum.org). For food products, a recent report of the Dutch National Institute for Public Health and the Environment (RIVM) in collaboration with the Dutch RIKILT-Institute for Food Safety (RIKILT) (Bouwmeester et al. 2007), and for consumer products two recent RIVM reports under the authority of respectively the Dutch Food and Consumer Product Safety Authority (VWA) (Dekkers et al. 2007a) and European Parliament's Committee on the Environment, Public Health and Food Safety (Dekkers et al. 2007b) have been used. For medical products, a RIVM report (Roszek et al. 2005) has been used and updated. All results of the product inventory are presented as Supplementary Material. One has to keep in mind that the results of the product inventory are based on information on the product as provided by the manufacturer. The claim that the products contain nanotechnology in general and nano-silver in particular cannot be verified from the information

presented. It can be expected that in some cases the claim of nanotechnology is not more than a marketing instrument. On the other hand, products that do contain nano-silver, but are not advertised as such, are missed, making the inventory results presented here somewhat biased. Another reason why this inventory cannot be exhaustive is the speed at which the products are developed. Still, this inventory can be seen as representative of the products available on the global market. Data on the quantities of silver in consumer products are hard to gather. However, the Woodrow Wilson database has recently made some data of nano-silver in consumer products available on its internet site. The concentration of nano-silver varies between <6 and 10000 ppm in consumer products, ranging from dietary supplements to cosmetics and wound dressings. The highest concentrations were found in so-called 'nano-silver master batches' that are not end-products itself, but are used in consumer products (http://www.nanotechproject.org/inventories/silver/).

Exposure via food

Nanotechnologies are being used throughout all phases of food production (production, processing, safety and packaging) (Nanoforum report 2004; Bouwmeester et al. 2007). The way nanotechnology is used within the food production leads to a first estimate of potential consumer exposure and thus can be used as a ranking of risks. Nanotechnology used for food production without introducing/adding nanoscale products or compounds in the food can be considered as low risk for the consumer. On the other hand, the ultimate direct consumer exposure can be expected when nanoparticles are included into food directly. The use of nano-silver includes the processing, conservation and consumption phase of the food production chain (Table III).

For food supplements with nanosized silver also statements about the function like 'Purifying and conservation of unknown targets', 'Supporting the immune system' and 'Helpful against severe illness' have been put on products. Since these statements have not been evaluated by, for instance, the European Medicines Evaluation Agency (EMEA), the European Food Safety Authority (EFSA) or the US Food and Drug Administration (FDA), the products are not medical products and are not intended to diagnose, treat, cure or prevent any disease.

The category Food and Beverages in the product inventory (Tables A1.1 and A1.2, Supplementary Material, online version only) was split up into four sub-categories, and contained 27 different products with nano-silver found on the global market representing different applications (Table IV). Furthermore, also relevant in the storage of food are two refrigerators found in the consumer products category Electronics. Further detailed product information (product names, manufacturers, country of origin) is presented in tables A1.1 and A1.2, Supplementary Material, online version only.

As already mentioned earlier, consumer exposure is expected to be high when nanoparticles are included in food, as is the case for the nano-silver supplements. With regard to the major use of nano-silver in coatings to prevent bacterial growth, the actual exposure of humans is hard to estimate. The expected consumer exposure remains low as long as the inert nano-silver particles are bound in the packaging materials or in the coatings on surfaces of packaging materials and food preparation devices. When nano-silver particles are bound to other materials, exposure to nano-silver is only expected to occur when there is a risk of wear-off or migration of nano-silver particles in the free or aggregated form into the food (SCENIHR 2006). However, there can be release of Ag^{+}, otherwise there may not be desired antimicrobial effect and no information is available on the release of (nano) silver ions taking place from the different types of silver application.

Exposure via consumer products

For nanotechnology consumer products, there are several existing inventories, which contain a wide variety of globally available products. The most extended publicly available inventory is the database of the Nanotechnology project of the Woodrow

Table III. Summary of applications of nano-silver in the food production chain.

Chain phase	Application	Nanotechnology	Function
Processing of food	Food preparation equipment	Incorporated nanosized silver particles	Anti-bacterial coating of food handling devices
Conservation	Refrigerators Storage containers	Incorporated nanosized silver particles	Anti-bacterial coating of storage devices
	Food products	Nanosized silver sprays	Antibacterial action
	Packaging materials	Incorporation of active nano-silver particles	Oxygen scavenging, prevention of growth of bacteria
Food consumption	Supplements	Colloidal metal nanoparticles	Claimed to enhance desirable uptake

Table IV. Number of Food and Beverages products per subcategory*.

Subtype of product	Matrix	No.	Example
Cleaning	Fluid/spray	1	Sterilizing spray
Cooking utensils, coatings	Coatings	6	Cutting and chopping boards, kitchen- and tableware, baby bottle brush
Storage	Solid	8	Fresh boxes, storage bags and containers, baby bottles and mugs
Supplements	Fluid	12	Silver particles in water

*Categories and subcategories were modified from the database of the Woodrow Wilson International Centre of Scholars.

Wilson International Centre for Scholars (www.nanotechproject.org).

Since this project on Emerging Nanotechnologies launched the first online inventory of manufacturer-identified nanotech goods in March 2006, the number of items has increased 175%, from 212–580 products in December 2007. In August of last year, the total number of products was further increased to 803 products, a rise of 279% when compared to the first inventory in 2006. This clearly indicates how fast the market for nano containing products is growing.

The focus of two previous RIVM inventories was on the Dutch and European markets (Dekkers et al. 2007a, 2007b). The possible exposure of (Dutch or European) consumers to products containing nanomaterials was reported as well as the availability of the products on the European market and the adequacy of the existing regulatory framework for nanomaterials. At the time the inventories were made (April 2007), in total 143 consumer products were identified to be on the Dutch market, in different product categories. This amount is much lower than the 475 products found in May 2007 in the Woodrow Wilson database, but can be explained by the region of origin of the products. Companies based in the USA produce most of the nano-containing consumer products (317), followed by companies in Asia (127), Europe (92), and elsewhere around the world (32). For nano-products produced outside Europe, consumers in Europe are dependent on European distributors or the possibility to order the products online.

Several nanomaterials are used in consumer products, like metal oxides (e.g., titanium dioxide, zinc oxide, silica), metals (e.g., silver, gold, nickel) and organic nanomaterials (e.g., nanovitamins, nanoclays, carbon nanotubes) (Dekkers et al. 2007b). However, the nanomaterial used in the highest number of different products at this moment appears to be silver (Ag), which manufacturers claim is in 233 consumer products, and in 33 food products in 2008. This is 30% of the Woodrow Wilson inventory, far more than other materials like carbon, gold or silica.

The inventory on nano-silver containing consumer products described in this report is mainly derived from the Woodrow Wilson database. In this database in total 126 consumer products were found in December 2007 (see also Tables A1, Supplementary Material for a detailed list, online version only). The application of (nano) silver in these consumer products is mainly based on the antibacterial property of silver. Apart from the Food and Beverages category, the product categories in which nano-silver is represented, are:

- Electronics
- Filtration, purification, neutralization, sanitization
- Personal care and cosmetics
- Household products/home improvement
- Textile and shoes

Within these categories, several subcategories were identified (Dekkers et al. 2007b, adapted from Woodrow Wilson database) and presented in Table V, together with some examples of relevant products. As can be concluded from this table, most nano-silver containing consumer products are in the product categories Textile and shoes (34), Personal care and cosmetics (30) and Electronics (29) with respectively Clothing, Skin care and Personal care as subcategories with the largest number of products. Also the categories Household products/home improvement (19) and Filtration, purification, neutralization, and sanitization (13) contain a substantial amount of products with nano-silver. Some products are difficult to classify and can be categorized in more than one group, therefore it is possible that discrepancies exist between this and former inventories.

Nano-silver products are mainly manufactured in Asian countries (81 products) and in the USA (60), only a very small amount of products has a European country of origin (nine). One of the reasons for this low number of European manufacturers in our inventory might be that the Woodrow Wilson database is probably mainly focused on the US market and a similar public European database is not available. Previous RIVM inventories show that

Table V. Product categories* with examples of products containing nano-silver. Values between brackets indicate the number of (sub)categories.

Categories	Subcategories	Examples
Personal care and cosmetics (30)	Skin care (14)	(Body) cream, hand sanitizer, hair care products, beauty soap, face masks
	Oral hygiene (6)	Tooth brush, teeth cleaner, toothpaste
	Hair care (3)	Hair brush, hair masks
	Cleaning (2)	Elimination wipes and spray
	Coating (2)	Make-up instrument, watch chain
	Baby care (2)	Pacifier, teeth developer
	Over the counter health products (1)	Foam condom
Textile and shoes (34)	Clothing (28)	Fabrics and fibers, socks, shirts, caps, jackets, gloves, underwear
	Other textiles (2)	Sheets, towels, shoe care, sleeves and braces
	Toys	Plush toys
Electronics (29)	Personal care (13)	Hair dryers, wavers, ions, shavers
	Household appliances (8)	Refrigerators, washing machines
	Computer hardware (6)	Notebooks, (laser) mouse, keyboards
	Mobile devices (2)	Mobile phones
Household products/home improvement (19)	Cleaning (9)	Cleaning products for bathroom, kitchen, toilets, detergents, fabric softener
	Coating (4)	Sprays, paint supplements
	Furnishing (3)	Pillows
	Furnishing/coating (3)	Showerheads, locks, water taps
Filtration, purification, neutralization, sanitization (13)	Filtration (8)	Air filters, ionic sticks
	Cleaning (6)	Disinfectant and aerosol sprays

*Categories and subcategories were modified from the database of the Woodrow Wilson International Centre of Scholars.

information on European manufacturers and distributors can be found with a more extended search (on the internet) (Dekkers et al. 2007a). However, we still think that the inventory is representative of the available products with nano-silver. With respect to the availability of the products in the current inventory to the European consumer, we investigated the countries of distributors and the possibility of ordering the products online. Of the 127 consumer products in the inventory, 68 products (54%) are available for Dutch/European consumers, of which 28 products (23%) are distributed by the manufacturer in many countries around the world (including Europe) and 40 products (31%) are easily available via internet.

Exposure via medical products

Silver has been known for decades for its antimicrobial properties in curative and preventive medicine. The most widespread uses of silver are silver salts, silver complexes, and metallic silver in pharmaceutical and homeopathic products (e.g., ointments, suspensions). Silver antibiotic salts such as silver sulfadiazide are used as prophylaxis of infections in patients with burns (Church et al. 2006).

Medical devices such as catheters, orthopedic implants, heart valves and wound care products are prone to bacterial adhesion, colonization, biofilm formation and adhesion of glycoproteins from tissue and blood plasma. Silver coatings, using silver salts or ion beam implantation of metallic silver, have been devised to address these problems. However, some coatings have shown disappointing clinical results as effective strategies to prevent medical device-related infections. For instance, in 2000 a voluntary recall of a silver-coated sewing cuff fabric for heart valve replacement was initiated due to elevated rates of paravalvular leakage (Schaff et al. 2002).

Recently, advanced silver nanotechnologies have been employed in an attempt to engineer out the risks of medical device-related infections. Several medical devices, mainly products for wound care management, incorporating nano-silver are on the market (Table VI and Table A2.1 in the Supplementary Material).

In general, nano-silver is deposited, impregnated or coated onto medical devices or fabrics rendering them suitable for controlling infections. Advanced nanotechnologies, such as physical vapor deposition, chemical vapor deposition, or ink-jet technology, are used to create thin layers of nano-silver on a broad

Table VI. Medical devices containing nano-silver. Values between brackets indicate the number of devices.

Medical domains	Examples
Anesthesiology	Catheter for administration of local anesthetic (1)
Cardiology	Battery used in implantable cardioverter-defibrillator (1)
Nephrology	Hemodialysis catheter (2)
Urology	Urinary catheter (2) Battery used in implantable electrical pulse generator (1)
Wound care	Burn and wound dressing, professional use (15) Burn and wound dressing, over the counter (2) Burn glove (1) Burn sock (1) Tubular stretch knit (1) (Adhesive) strip, professional use (2) (Adhesive) strip, over the counter (2) Gel (1) Compress (2) IV/catheter dressings (2)

range of substrates, e.g., metals, ceramics, polymers, glass, and textiles. Silver nanotechnologies that have been launched for antimicrobial coatings are Bactiguard® (Bactiguard AB, Sweden), HyProtect™ (Bio-Gate AG, Germany), Nucryst's nanocrystalline platform technology (Nucryst Pharmaceuticals Corp., USA), Spi-Argent™ (Spire Corp. USA), Surfacine® (Surfacine Development Company LLC, USA), and SylvaGard® (AcryMed Inc., USA). Currently, nano-silver is extensively used for wound management, particularly in medical devices for the treatment of burns (Tredget et al. 1998), chronic wounds (Yin et al. 1999; Sibbald et al. 2001), burns in children (Dunn and Edwards-Jones 2004), burn injuries in neonates (Rustogi et al. 2005), rheumatoid arthritis-associated leg ulcers (Coelho et al. 2004), diabetic ulcers (Thomas 2007), venous ulcers (Sibbald et al. 2007), toxic epidermal necrolysis (Asz et al. 2006), for healing of donor sites (Innes et al. 2001), and for meshed skin grafts (Demling and Leslie DeSanti 2002).

Advanced silver nanotechnologies are also used to improve battery performance in next-generation active implantable medical devices. For instance, nano-silver in combination with vanadium oxide is applied in cell components resulting in improved cathode material homogeneity.

Currently, the application of nano-silver in medical products is emerging in the field of medical devices and pharmaceutical research and development (Table VII).

Other potential applications of nano-silver coated/deposited/impregnated medical devices are infusion ports, orthopedic protruding fixation devices, endovascular stents, urological stents, endoscopes, electrodes, peritoneal dialysis devices, subcutaneous cuffs, surgical and dental instruments. In addition, silver nanoparticles can be deposited on various natural and synthetic textile and fabrics which can be useful in hospitals to control infection (Lee et al. 2003).

In conclusion, incorporation of nano-silver into medical products has been of great interest in recent years. Properties of nano-structured silver can be controlled and tailored in a predictable manner and impart them with biological properties and functionalities that can bring new and unique capabilities to a variety of medical applications ranging from implant technology and drug delivery, to diagnostics and imaging.

High versus low potential exposure

The growing application of nano-silver in food products, medical applications, sprays and other consumer products and the increasing use and disposal of nano-silver in the environment (including their use as water purifier), indicates that human exposure to nano-silver is relevant and implies that this exposure is expected to increase in the (near) future. The potential exposure to nano-silver is determined by a series of characteristics that is summarized in Table VIII.

The characteristic of main importance is the way the nanomaterials were incorporated into the product (free nanoparticles or nanomaterials integrated into larger scale structures) in combination with the application of the product (with either direct or indirect human exposure). For example, products containing free nanoparticles with direct human exposure (e.g., food supplements or sunscreen products) are considered to have a high potential exposure, while products in which nanomaterials are integrated into larger scale materials with indirect human exposure (e.g., food storage bags or computers) are considered to have a low potential exposure. High potential exposure means that there may either be a high probability of exposure, or a probability of high exposure, or both. It is stressed that the qualification of 'high' and 'low' potential exposure should be interpreted in relative, but not absolute terms. Furthermore, the route of exposure is also very important for the definite internal exposure to nano-silver. Inhalation exposure via sprays or oral exposure of food supplements are considered to have the highest risk. For medical applications, especially for coated catheters and orthopaedic implants, more

Table VII. Emerging applications of nano-silver in medical products.

Medical domains	Examples	References
Anesthesiology	Coating of breathing mask	Patent
	Coating of endotracheal tube for mechanical ventilatory support	–
Cardiology	Coating of driveline for ventricular assist devices	–
	Coating of central venous catheter for monitoring	–
Dentistry	Additive in polymerizable dental materials	Patent
	Silver-loaded SiO_2 nanocomposite resin filler	Jia et al. (2008)
Diagnostics	Nano-silver pyramids for enhanced biodetection	Walt (2005)
	Ultrasensitive and ultrafast platform for clinical assays for diagnosis of myocardial infarction	Aslan and Geddes (2006)
	Fluorescence-based RNA sensing	Aslan et al. (2006)
	Magnetic core/shell Fe_3O_4/Au/Ag nanoparticles with tunable plasmonic properties	Xu et al. (2007)
Drug delivery	Remote laser light-induced opening of microcapsules	Skirtach et al. (2006)
Eye care	Coating of contact lens	Weisbarth et al. (2007)
Imaging	Silver/dendrimer nanocomposite for cell labelling	Lesniak et al. (2005)
	Fluorescent core-shell Ag@SiO_2 nanoballs for cellular imaging	Aslan et al. (2007)
	Molecular imaging of cancer cells	Tai et al. (2007)
Neurosurgery	Coating of catheter for cerebrospinal fluid drainage	Bayston et al. (2007)
		Galiano et al. (2007)
Orthopedics	Additive in bone cement	Alt et al. (2004)
	Implantable material using clay-layers with starch-stabilized silver nanoparticles	Podsiadlo et al. (2005)
	Coating of intramedullary nail for long bone fractures	Alt et al. (2006)
	Coating of implant for joint replacement	Chen et al. (2006)
	Orthopedic stockings	Pohle et al. (2007)
Patient care	Superabsorbent hydrogel for incontinence material	Lee et al. (2007)
Pharmaceutics	Treatment of dermatitis	Bhol et al. (2004)
		Bhol and Schechter (2005)
	Inhibition of HIV-1 replication	Elechiguerra et al. (2005)
		Sun et al. (2005)
	Treatment of ulcerative colitis	Bhol and Schechter (2007)
	Treatment of acne	Patent
Surgery	Coating of hospital textile (surgical gowns, face mask)	Li et al. (2006)
Urology	Coating of surgical mesh for pelvic reconstruction	Cohen et al. (2007)
Wound care	Hydrogel for wound dressing	Yu et al. (2007)

specific exposure routes are possible, dependent on the location of application. Most of the time, this is local exposure (intrathecal/intravesical/urethral/intramedullary), however, intravascular catheterization can lead to intravenous and thus systemic exposure. See Table IX for a ranking of the potential human exposure to nano-silver.

The fact that a product category is ranked with either a high or low potential exposure in abovementioned table should not be seen as evidence for absolute high exposures or the lack thereof, but as an indication of potentially high exposures (Dekkers et al. 2007b). These rankings are based on the current knowledge and may need modifications when new information becomes available. Another point of interest for the future may be the cumulative exposure; currently no information on this is available.

In conclusion, to determine the risk for exposure, more information is needed on the concentrations of nano-silver in the product, the size and the form in which it is present (aggregates, agglomerates) and the probability of release of (nano) Ag^+ from the products.

Human aspects – toxicokinetics of nano-silver

To date, almost all toxicological experiments dealing with nanoparticles describe the total ingested, inhaled or dermally applied dose of nanoparticles. In kinetics, this is called external exposure. The internal exposure is the part of the external exposure that is absorbed from the port of entry and reaches the systemic circulation (and thus may reach other organs and tissues). From a toxicological perspective, a toxic effect is only provoked if sufficient

Table VIII. Main characteristics for human exposure to nanomaterials from food, consumer and medical products.

Characteristic	Comments
Type of nanomaterials	Free nanoparticles or integrated nanostructures into larger materials
Exposure route	Inhalation, dermal or oral exposure Intravascular, intrathecal, intravesical, urethral, ophthalmic intramedullary, intraperitoneal exposure*
Physical form of product	Spray, powder, liquid, emulsion or solid (coating)
Application of the consumer product	Applications with direct human exposure (e.g., sunscreen products, medical applications) or indirect human exposure (e.g., food storage bags, computers). Applications with direct emissions to an environmental compartment (e.g., tooth paste) or without direct emissions to the environment (e.g., computers).
Type, use of the consumer product	Widely used or rarely use product Frequency and amount of product used
Concentration of nanomaterial in product	Unknown

*These exposure routes are only relevant for medical applications and cause mainly local effects (with the exception of intravascular).

Table IX. Ranking of the potential human exposure to nano-silver.

Category	Sub category	Exposure route	Potential exposure*
Food and beverages	Cleaning	Inhalation/dermal	High
	Cooking utensils, coatings	Dermal	Low
	Storage	Dermal	Low
	Supplements	Oral	High
Personal care and cosmetics	Skin care	Dermal	High
	Oral hygiene	Oral	High
	Cleaning	Dermal	High
	Hair care	Dermal	Low?
	Baby care	Dermal	High?
	Over the counter products	Dermal?	High?
Textile and shoes	Clothing	Dermal	?
	Other textiles	Dermal	?
	Toys	Dermal/Oral	?
Electronics	Personal care	Dermal	Low
	Household appliances	Dermal	Low
	Computer hardware	Dermal	Low
	Mobile devices	Dermal	Low
Household products/home improvement	Cleaning	Inhalation/dermal	High
	Coating	Dermal	High??
	Furnishing	Dermal	Low
	Furnishing/coating	Dermal	Low
Filtration, purification, neutralization, sanitization	Filtration	Inhalation	?
	Cleaning	Inhalation/dermal	High
Medical products	Breathing mask	Inhalation	?
	Endotracheal tube	Inhalation	?
	Gastrointestinal tube	Oral	?
	Catheters	Intravascular/intrathecal/ intravesical/urethral	?
	Contact lens	Ophthalmic	?
	Incontinence material	Dermal	?
	Orthopedic implants	Intramedullary	?
	Orthopedic stockings	Dermal	?
	Pharmaceuticals	Oral/dermal	?
	Sling for reconstructive pelvic surgery	Intraperitoneal	?
	Surgical mask/textile	Inhalation/dermal	?
	Wound dressings	Dermal	High

*'High' indicates either a high probability of exposure, or a possibility of high exposure, or both. 'Low' indicates either a low probability of exposure, or a possibility of low exposure, or both. '?' indicates that there is no sufficient information available.

quantities of (an active metabolite of) substances reach a target site (receptor, cell or organ), which in turn is a function of the duration of exposure and dose rate. In general, the kinetics of a particle consists of four processes: absorption, distribution, metabolism, and excretion (ADME).

As already mentioned above, human exposure to nano-silver from different routes of exposure can be expected: e.g., via inhalation of a hygiene spray, after dermal contact with a wound dressing and after ingestion of a food supplement. Even so, it can be anticipated that nano-silver, used in medical implants (e.g., dental or in bone cement) can interact directly with the central blood circulation. Another uncommon route of exposure represents the female genital tract, since nano-silver products are also used in personal hygiene products and even condoms. Up till now, little kinetic data are available for this exposure route.

More than one route of exposure may occur for nano-silver. When, for example, nano-silver is inhaled, ingestion may occur from a secondary route of exposure due to the coughing up and subsequently swallowing of the inhaled nano-silver.

Absorption

Absorption of nano-silver into the human body may occur via inhalatory, oral, and dermal routes of exposure. In kinetic terms, absorption represents the process by which unchanged compounds (e.g., nano-silver) proceed from the site of administration to the central blood circulation and subsequently to the organs (site of measurement).

Lung. The respiratory system represents a major port of entrance for nano-silver. Sprays containing nano-silver are already available on the market, indicating that this is a relevant exposure route. The distribution and disposition of nano-silver in the respiratory tract depends on various factors including particle size and breathing force. In addition, due to the small diameter of the nano-silver, Brownian diffusion also determines deposition, resulting in a deep penetration of nano-silver in the lungs and diffusion to the high lung surface area presented in the alveolar region.

Deposition of (nano)particles can be modeled based on size (International Commission on Radiological Protection [ICRP] 1994) (Price et al. 2002) by means of mathematical models (Multiple-Path Particle Dosimetry [MPPD] model [Price et al. 2002]).

Figure 1 shows that, according to this model, between 30% and 80% of the inhaled nanoparticles (< 100 nm) may be deposited in the respiratory

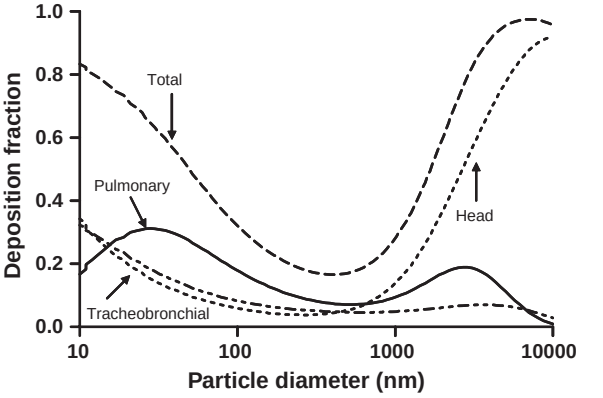

Figure 1. Modeled deposition of particles (10 nm–10 μm) in the respiratory tract.

tract. Nanoparticles up to 50 nm are expected to be deposited also in the upper airways due to strong diffusion before transportation into the deep lung (Maynard and Kuempel 2005).

The deposition of particles in the respiratory tract shown in Figure 1 is modeled with the MPPD model assuming an adult nasal breathing at 7.5 $l.min^{-1}$. Below 10 nm, reliable prediction is not possible, due to model restraints. This model predicts the deposition of inhaled, 'unspecified' particles, i.e., not for nano-silver specific. It was calculated with MPPD v 1.0 (Price et al. 2002).

Two inhalation studies with rats demonstrated that inhalation of nano-silver of ~ 15 nm resulted in the absorption of (nano)silver from the lungs into the systemic circulation (Takenaka et al. 2001; Ji et al. 2007).

The olfactory nervous system. An additional absorption route for inhaled nano-silver could be from the olfactory mucosa of the respiratory tract into the central nerve system via the olfactory nerve (Oberdörster et al. 2004). Indeed, inhaled 15 nm nano-silver has been demonstrated to be present in the olfactory nerve and brain of rats after inhalation (Takenaka et al. 2001). This suggests that for inhaled nano-silver, the olfactory nerve represents an additional port of entry into the brain, circumventing the restricted blood-brain barrier (Oberdörster et al. 2004, 2005a,b). However, the relevance and extent of this neuronal absorption route for nano-silver and its presence in humans is unknown (Elder et al. 2006).

Gastrointestinal absorption. The gastrointestinal tract represents an important port of entry for nano-silver at this very moment since specific food products, which are on the market, already contain nano-silver (Maynard and Michelson 2005). In addition, inhaled nano-silver particles can, in principle, be

excreted via the mucociliary escalator and subsequently be ingested into the GI tract. However, there is at the moment no direct evidence confirming this route.

Absorption of silver (both nano-silver and colloidal silver) after oral exposure has been reported. Colloidal silver is characterized as a liquid where silver particles of unknown size, but mainly in nanoscale range, remain in suspension. Absorption of colloidal silver into the systemic circulation is observed to some extent (White et al. 2003; Mirsattari et al. 2004; Chang et al. 2006). A recent oral toxicity study with 60 nm silver nanoparticles, revealed a dose-dependent accumulation of silver content in a broad range of tissues (Kim et al. 2008). This indicates that this accumulated silver content must have been absorbed, reached the systemic circulation, and distributed to other tissues. It remains unclear whether silver ions or the silver nanoparticles were absorbed by the gastrointestinal tract and transported into the body.

Dermal absorption. Dermal exposure represents an important potential absorption route for nano-silver. Antibacterial textiles and wound dressings that contain nano-silver are already on the market. Especially, wound dressings are used on impaired and burned skin and there is direct proof of dermal absorption of (nano-)silver after treatment of burned skin with 15 nm nano-silver coated wound dressings (Acticoat). After one week of local treatment, elevated silver levels in plasma and urine were detected (Trop et al. 2006). This finding was later confirmed by a study with 30 patients treated with Acticoat for small burns (Vlachou et al. 2007). It is, however, unclear from these studies whether silver ions or nano-silver particles were actually transported into the body.

Taken together, it seems that the absorption of nano-silver (and colloidal silver) for various routes of exposure has been identified. However, it remains unclear whether nano-silver particles or silver ions, released from nano-silver at the side of application, were absorbed into the body. Analytical tools for silver measurements do not discriminate between these two types of silver in the kinetic studies reported so far.

This observation may have significant impact on the expectations of the toxicology of nano-silver. In the case that only silver ions will enter the body, toxicological studies need to focus on the rate and extent of release of ions from the nano-silver form. In the case that only nano-silver itself will enter the body, then toxicity studies should be performed regarding nano-silver as a new chemical entity. This implies that future research needs to focus on:

(1). The rate and extent of release of silver ions from nano-silver at the site of entry;
(2). Probability and extent of absorption of nano-silver particles from the site of entry

Distribution

When nano-silver has passed the barriers (i.e., lung epithelia, intestinal lining, dermis) at the site of entry, the systemic circulation may be reached. Further distribution throughout the entire body may take place via the systemic circulation.

Protein binding. In principle, the binding of plasma proteins influences the ability of a particle to traverse cell membranes and other kinetic parameters (e.g., its distribution and half-life), half life plasma-protein binding. In general for compounds in the blood (e.g., pharmaceuticals), the unbound fraction exhibits the observed effect.

When nano-silver reaches the systemic circulation, the particles can, potentially, interact with plasma-proteins, coagulation factors, platelets and red and white blood cells. An effect of plasma-proteins on the distribution, elimination and toxic potency of nano-silver particles can be expected, similar to described protein (serum albumin) effects on quantum dots (Lovric et al. 2005).

Distribution to organs and tissues. The previously discussed inhalation studies with 15 nm nano-silver particles in rats revealed low, but detectable, concentrations of silver in blood and subsequent distribution to organs including liver, kidney, heart, lymph nodes and brain (Takenaka et al. 2001; Ji et al. 2007). The route by which the brain is reached (via olfactory bulb, via blood brain barrier passage or both) is, however, not known.

Orally ingested colloidal silver resulted in high levels of silver in plasma in one case report, while in another case report, a blue-gray hyperpigmentation of the skin, called argyria was observed. Brown-black granules in a skin biopsy verified colloidal silver as the source of the dyspigmentation (White et al. 2003; Chang et al. 2006). The finding of argyria indicates that ingested colloidal silver is absorbed by the gastrointestinal tract, distributed by the blood to organs and eventually accumulates (partially) in the skin. Kim et al. (2008) found a dose-dependent accumulation of silver content in a broad range of tissues including blood, liver, lungs, kidneys, stomach, testes and brain) in a recent oral toxicity study of 60 nm silver nanoparticles in rats.

Also after dermal exposure of burned skin with nano-silver containing wound dressings (Acticoat) the formation of argyria has been reported (Trop et al.

2006). In this case report, silver plasma concentrations were detected, suggesting dermal absorption, probably of silver, through burned skin and subsequent distribution to tissues such as the skin.

An interesting *in vivo* imaging study with nano-silver in zebra fish embryos revealed nano-silver transport into and out of the zebra fish embryos at each developmental stage studied (Lee et al. 2007, as described above), indicating that (nano-)silver may enter embryonic stages of zebra fish. Increasing concentrations of nano-silver in the exposure medium (in a fraction of particles ranging from 5–46 nm) resulted in increased numbers of deformed and dead zebra fish, suggesting that developmental toxicity is highly dependent on the dose of nano-silver (Lee et al. 2007). Although a zebra fish is not readily comparable to humans, this result may indicate that exposure of human fetus cannot be ruled out.

In conclusion, literature on distribution following exposure to nano-silver does not reveal whether silver reaches tissues and organs as nanoparticles. Only silver concentrations were measured in blood and in organs/tissues. When it has become clear that nano-silver can pass the ports of entry, then it will be relevant to perform additional research on distribution of nano-silver in the body. Such research should include interaction with plasma proteins and distribution to critical tissues like reproductive organs, brain and transplacental passage.

Metabolism

Once nanoparticles are absorbed by the gastrointestinal tract, they will be transported directly to the liver via the portal vein. In general, the liver is able to actively remove compounds from the blood and transform them to chemical forms that can easily be excreted. However, no evidence exists for metabolism of nano-silver by enzymes in the liver and the rest of the body.

It is plausible to assume that nano-silver is able to bind specifically to metallothioneins. Metallothionein proteins that are present in all living cells have a unique structure, depending on their ability to bind metals like zinc and silver. They regulate the cellular metal homeostasis and play a cytoprotective role (Coyle et al. 2002; Lansdown 2003).

More research is required to determine rate and extent of the involvement of metabolism and metallothioneins as these processes may play an important role in the toxicity of nano-silver.

Excretion

Renal elimination is a likely excretion route for nano-silver since it was reported that treatment of burn wounds with nano-silver containing wound dressings (acticoat) lead to detectable levels of silver in urine of the patient (Trop et al. 2006). It is, however, unclear whether nano-silver or silver ions were excreted in urine.

Uptake of nano-silver by the liver and subsequent excretion in the bile represents another possible excretion route. After inhalation of nano-silver particles of 12.6–15.3 nm (Takenaka et al. 2001; Ji et al. 2007), silver was detected in the liver indicating that silver was absorbed. However, excretion via bile and subsequent elimination via feces was not studied in these reports.

Taken together, additional research is recommended to elucidate to what extent nano-silver is excreted via urine, bile and feces. Also other possible excretion routes for nano-silver (e.g., via sweat, lungs, saliva) are not studied up until now, but seem to play a less important role.

Conclusions on kinetics

In conclusion, a few kinetically relevant routes of exposure and target organs for nano-silver are confirmed by animal studies and clinical case reports (Takenaka et al. 2001; Trop et al. 2006; Ji et al. 2007; Kim et al. 2008) (Figure 2), but only for nano-silver particles with a size of about 15 nm, respectively 60 nm. Although several routes are confirmed in animal studies, the rate and extent of all indicated arrows is not known. Up until now, only case studies concerning colloidal silver were reported. Note that several routes are not yet confirmed for nano-silver and colloidal silver. These include the neuronal absorption route via the olfactory nerve, the oral exposure of inhaled particles and binding of silver to bile and the subsequent elimination of the bile-silver complex in the feces.

To date, the current knowledge of the kinetics of nano-silver is too limited to allow a proper foundation of human risk assessment of nano-silver. To close the knowledge gaps, an important research question is the elucidation whether and to what extent nano-silver particles themselves enter the body or whether silver ions originating from nano-silver will be absorbed. The answer to this question will have high consequences for further toxicological research and risk assessment.

In case nano-silver particles really are absorbed into the body, then research of the whole kinetic spectrum of nano-silver in the body will be required, including absorption, distribution and metabolism and excretion processes over time. More research for the different ADME processes is needed after different exposure routes but also for nano-silver particles of various sizes and forms. With the

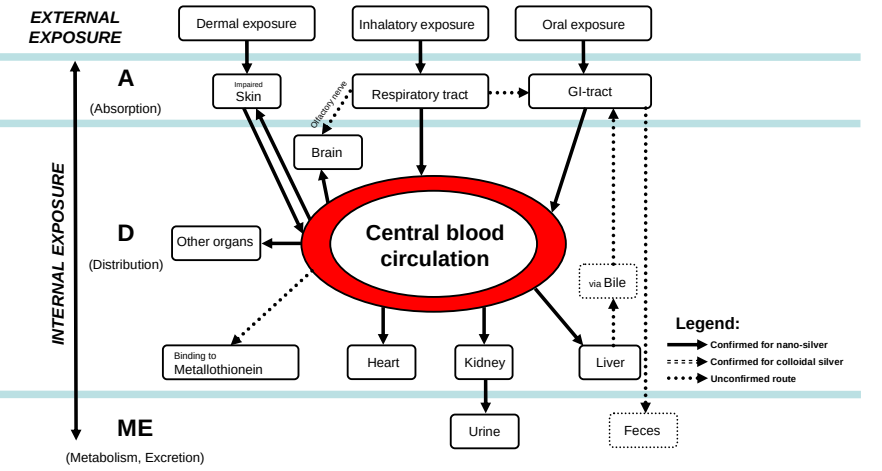

Figure 2. ADME processes of nano-silver.

obtained (quantitative) nano-silver data, whole body Physiologically Based Kinetic (PBK) modeling will be possible. This model provides a mechanistic approach to understand the kinetic properties of nano-silver in the body over time. The advantage of a PBK model is that additional data and parameters from different sources (*in vitro, in vivo* studies and existing/new literature) can be incorporated. If the necessary kinetic data are available for these models, various extrapolations (cross dose, cross species and route-to-route) might allow quantitative risk assessment (Kuempel et al. 2006).

Human aspects – toxicity of nano-silver

In sharp contrast to the emphasis on the application of (silver) nanoparticles, information on the toxicological implication of the use of silver nanoparticles is limited (Chen and Schluesener 2008). Between the different toxicological studies that are reported so far, the compositions of the silver nanoparticles vary widely. Also the descriptions of used silver formulations diverge from detailed to very limited, with variable attention paid to the size, solubility and aggregation of the nanoparticles. This information may be highly relevant, since a good dispersion of the silver nanoparticles is required for effective (antibacterial) activities and might influence its subsequent toxicity (Lok et al. 2007). Furthermore, toxicity of nano-silver particles may be dependent on the size (distribution) of the particles used (Ji et al. 2007).

Although the oxidation state of the silver nanoparticles may influence their (biological and toxicological) activity, little attention has been paid to the oxidation state of the silver nanoparticles in literature. Only oxidized silver nanoparticles exert an antibacterial effect, most likely due to the combination of nanocarrier material (i.e., silver nanoparticle) and the Ag^+ ions which are tightly adsorbed/chemisorbed (adsorption by means of chemical instead of physical forces) on the particle surface (Lok et al. 2007), It should be noted that reduced silver nanoparticles appeared very unstable and can easily be oxidized (Lok et al. 2007). Furthermore, it is because of the antimicrobial properties why (nano-) silver is mostly used and studied and these properties are supposed to be dependent upon the biological activity of silver ions (Ag^+; Lansdown 2007). Therefore it may be assumed that most of the silver nanoparticles used in the studies discussed in this review are in the oxidized form.

Colloidal silver represents another formulation with silver particles. The size of the silver particles in colloidal suspension is assumed to be mainly in the range of 250–400 nm. These particles are aggregates/agglomerates of smaller sized nanoparticles (<100 nm), that under certain conditions can disaggregate/disagglomerate. Therefore, reports on colloidal silver have also been included in this survey.

An additional potential nano-silver application may be the coating of foreign materials such as heart valves, cardiac catheters, urinary catheters and recently also orthopaedic endoprostheses. In most of the studies on these medical devices, information on the actual thickness of the layer is difficult to find (or not stated clearly). The coating thickness may be in the nano-scale range, but could also be in the μm-scale. No or very limited safety/toxicity data have been collected for these applications. Because of these two issues we do not discuss the toxicity of (nano-) silver coated medical devices in this review.

In vitro *toxicity data*

There are various *in vitro* studies on the effects of silver nanoparticles with a size varying between 1 and 100 nm. The uptake of nanoparticles by

different cell types has been shown *in vitro* in several, but not all publications (Hussain et al. 2005; Park et al. 2007; Skebo et al. 2007; Suzuki et al. 2007). There is no consensus on the cytotoxicity of nano-silver, however most publications do show reduced cell viability following exposure. Additional toxic effects seen in the *in vitro* studies are glutathione depletion, mitochondrial deviations or destruction and damage to cell membranes.

In vitro exposure of human peripheral blood mononuclear cells (PBMCs) to silver nanoparticles (1–2.5 nm, 72 h) resulted in inhibition of phytohemagglutinin (PHA) induced proliferation (at a concentration $\geq$15 ppm) (Shin et al. 2007). Effects on cytokine production were already seen at a low, non-cytotoxic concentration of 5 ppm. IFNγ and TNF-α production were more severely suppressed than IL-5 production (Shin et al. 2007).

Hussain et al. (2005) evaluated the *in vitro* toxicity of several nanoparticles, including nano-silver (15 and 100 nm) on a rat liver derived cell line (BRL 3A). Following 24 h after exposure the mitochondrial function and membrane integrity (measured as LDH leakage) were significantly decreased (at $\geq 5\,\mu g.ml^{-1}$ and $\geq 10\,\mu g.ml^{-1}$, respectively). LDH leakage was dose dependent and more severe for 100 nm than for 15 nm silver nanoparticles. Visual microscopic evaluation indicated that not all nanoparticles accumulated in the cell, but some remained associated with membranes. All other tested nanoparticles (Fe_3O_4, Al, MoO_3, MnO_2) appeared to be less toxic than nano-silver. The observed cytotoxicity was attributed to be mediated by oxidative stress, as indicated by the detection of GSH depletion, reduced mitochondrial potential, and increased reactive oxygen species (ROS) levels. A similar concentration-dependent cytotoxicity was observed when the effects of the same nano-silver particles on a mouse cell line with spermatogonial stem cell characteristics was studied (Braydich-Stolle et al. 2005). Here, a concentration-dependent effect on mitochondrial function, cell viability and membrane integrity (LDH leakage) was seen, albeit at somewhat lower concentrations.

In another study nano-silver particles ($\sim$ 30 nm) were classified again to be amongst the most cytotoxic nanoparticles (other nanoparticles were TiO_2, Fe_2O_3, Al_2O_3, ZrO_2, Si_3N_4) when tested on a murine alveolar macrophage cell line, a human alveolar macrophage cell line and epithelial lung cell line (Soto et al. 2005, 2007).

Using a human alveolar epithelial cell line (A549), Park et al. (2007) confirmed that various metallic nanoparticles (Ag, TiO_2, Ni, Zn, Al) induce variable extents of cellular toxicity in a dose dependent manner. However, in this study nano-silver (mean diameter 150 nm, 24 h exposure, and concentrations up to $200\,\mu g.ml^{-1}$) were found to be among the least cytotoxic.

Also neuroendocrine cells were found to be sensitive to the cytotoxic activity of silver nanoparticles (15 nm) (Hussain et al. 2006). Inhibition of dopamine production was only seen at the highest cytotoxic levels, while other known neurotoxic agents (Mn^{2+}, or 40 nm Mn) already reduced neurotransmitter secretion at sub-cytotoxic concentrations.

In contrast, addition of 1.0% silver nanoparticles (5–50 nm) to bone cement, a dose at which antibactericidal activity was seen, did not result in (additional) cytotoxicy towards mouse fibroblasts (L929), or ongrowth of human osteoblast cell line (hFOB 1.19) (Alt et al. 2004).

Acticoat dressing (wound dressing containing nano-silver) was found to be cytotoxic to primary keratinocytes cultured on a pliable hyaluronate-derived membrane (Laserskin) (Lam et al. 2004). Furthermore, reduced mitochondrial metabolism, as well as reduced viability of human keratinocytes and fibroblast cultured on a collagen substrate were detected (cultured skin substitutes, CSS) (Supp et al. 2005). Similar effects (cytotoxicity and disordered morphology) on keratinocytes were reported for extracts of various silver-containing dressings (including Acticoat) (Paddle-Ledinek et al. 2006). Fibroblasts appear to be more sensitive for these effects than keratinocytes (Poon and Burd 2004). However, when the complexity of the environment increased, e.g., after 3-d culture in collagen lattices, the toxic effect of silver appears to decrease (Poon and Burd 2004).

Silver colloid becomes adsorbed onto the cell surface (Rospendowski et al. 1992). Treatment of intact human erythrocytes with silver citrate coated colloid ($\sim$ 30 nm) induced a large depletion of intracellular glutathione (GSH) (Garner et al. 1994), while bismuth citrate colloid induced oxidation of GSH and no effect of gold colloid on GSH was observed. In lysates of erythrocytes the silver citrate colloid induced oxidation of GSH which was associated with the replacement of the citrate moiety for other naturally occurring species.

Silver nanoparticles (11 nm) were found to enhance the electron-transfer reactivity of myoglobin and peroxidase catalytic activity in phosphate buffered solution (PBS) probably by influencing the heme-group environment (Gan et al. 2004). However, silver nanoparticles might not only help the protein structure to keep its biological activity, but may also act as a conducting wire between the protein and the electrode that is used for measuring. Whether these are *in vitro* artefacts or whether silver

nanoparticles could have a similar effect *in vivo* has not been studied.

Animal studies

Clinical observations. Death has been observed in rats following exposure to very high doses of colloidal silver after intravenous administration (LD50, 67 $mg.kg^{-1}$) (Schmaehl and Steinhoff 1960) and after oral ingestion (1680 mg $Ag.kg^{-1}.day^{-1}$ for four days) (Dequidt et al. 1974, in ATSDR 1990). Following the intravenous injection of colloidal silver, rats died from lung oedema; while liver, spleen and kidney showed signs of brown discoloration (Schmaehl and Steinhoff 1960). The cause of death following oral intake was not reported.

Chronic subcutaneous administration of colloidal silver (1.75–2.5 mg weekly) appeared relatively well tolerated, apart from the development of argyria. Very limited health effects were observed in a 28-day inhalation toxicity study (Ji et al. 2007) and a 28-day oral toxicity study (Kim et al. 2008) with silver nanoparticles in Sprague Dawley rats despite systemic absorption. In the Ji study rats inhaled 12–16 nm sized silver nanoparticles 6 $h.day^{-1}$, 5 $d.week^{-1}$, for four weeks. Three exposure levels were used, a low exposure of $1.73 \times 10^{4}.cm^{-3}$, a medium exposure of $1.27 \times 10^{5}.cm^{-3}$, and a high exposure of 1.3×10^{6} $NP.cm^{-3}$ (approximately 61 $\mu g.m^{-3}$, which is near the American Conference of Governmental Industrial Hygienists (ACGIH) silver dust threshold limit of 0.1 $mg.m^{-3}$). The Kim study was an OECD GLP-compliant 28-day study in which the rats received 30, 300 or 1000 mg/kg/day of 60 nm nano-silver particles in vehicle.

Central nervous system. As already mentioned above, silver was found in the brain of rats systemically exposed to silver nanoparticles via inhalation (Takenaka et al. 2001; Ji et al. 2007), but no toxicity endpoints were monitored in the brain. Furthermore, passage of the blood brain barrier (BBB) was also not investigated. According to a recent review on neurotoxicity of silver (not specifically nano-silver) (Lansdown 2007), most animal studies indicate that after silver exposure silver was contained within the BBB but did not pass it.

Respiratory system. No distinct clinical and histopathological effects on the respiratory system of silver nanoparticles were seen during a 28 days inhalation study in rats (Ji et al. 2007). However, the study lacks specific examinations of the respiratory system such as respiratory rate, airway resistance, tidal volume, haemoglobin oxygen saturation as well as inflammation status. In the Takenaka study (Takenaka et al. 2001), silver accumulation was seen in the lungs of the rats (1.7 μg) of which 4% was still left after seven days, but again additional toxicity parameters were not included. Sung et al. (2008) performed a 90 days inhalation rat study (18 nm sized silver nanoparticles 6 $h.day-1$, 0.7, 1.4 and 2.9×10^{6} $particles/cm^{3}$) where they did show lung function decrease (including tidal volume, minute volume and peak inspiration flow), as well as inflammatory lesions in the lung morphology and effects on inflammatory markers.

Liver. Significant amounts of silver in the liver were observed after inhalation (Takenaka et al. 2001; Ji et al. 2007). At each time point analyzed, 9–21% of the nano-silver lung content was observed in the liver (Takenaka et al. 2001). Histopathology of the liver revealed cytoplasmic vacuolization in both sexes with a clear dose dependent increase in females. In addition, several cases of hepatic focal necrosis were seen in the high dose groups (Ji et al. 2007). No effect on the liver enzyme alkaline phosphatase (ALP) was observed. In contrast, repeated oral doses of 60 nm silver nanoparticles during 28 days did induce liver toxicity, as shown by increases in ALP and histopathological observations of dilatation of the central vein, bile-duct hyperplasia and increased foci (Kim et al. 2008).

Immune system. No treatment related effects on haematology and blood cell subset distribution (% lymphocytes, monocytes etc) was seen after inhalation of nano-silver particles. Of note, nano-silver particles were detectable in the spleen in the Takenaka study (Takenaka et al. 2001), but not in the Ji study (Ji et al. 2007). In the 90-days inhalation study of Sung et al. (2008), the presence of nano-silver particles in the lung may have induced a local inflammatory response in the high dose group. Parameters on potential systemic immune effects were not monitored in this study (Sung et al. 2008).

In mice, application of a 1% nano-silver cream (96.1% is <50 nm) inhibited DNB-induced allergic contact dermatitis (Bhol and Schechter 2005). It was found that the expression of two cytokines (TNFα and IL-12) was suppressed (histopathological staining) and apoptosis of inflammatory cells but not keratinocytes was induced. Similar concentration-dependent anti-inflammatory effects have also been seen in guinea pigs by the same group (Bhol et al. 2004). These latter data may suggest that silver nanoparticles are especially effective at inhibiting inflammations and may thus be used to treat immunologic and inflammatory diseases (Shin et al. 2007), however, one should be cautious since also local inflammatory responses may be induced

when applying high doses of nano-silver particles (see Sung et al. 2008).

Other blood effects/oxygen transport. Apart from a small increase in blood calcium, no additional effects of systemic exposure of nano-silver on hematology and blood chemistry parameters have been reported after inhalation exposure (Ji et al. 2007). Oral administration of 60 nm silver nanoparticles induced some changes in the red blood cell compartment (increased red blood cell count, hemoglobin, and hematocrit) and on coagulation parameters (decreased active partial protrombine time) (Kim et al. 2008).

Reproductive system. In the Ji study (Ji et al. 2007) no effect on the histopathology of the epididymis was noted. No additional *in vivo* data on the potential toxic effect of nano-silver on female or male reproductive function (e.g., female egg development or male sperm formation) have been located so far.

Genotoxicity, carcinogenicity. In a chronic subcutaneous administration of colloidal silver (1.75–2.5 mg weekly) eight of the 26 (31%) animals that survived longer than 16 months developed malignant tumors. In six of the animals, the tumor arose at the site of subcutaneous injection. This was significantly higher than the historical control tumor levels that were between 1–3% (Schmaehl and Steinhoff 1960). In contrast, no tumor induction at the site of injection was found in rats after intramuscular injection of a suspension of fine silver powder (−300 mesh) in trioctanoin (Furst and Schlauder 1978).

Kim et al. (2008) investigated the *in vivo* genotoxicity using a bone marrow micronucleus test after the oral administration of 60 nm silver nanoparticles for 28 days at various doses. They found no statistically significant effects.

Skin. In a porcine model of wound healing, nano-silver wound dressing promoted rapid wound healing of full-thickness wounds on the back of pigs (Wright et al. 2002). The proteolytic environment of the wounds treated with nano-silver was characterized by reduced levels of metalloproteinases (known to be present in high levels in chronic ulcers and associated with non-healing nature of these wounds) and enhanced cellular apoptosis.

Application of Acticoat on cultured skin substitutes (consisting of collagen based substrates populated with human fibroblast and keratinocytes) grafted on nude mice did not inhibit nor promote wound healing (Supp et al. 2005). In mice, application of a 1% nano-silver cream (96.1% is <50 nm) induced apoptosis of inflammatory cells but not of keratinocytes.

Human data

Clinical observations. Acticoat is a topical wound dressing consisting of a polyethylene mesh coated with nano-silver (average size 15 nm). There is one case report of silver poisoning after the use of Acticoat for treatment of severe burns to the legs (Trop et al. 2006). On day 6 post injury the patient developed a grayish discoloration, complained of being tired and having a lack of appetite. On day 7 silver levels in urine and blood were found to be elevated (28 and 107 $\mu g.kg^{-1}$, respectively). Acticoat was removed and the discoloration of the face gradually faded and liver function test returned to normal values. Elevated blood silver levels were seen seven weeks post injury, but were hardly detectable after 10 months. These observed adverse effects may be associated with the release of Ag^{+} ions from the nano-silver dressing. Absorption of silver from Acticoat was confirmed in 30 patients treated in another study (Vlachou et al. 2007). However, despite measurable amounts of serum silver levels (median 59 $\mu g.l^{-1}$) very limited changes in hematological or biochemical indicators of toxicity associated with the silver absorption were observed.

Central nervous system. Epileptic seizures and coma following daily ingestion of colloidal silver for four months were notified in one case report (Mirsattari et al. 2004). The authors suggest that silver caused these signs of irreversible neurological toxicity which eventually lead to death.

Liver. In the case report of Trop et al. (2006), elevated liver enzymes (aspartate amino transferase, alanine aminotransferase and gamma-galactosyl transferase) after the use of Acticoat were reported. Levels returned to normal following cessation of exposure. The patient did not receive any other potentially hepatotoxic medication.

Immune system. Very limited changes in haematological or biochemical indicators of toxicity were associated with the silver absorption from Acticoat in humans (Vlachou et al. 2007), despite measurable amounts of silver in serum. Another case report possibly involving uptake of silver particles is the finding of small electron-dense particles, probably silver nanoparticles, in mast cells following 20 years of local acupuncture (Kakurai et al. 2003). The mast cells showed focal or partial loss of granule content suggesting degranulation (activation) associated with pruritus (itching) and an inflammatory reaction.

Skin. In a moist environment silver is released from the Acticoat dressing (possibly as nanocrystals) and

improve microbial control of the wound. Acticoat has been tested in small clinical trials (Tredget et al. 1998; Innes et al. 2001) with contradictory results. No adverse effects were found in the Tredget study, in which silver absorption was not assessed (Tredget et al. 1998). Innes et al. (2001) reported delayed re-epithelialization and temporarily worse scars while in another study an increase in re-epithelization was found in meshed skin grafts (Demling and Leslie DeSanti 2002). An additional case of delayed wound healing has recently been reported (Trop et al. 2006). However, all the studies were small scale and used different controls, thus interstudy comparison is hardly possible.

Conclusions – toxicity

Several factors influence the ability of a metal to produce toxic effects on the body. These include the solubility of the metal, its ability to bind to biological sites, and the degree to which the complexes formed are sequestered or metabolized and excreted. For nano-sized particles additional parameters such as size and surface area are recognized as important determinants for toxicity (Ji et al. 2007). Nanoparticles can pass through biological membranes. After administration, nanoparticles are small enough to penetrate even very small capillaries throughout the body.

Silver nanoparticles are generally used because of the antibacterial activity of silver. The antibacterial action of silver (ions) may have several mechanisms. It has been suggested that the primary mechanism of action is cell death due to the uncoupling of oxidative phosphorylation (Holt and Bard 2005) or the induction of free radical formation (Kim et al. 2007). However, interference with respiratory chain at the cytochrome C level, and/or with components of microbial electron transport system, has also been reported (Muangman et al. 2006). Also interactions with membrane bound enzymes and protein thiol groups that may result in compromised cell wall integrity have been postulated (Bragg and Rainnie 1974; Silver 2003; Zeiri et al. 2004; Lok et al. 2006). Furthermore, it has also been suggested that silver ions bind to DNA and thus may cause DNA strand breaks and DNA replication (ATSDR 1990; Russell and Hugo 1994).

The reason why eukaryotic (mammalian) cells appear less sensitive to this action of silver can be explained by the higher structural and functional redundancy and size of eukaryotic compared to prokaryotic (bacterial) cells. This may increase the silver concentration needed to achieve comparable toxic effects on eukaryotic cells than for bacterial cells (Alt et al. 2004). Thus, there may be a therapeutic window in which bacterial cells are successfully attacked, at which harmful effects on eukaryotic cells cannot yet be observed. However, the effective concentration for silver nanoparticles is much lower in comparison to Ag^+ ions (nmol vs. μmol levels) (Lok et al. 2006). Therefore given the potential higher toxicity and the specific concerns associated with the use of nano-sized materials particular attention to the toxicity of silver nanoparticles may be warranted.

Information on the toxicological implication of the use of silver nanoparticles is limited (Chen and Schluesener 2008). Toxicity of silver nanoparticles is mostly determined *in vitro* with particles ranging in size from 1–100 nm. The available *in vivo* animal studies are generally relative short term (max 28 days), except for one 90 days inhalation study and using one size of silver nanoparticles (Sung et al. 2008). Only limited health effects of the use of nano-silver in humans have been documented. Argyria or argyrosis was rarely reported, and appeared to occur only after intake of large amounts of silver particles (usually colloidal, a suspension with nano-silver of different sizes).

Potential target organs for nano-silver toxicity may involve the liver and the immune system. Accumulation and histopathological effects were seen in livers from rats systemically exposed to silver 10–15 nm nanoparticles (Ji et al. 2007), while an effect on liver enzymes was noted in one human case study with dermal exposure to particles with an average of the same size (Trop et al. 2006). Accumulation, histopathological effects and increased liver enzymes were reported after oral exposure to 60 nm nano-silver (Kim et al. 2008). It is not known if the silver reaches the liver as silver nanoparticles or as ions, nor has the location of the silver (nanoparticles) within the liver been studied.

Effects on the immune system, especially cytokine excretion, have been noted *in vitro* and *in vivo,* where application of a 1% nano-silver cream with <50 nm particles, inhibited DNB-induced allergic contact dermatitis (Bhol and Schechter 2005), and accumulation in the spleen has also been noted (Takenaka et al. 2001). It has been suggested that silver nanoparticles are especially effective at inhibiting inflammations and may thus be used to treat immunologic and inflammatory diseases (Shin et al. 2007). However, there were only very limited changes in haematological or biochemical indicators of toxicity associated with the systemic silver absorption from 15 nm nano-silver containing dressings in humans (Vlachou et al. 2007), and after inhalation in rats (Ji et al. 2007). Oral administration of 60 nm silver particles to rats induced some local inflammatory effects (Kim et al. 2008). As mentioned before,

parameters on potential systemic immune effects were not monitored in this study. Whether silver nanoparticles indeed have a (systemic) effect on immune function *in vivo* needs to be explored further.

The effect of nano-silver on other blood components is not well studied either. In one study nano-silver particles appear toxic to erythrocytes in one in vitro study (Garner et al. 1994), while an increase in red blood cells was seen after oral administration of 60 nm silver particles (Kim et al. 2008) but not after inhalation of 15 nm silver particles (Ji et al. 2007). In addition to blood erytrocytes also blood coagulation may be affected (Kim et al. 2008). More data needs to be generated before a well founded conclusion on the potential effects of nano-silver exposure on blood parameters and their clinical relevance can be drawn.

(Damaged) skin is one of the organs which have been exposed to nano-silver due to the use of wound dressings containing nano-silver (average size of particles is 15 nm) in the treatment of burn wounds. As mentioned above, the reports on the effect of silver nanoparticles on re-epithelization of these wounds in humans are conflicting, delayed as well as increased re-epithelialization have been reported (Innes et al. 2001; Demling and Leslie DeSanti 2002; Trop et al. 2006). However, because of the small scale of the studies and differences in controls, interstudy comparison is not possible.

There has been an *in vitro* study suggesting that nano-silver may have a toxic effect on mammalian (mouse) spermatogonial germline stem cells (Braydich-Stolle et al. 2005). However, this is not supported by *in vivo* data (thus far), and therefore the clinical relevance of this *in vitro* study remains uncertain. Since developmental toxicity will have dramatic consequences, there is a need to especially examine the reproductive and developmental toxicity of silver nanoparticles in more detail.

Lansdown concluded that there is no evidence available to demonstrate that silver is a cause of neurotoxic damage even though silver deposits have been identified in the region of cutaneous nerves (Lansdown 2007).

The respiratory system seemed relatively unaffected by the exposure to nano-silver *in vivo* in a 28 days study from Ji et al. (2007), while it is known that nano-silver can have a cytotoxic effect on alveolar macrophages and alveolar epithelial cells *in vitro* (Soto et al. 2005, 2007; Park et al. 2007). Sung et al. (2008) performed a 90 days inhalation study where they did show lung function decrease (including tidal volume, minute volume and peak inspiration flow), as well as inflammatory lesions in the lung morphology and effects on inflammatory markers.

No studies or reports were described regarding genotoxic effects or carcinogenicity of exposure to silver nanoparticles in humans, animals or *in vitro*, except the bone marrow micronucleus test performed as part of the 28-day oral administration study by Kim et al. (2008). No significant genotoxic potential of oral exposure to 60 nm silver particles was found in this study. An increase in (mostly local) malignant tumors was found following chronic subcutaneous administration of high doses colloidal silver (Schmaehl and Steinhoff 1960). Even though it has been suggested that silver ions bind to DNA in solution *in vitro*, and may cause DNA strand breaks and DNA replication, silver (not in nano form) has not been found to be mutagenic in bacteria (ATSDR 1990). Given the equivocal carcinogenicity effects additional information on the potential carcinogenic effect of nano-silver would be welcomed.

No reports on effects of silver nanoparticles on the cardiovascular, renal/urinary or gastrointestinal systems have been found, however, specific studies addressing these organs have not been identified.

In conclusion, there are very limited well controlled studies on the potential toxicities of nano-silver. Additional long term, higher dosed studies, preferably using multiple particle sizes, are needed to better characterize the risk of the use of silver nanoparticles.

Discussion and conclusions

Nano-silver versus regular silver

Nano-silver is often stated to be a relatively new and a different type of silver with different chemical and physical properties. Nano-silver particles are generated by several methods from metallic silver and are generally used in food, consumer products and medical products because of their antibacterial activity.

Because of its small size, nanoparticles can potentially pass through biological membranes and reach more and different organs and tissues in the body where the silver can exert its antibacterial effects. Since the prevailing view is that silver is relatively non-toxic (Chen and Schluesener 2008), additional toxic effects, such as generation of oxidative stress, of nano-silver can be attributed to the nano-characteristics of the particle, such as the large surface area and associated high reactivity.

The question is whether a clear distinction can be made between 'regular' silver and nano-silver. For instance, colloidal silver is a suspension of silver particles in various sizes, including microsized and nanosized particles. Furthermore, nano-silver may not be that new, since colloidal silver has been used

already for more than 10 years as medical application. In the kinetic and toxicity studies done so far with nano-silver, the compositions of the nano-silver particles vary widely. Also the descriptions of silver formulations used diverge from detailed to very limited, with variable attention paid to the size, solubility and aggregation of the nanoparticles. This information is highly relevant, since a good dispersion of the nano-silver particles is required for effective (antibacterial) activities and might influence its subsequent toxicity. In conclusion, there is not one form of nano-silver, and a more systematic approach is needed for determination of effects of different sizes of nano-silver.

Available data and knowledge gaps

Information on occurrence of nano-silver in the environment is, in contrast to the information on regular silver, very scarce. Although concentrations of bioavailable free silver ions in the natural environment in general are too low to lead to toxicity, it is not known until now whether nano-silver particles present a threat to the environment. Furthermore, the only data that are available are from the aqueous environment, no data on nano-silver in soils were found.

Nano-silver is widely applied in various food, consumer and medical products, indicating that human exposure to nano-silver is very relevant. However, data on concentrations of nano-silver in these products as well as the size and form in which it is present (aggregates, agglomerates) are not or hardly available (Tables A1 and A2, Supplementary Material, online version only). Also the probability of release of (nano) Ag^+ from the products is not known, which is not only important for human exposure but also for leakage and emissions in the environment. For a full risk assessment of nano-silver, apart from exposure, also data on the hazard of nano-silver are needed. With respect to toxicokinetics, a few animal studies and case reports confirm some kinetic relevant routes for nano-silver. However, the available studies use different sizes of nano-silver particles exposed via various exposure routes (12–15 nm for inhalation and 15 nm dermal) (Appendix 3, Supplementary Material).

With respect to absorption of nano-silver, it remains unclear what type of silver is found in the blood, organs and tissues of the organisms studied so far. It is therefore of main importance that in future research, it becomes clear whether and to what extent nano-silver particles themselves enter the body, or whether silver ions originating from nano-silver are absorbed. It is conceivable that research on determining factors influencing this absorption will help to gain insight how to extrapolate from absorption of one type of nano-silver to another. The answer to this question will have high consequences for further toxicological research and risk assessment (Figure 3).

Also for the reported toxicity studies, the compositions of the nano-silver particles vary widely. Descriptions of the used silver formulations diverge from detailed to very limited, with variable attention paid to the solubility/aggregation of the nanoparticles (Table A2, Supplementary Material, online version only). Furthermore, the size of the used colloidal silver is assumed partly to be in the nanoscale range, but this is not exactly known.

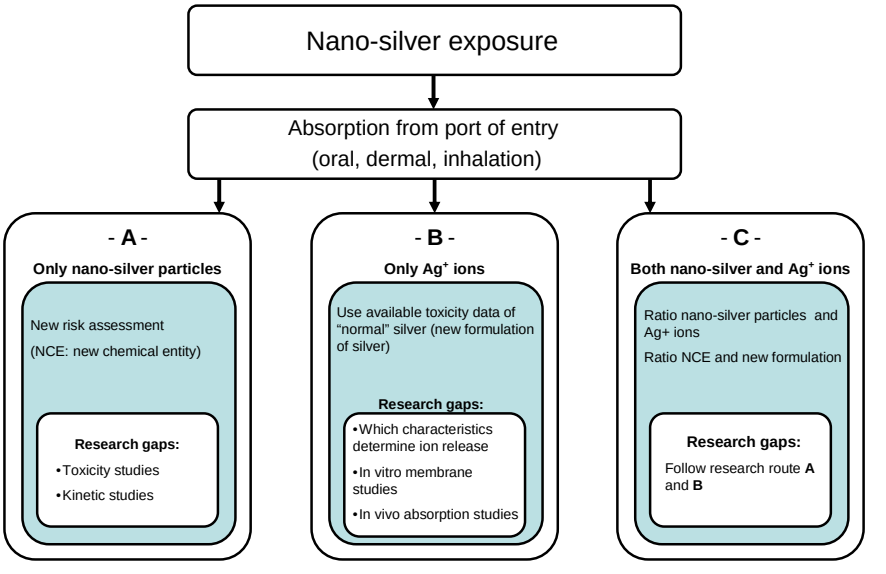

Figure 3. Overview of options for further toxicological research.

Most toxicity studies are determined *in vitro* with particles ranging in size between 1 and 100 nm and the available *in vivo* animal studies are generally relatively short term using low doses of nano-silver. Some case reports with human patients are available; mainly for wound dressings, but inter study comparison is not possible because of the small scale of the studies and differences in controls. Potential target organs of nano-silver may be the liver and the immune system. No effects on other organ systems have been reported so far. Developmental toxicity and neurotoxicity will have dramatic consequences and given the equivocal carcinogenicity effects, additional information on these long-term endpoints is needed. Therefore, additional long term, higher dosed studies, preferably using multiple sized particles, are needed to better characterize the risk of the use of nano-silver particles.

Given the available data, an important research question is the validation of our '0-hypothesis' of toxic effects of nano-silver being proportional to the activity of the free silver ions released by the nano-silver particles. This is a two-steps hypothesis; first it has to be determined whether and to what extent nano-silver particles themselves enter the body. Alternatively, it has to be determined whether nano-silver releases silver ions and to what extent they will be absorbed. Subsequently, it has to be elucidated whether the observed toxicity is due to the nano-silver particles, the silver ions or a combination of both, as was proposed for the antibacterial mode of action (Hwang et al. 2008). Also determinants for Ag^+ generation have to be determined such as pH, media, solubility. For this, proper analytical methods for measurement of Ag^+ ions as well as nano-silver particles in different media need to be identified or developed. Characteristics of nano-silver in relation to release of Ag-ions, absorption and toxicity can, as a first tier, be investigated *in vitro*, but conclusive results can only by obtained by *in vivo* studies.

Answers to these questions will have high consequences for requirements for further toxicological research and risk assessment (Figure 3). In case only silver ions will cross the port of entry, existing toxicological information on silver can be used in the risk assessment of nano-silver.

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Supplementary Material

Appendix 1: Inventory of food and consumer products containing nano-silver

Table A1.1. Product categories and source.

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Type product (category as in Woodrow Wilson/ RIVM/SIR advisory report 11014)	Subtype product	Source	Website product
1	IOGEAR® Germ Free Wireless Laser Mouse	IOGEAR®, Inc.	USA	Electronics	Computer hardware	Woodrow Wilso	http://www.iogear.com
2	IOGEAR® Laser Travel Mouse with Nano Coating Technology	IOGEAR®, Inc.	USA	Electronics	Computer hardware	Woodrow Wilso	http://www.iogear.com
3	IOGEAR® Long Range Wireless Keyboard/Mouse with Nano Tech	IOGEAR®, Inc.	USA	Electronics	Computer hardware	Woodrow Wilso	http://www.iogear.com
4	IOGEAR® Personal Security Mouse with Nano Technology	IOGEAR®, Inc.	USA	Electronics	Computer hardware	Woodrow Wilso	http://www.iogear.com
5	IOGEAR® Wireless Keyboard/Optical Mouse combo w/ Nano Tec	IOGEAR®, Inc.	USA	Electronics	Computer hardware	Woodrow Wilso	http://www.iogear.com
6	Samsung® Notebooks--Q40 and R20	Samsung®	Korea	Electronics	Computer hardware	Woodrow Wilso	http://www.samsung.com/
7	Daewoo® Vacuum Cleaner	Daewoo® (UK)	Korea	Electronics	Household appliance	Woodrow Wilso	http://www.daewooelectronics.co.uk
8	Daewoo® Refrigerator	Daewoo® (Germany)	Korea	Electronics	Household appliance	Woodrow Wilso	http://www.daewoo-electronics.de
9	Daewoo® Washing Machine	Daewoo® (Germany)	Korea	Electronics	Household appliance	Woodrow Wilso	http://www.daewoo-electronics.de
10	LaundryPure™ Cleaning Process	EcoQuest	USA	Electronics	Household appliance	Woodrow Wilso	http://www.selllaundrypure.com
11	LG® Refrigerator	LG® Electronics	Korea	Electronics	Household appliance	Woodrow Wilso	http://www.lge.com/
12	LG® Vacuum Cleaner	LG® Electronics	Korea	Electronics	Household appliance	Woodrow Wilso	http://www.lge.com/
13	LG® Washing Machine	LG® Electronics	Korea	Electronics	Household appliance	Woodrow Wilso	http://www.lge.com/
14	Samsung® Washing Machine	Samsung®	Korea	Electronics	Household appliance	Woodrow Wilso	http://www.samsung.com/
15	LG® Antibacterial Mobile Phone	LG® Electronics	Korea	Electronics	Mobile devices	Woodrow Wilso	http://www.lge.com/
16	SAMSUNG Anycall E628 Silver Nano Mobile Phone	Samsung®	Korea	Electronics	Mobile devices	Woodrow Wilso	http://www.samsung.com/
17	Nano Dryer	CHI® Cationic Hydration Interlink	USA	Electronics	Personal Care	Woodrow Wilso	http://www.chiretail.com
18	Helix™ Deep Waver	Hot tools®	USA	Electronics	Personal Care	Woodrow Wilso	http://www.hottools.com/
19	Helix™ Dryer	Hot tools®	USA	Electronics	Personal Care	Woodrow Wilso	http://www.hottools.com/
20	Helix™ Flat Irons	Hot tools®	USA	Electronics	Personal Care	Woodrow Wilso	http://www.hottools.com/
21	Helix™Curling Irons	Hot tools®	USA	Electronics	Personal Care	Woodrow Wilso	http://www.hottools.com/
22	Ag plus Nano Technology Ionic Dryer	Metropolis	USA	Electronics	Personal Care	Woodrow Wilso	http://www.metropolistechnology.com
23	S-Nano Ionic Brushes	Metropolis Technology	USA	Electronics	Personal Care	Woodrow Wilso	http://www.metropolistechnology.com
24	S-Nano Ionic Dryer	Metropolis Technology	USA	Electronics	Personal Care	Woodrow Wilso	http://www.metropolistechnology.com
25	S-Nano Ionic Iron	Metropolis Technology	USA	Electronics	Personal Care	Woodrow Wilso	http://www.metropolistechnology.com
26	CleanXchange™ Foil Shaver	Remington	USA	Electronics	Personal Care	Woodrow Wilso	http://www.remington-products.com/
27	T-Studio Nano Collection	Remington	USA	Electronics	Personal Care	Woodrow Wilso	http://www.remington-products.com/
28	High Precision™ Personal Grooming Kit	Remington®	USA	Electronics	Personal Care	Woodrow Wilso	http://www.remington-products.com/
29	Hair Iron	SE International	Korea	Electronics	Personal Care	Woodrow Wilso	http://www.goodsei.com/
30	Air Sanitizer	Shenzhen Become Industry & Trade Co., Ltd.	China	Filtration, purification, neutralisa	Cleaning	Woodrow Wilso	http://www.aircleanermedium.com
31	Air Sanitizer, Nano Silver Photocatalyst	Shenzhen Become Industry & Trade Co., Ltd.	China	Filtration, purification, neutralisa	Cleaning	Woodrow Wilso	http://www.aircleanermedium.com
32	HGT Nano Silver Photocatalyst Aerosol Spray	Daido Corporation	Japan	Filtration, purification, neutralisa	Cleaning	Woodrow Wilso	http://www.hgt.com.hk/
33	NANOVER™ Disinfectant Spray	GNS Nanogist	Korea	Filtration, purification, neutralisa	Cleaning	Woodrow Wilso	http://www.nanogist.com
34	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® AC filter liquid	Quan Zhou Hu zheng Nano Technology Co.,	China	Filtration, purification, neutralisa	Cleaning	Woodrow Wilso	not found
35	Nanbabies® Element 47 Moisturizing Spray	Nanbabies®	USA	Filtration, purification, neutralisa	Cleaning	Woodrow Wilso	http://nanbabies.com
36	Carrier® Pure Dew Filtration	Carrier	Singap	Filtration, purification, neutralisa	Filtration	Woodrow Wilso	http://www.carrier.com.sg/
37	Germ Guardian™ Digital and Manual Ultrasonic Humidifiers	Germ Guardian™	USA	Filtration, purification, neutralisa	Filtration	Woodrow Wilso	http://www.guardiantechnologies.com
38	nanoFresh™	Inspiraz Technology Pte Ltd.	Singap	Filtration, purification, neutralisa	Filtration	nanoshop.com	http://www.inspiraz.com.sg
39	nanoCotz™ eco-refresh	Inspiraz Technology Pte Ltd.	Singap	Filtration, purification, neutralisa	Filtration	nanoshop.com	http://www.inspiraz.com.sg

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Type product (category as in Woodrow Wilson/ RIVM/SIR advisory report 11014)	Subtype product	Source	Website product
40	Plaston™ Ionic Silver Stick	Plaston™	Zwitser	Filtration, purification, neutralisa	Filtration	Woodrow Wilso	http://www.ioniosilverstick.ch
41	Samsung® Air Conditioner	Samsung®	Korea	Filtration, purification, neutralisa	Filtration	Woodrow Wilso	http://www.samsung.com/
42	Nano Air-filter	SongSing Nano Technology Co., Ltd	Taiwan	Filtration, purification, neutralisa	Filtration	Woodrow Wilso	http://www.ssnano.net
43	Winix PlasmaWave™ Air Cleaner 9000	Winix Inc.	USA	Filtration, purification, neutralisa	Filtration	Woodrow Wilso	http://www.winixinc.com/
44	Nano Silver Spray	SongSing Nano Technology Co., Ltd	Taiwan	Food and Beverages	Cleaning cooking	Woodrow Wilso	http://www.ssnano.net
45	Nano Silver Anti-Bacterial Baby Bottle Brush	Sang Shin Industrial Co., Ltd	Korea	Food and Beverages	Cooking utensils, co	Woodrow Wilso	http://www.i-sangshin.com/
46	Nano Silver Cutting Board	A-DO Global	Korea	Food and Beverages	Cooking utensils, co	Woodrow Wilso	http://www.adox.info
47	Nano Silver Chopping Board	Fine Polymer Inc	Korea	Food and Beverages	Cooking utensils, co	RIVM/SIR advis	http://www.welmering.de/
48	Antibacterial Kitchenware	Nano Care Technology Ltd.	China	Food and Beverages	Cooking utensils, co	Woodrow Wilso	http://www.nanocaretech.com
49	Antibacterial Table Ware	Nano Care Technology, Ltd.	China	Food and Beverages	Cooking utensils, co	Woodrow Wilso	http://www.nanocaretech.com
50	Nano Silver Teapot	SongSing Nano Technology Co., Ltd	Taiwan	Food and Beverages	Cooking utensils, co	Woodrow Wilso	http://www.ssnano.net
51	Nano Silver Baby Mug Cup	Baby Dream® Co., Ltd.	Korea	Food and Beverages	Storage	Woodrow Wilso	http://babydream.en.ec21.com/
52	Silver Nano Baby Milk Bottle	Baby Dream® Co., Ltd.	Korea	Food and Beverages	Storage	Woodrow Wilso	http://babydream.en.ec21.com/
53	Food container (NS)	A-DO Global	Korea	Food and Beverages	Storage	Woodrow Wilso	http://www.adox.info
54	BlueMoonGoods™ Fresh Box Silver Nanoparticle Food Storage	BlueMoonGoods, LLC	USA	Food and Beverages	Storage	Woodrow Wilso	http://www.bluemoongoods.com/index.h
55	Nano Silver Freshbox®	Fine Polymer Inc	Korea	Food and Beverages	Storage	RIVM/SIR advis	http://www.welmering.de/
56	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® Nano-silver St	Quan Zhou Hu zheng Nano Technology Co.,	China	Food and Beverages	Storage	Woodrow Wilso	not found
57	FresherLonger™ Miracle Food Storage	Sharper Image®	USA	Food and Beverages	Storage	Woodrow Wilso	http://www.sharperimage.com
58	FresherLonger™ Plastic Storage Bags	Sharper Image®	USA	Food and Beverages	Storage	Woodrow Wilso	http://www.sharperimage.com
59	ASAP Health Max30	Americal Biotech labs	USA	Food and Beverages	Supplements	Woodrow Wilso	http://www.amsilver.com/index.html
60	NanoSil™-10	Greenwood Consumer Products	USA	Food and Beverages	Supplements	Woodrow Wilso	http://www.nanosil10.com/
61	MaatShop™ Crystal Clear Nano Silver	MaatShop™	USA	Food and Beverages	Supplements	Woodrow Wilso	http://spiritofmaat.com/maatshop
62	MaatShop™ Nano-2+	MaatShop™	USA	Food and Beverages	Supplements	Woodrow Wilso	http://spiritofmaat.com/maatshop
63	Silvix3®	Natural Care® Products	USA	Food and Beverages	Supplements	Woodrow Wilso	http://www.enaturalcare.com
64	Sovereign Silver™	Natural-Immunogenics Corp.	USA	Food and Beverages	Supplements	Woodrow Wilso	http://www.natural-immunogenics.com/
65	MesoSilver®	Purest Colloids, Inc.	USA	Food and Beverages	Supplements	Woodrow Wilso	http://www.purestcolloids.com/
66	Nanoceuticals™ Silver 22	RBC Life Sciences®, Inc	USA	Food and Beverages	Supplements	Woodrow Wilso	http://www.rbclifesciences.com/
67	Colloidal Silver Cream	Skybright Natural Health	New Ze	Food and Beverages	Supplements	Woodrow Wilso	http://www.skybright.co.nz
68	Colloidal Silver Liquid	Skybright Natural Health	New Ze	Food and Beverages	Supplements	Woodrow Wilso	http://www.skybright.co.nz
69	Biodream Colloid Plus	Special Health Products VOF	NL	Food and Beverages	Supplements	RIKILT/RIVM re	http://www.biodreamshop.nl/
70	Utopia Silver Supplements® Advanced Colloidal Silver	Utopia Silver Supplements®	USA	Food and Beverages	Supplements	Woodrow Wilso	http://www.utopiasilver.com/
71	NANOVER™ Detergent	GNS Nanogist	Korea	Household products/ home imp	Cleaning	Woodrow Wilso	http://www.nanogist.com
72	nanoCotz™ Eco-Clean	Inspiraz Technology Pte Ltd.	Singap	Household products/ home imp	Cleaning	nanoshop.com	http://www.inspiraz.com.sg
73	nanoCotz™ Bio Green	Inspiraz Technology Pte Ltd.	Singap	Household products/ home imp	Cleaning	nanoshop.com	http://www.inspiraz.com.sg
74	nanoCotz™ Crystal Clear	Inspiraz Technology Pte Ltd.	Singap	Household products/ home imp	Cleaning	nanoshop.com	http://www.inspiraz.com.sg
75	Lion® Look Kirei no Mist for Bathrooms	Lion® Corporation	Japan	Household products/ home imp	Cleaning	Woodrow Wilso	http://www.lion.co.jp
76	Lion® Look Kirei no Mist for Kitchens	Lion® Corporation	Japan	Household products/ home imp	Cleaning	Woodrow Wilso	http://www.lion.co.jp
77	Lion® Look Kirei no Mist for Toilets	Lion® Corporation	Japan	Household products/ home imp	Cleaning	Woodrow Wilso	http://www.lion.co.jp

Table A1.1. Product categories and source (continued)

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Type product (category as in Woodrow Wilson/ RIVM/SIR advisory report 11014)	Subtype product	Source	Website product
78	Maha Corp™ Klenz Nano Cleaning Tool	Maha Corp™	Korea	Household products/ home imp	Cleaning	Woodrow Wilso	http://mahacorp.b2bgiant.com
79	Fabric Softener IRIN	Aeykung	Korea	Household products/home imp	Cleaning	Woodrow Wilso	http://www.aekyung.co.kr
80	nanoCotz™ (glass, ceramic, stone, fabric)	Inspiraz Technology Pte Ltd.	Singap	Household products/ home imp	Coatings	nanoshop.com	http://www.inspiraz.com.sg
81	Silverex Spray	Inspiraz Technology Pte Ltd.	Singap	Household products/ home imp	Coatings	nanoshop.com	http://www.inspiraz.com.sg
82	Nano Silver Antimicrobial Paint Supplement	Shanghai Huzheng Nano Technology CO.,LT	China	Household products/ home imp	Coatings	internet search/	www.hznano.com
83	Antibacterial Pets Products	Nano Care Technology Ltd.	China	Household products/ home imp	Coatings	Woodrow Wilso	http://www.nanocaretech.com
84	Contour-Foam™ Silver Back-Support Pillow	Sharper Image®	USA	Household products/ home imp	Furnishing	Woodrow Wilso	http://www.sharperimage.com
85	Contour-Foam™ Silver Crescent Travel and Nap Pillow	Sharper Image®	USA	Household products/ home imp	Furnishing	Woodrow Wilso	http://www.sharperimage.com
86	Contour-Foam™ Silver Neck-Support Pillow	Sharper Image®	USA	Household products/ home imp	Furnishing	Woodrow Wilso	http://www.sharperimage.com
87	Silverex showerhead	Inspiraz Technology Pte Ltd.	Singap	Household products/ home imp	Furnishing coatings	nanoshop.com	http://www.inspiraz.com.sg
88	Antibacterial Lock	Nano Care Technology Ltd.	China	Household products/ home imp	Furnishing coatings	Woodrow Wilso	http://www.nanocaretech.com
89	Antibacterial Water Tap	Nano Care Technology, Ltd.	China	Household products/ home imp	Furnishing coatings	Woodrow Wilso	http://www.nanocaretech.com
90	Nano Silver Teeth Developer	Baby Dream® Co., Ltd	Korea	Personal care and cosmetics	Baby care	Woodrow Wilso	http://babydream.en.ec21.com/
91	Nano Pacifier	SongSing Nano Technology Co., Ltd	Taiwan	Personal care and cosmetics	Baby care	Woodrow Wilso	http://www.ssnano.net
92	X-SystemTM Scent Eliminating Wipes	ARC Technologies®	USA	Personal care and cosmetics	Cleaning	Woodrow Wilso	http://www.xsystem.com
93	X-SystemTM Scent Elimination Spray	ARC Technologies®	USA	Personal care and cosmetics	Cleaning	Woodrow Wilso	http://www.xsystem.com
94	Antibacterial Make-up Instrument	Nano Care Technology Ltd.	China	Personal care and cosmetics	Coatings	Woodrow Wilso	http://www.nanocaretech.com
95	Antibacterial Watch Chain	Nano Care Technology, Ltd.	China	Personal care and cosmetics	Coatings	Woodrow Wilso	http://www.nanocaretech.com
96	NANOVER™ Hair Care	GNS Nanogist	Korea	Personal care and cosmetics	Hair care	Woodrow Wilso	http://www.nanogist.com
97	Nanoseal-Hairna essence	NanoPlasma Center Company, Ltd.	Korea	Personal care and cosmetics	Hair care	Woodrow Wilso	http://www.nanoplasmacenter.com/
98	Professional Hair Brush	Sang Shin Industrial Co., Ltd.	Korea	Personal care and cosmetics	Hair care	Woodrow Wilso	http://www.i-sangshin.com/
99	NANOVER™ Toothpaste	GNS Nanogist	Korea	Personal care and cosmetics	Oral hygiene	Woodrow Wilso	http://www.nanogist.com
100	Nanoseal Toothpaste	NanoPlasma Center Company, Ltd.	Korea	Personal care and cosmetics	Oral hygiene	Woodrow Wilso	http://www.nanoplasmacenter.com/
101	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® Nano-silver To	Quan Zhou Hu zheng Nano Technology Co.,	China	Personal care and cosmetics	Oral hygiene	Woodrow Wilso	not found
102	Nano & UV Artificial Teeth Cleaner	Digimax Innovative Products Ltd	Taiwan	Personal care and cosmetics	Oral hygiene	Woodrow Wilso	not found
103	Nano Toothbrush	SongSing Nano Technology Co., Ltd.	Taiwan	Personal care and cosmetics	Oral hygiene	Woodrow Wilso	http://www.ssnano.net
104	NanoSilver toothbrush	Zerahun Co	Korea	Personal care and cosmetics	Oral hygiene	internet search/	http://www.zerahun.com/
105	Nanometer-Silver Foam Condom	Blue Cross Bio-Medical (Beijing) Co.,Ltd	China	Personal care and cosmetics	Over the counter hea	Woodrow Wilso	http://www.bcbmcn.com
106	Platinum Silver Nanocolloid Cream	DHC Skincare	Japan	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.dhccare.com/
107	Platinum Silver Nanocolloid Milky Essence	DHC Skincare	Japan	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.dhccare.com/
108	Nano Silver Hand Sanitizer	Fine Polymer Inc	Korea	Personal care and cosmetics	Skin care	RIVM/SIR advis	http://www.welmering.de/
109	NANOVER™ Mask Pack	GNS Nanogist	Korea	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.nanogist.com
110	Cyclic Nano Silver Cleanser	NanoCyclic, Inc.	USA	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.nanocyclic.com/
111	Cosil Nano Beauty Soap	Natural Korea Company, Ltd	Korea	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.naturalkorea.co.kr/
112	Cosil Whitening Mask	Natural Korea Company, Ltd	Korea	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.naturalkorea.co.kr/
113	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® Nano-gold Ma	Quan Zhou Hu zheng Nano Technology Co.,	China	Personal care and cosmetics	Skin care	Woodrow Wilso	not found
114	Susie-K Nano Beauty Soap	Segae-I Pte Ltd	Korea	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.segaei.com/
115	Susie-K Whitening Mask	Segae-I Pte Ltd	Korea	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.segaei.com/

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Type product (category as in Woodrow Wilson/ RIVM/SIR advisory report 11014)	Subtype product	Source	Website product
116	NANOVER™ Cleansing Soap	GNS Nanogist	Korea	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.nanogist.com
117	Nanbabies® Face Masks	Nanbabies®	USA	Personal care and cosmetics	Skin care	Woodrow Wilso	http://nanbabies.com
118	NANOVER™ Wet Wipes	GNS Nanogist	Korea	Personal care and cosmetics	Skin care	Woodrow Wilso	http://www.nanogist.com
119	Acticoat various wound dressings	Smith & Nephew	USA/UI	Personal care and cosmetics	Skin care	Woodrow Wilso	http://wound.smith-nephew.com
120	Business Black Sock	AgActive	UK	Textile and Shoes	Clothing	Woodrow Wilso	http://www.agactive.co.uk
121	Sport Anklet Sock	AgActive	UK	Textile and Shoes	Clothing	Woodrow Wilso	http://www.agactive.co.uk
122	Sport Half Length Sock	AgActive	UK	Textile and Shoes	Clothing	Woodrow Wilso	http://www.agactive.co.uk
123	Sports Long Sock	AgActive	UK	Textile and Shoes	Clothing	Woodrow Wilso	http://www.agactive.co.uk
124	E47 SmartSilver™ Fibers and Fabrics	ARC Technologies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.e47nano.com/
125	X-SystemTM Base Layer Shirts	ARC Technologies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.xsystem.com
126	X-SystemTM Hats--Balaclava, Head Cover, Hunting Cap, and Rad	ARC Technologies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.xsystem.com
127	X-SystemTM Plantation Jacket	ARC Technologies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.xsystem.com
128	X-SystemTM Scent Eliminating Boot Socks	ARC Technologies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.xsystem.com
129	X-SystemTM Shooters Gloves	ARC Technologies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.xsystem.com
130	SmartSilver™ and Dri-Lex® Shoe Lining	Faytex Corporation	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.nanohorizons.com/
131	Nano Silver Long Johns	Goodweaver Textiles Co. Ltd.	Taiwan	Textile and Shoes	Clothing	Woodrow Wilso	http://www.goodweaver.com/
132	Nano Silver Polo Shirt	Goodweaver Textiles Co. Ltd.	Taiwan	Textile and Shoes	Clothing	Woodrow Wilso	http://www.goodweaver.com/
133	Nano Silver Socks	Goodweaver Textiles Co. Ltd.	Taiwan	Textile and Shoes	Clothing	Woodrow Wilso	http://www.goodweaver.com/
134	Nano Silver Socks and Shoe Pads	Goodweaver Textiles Co. Ltd.	Taiwan	Textile and Shoes	Clothing	Woodrow Wilso	http://www.goodweaver.com/
135	SoleFresh™ Socks	JR Nanotech PLC	UK	Textile and Shoes	Clothing	Woodrow Wilso	http://jrnanotech.com/
136	Lexon Nano-Silver Sock	Lexon Nanotech Inc..	USA	Textile and Shoes	Clothing	Woodrow Wilso	www.lexonnanotech.com
137	Nanorama - Nano-silver sock	Lexon Nanotech, Inc	USA	Textile and Shoes	Clothing	Woodrow Wilso	www.lexonnanotech.com (werkt niet)
138	Mipan® Magic Silver Nano	Mipan®	Korea	Textile and Shoes	Clothing	Woodrow Wilso	http://www.mipan.co.kr
139	Silver Nano Odor Free Rubber Gloves	Misian Co., Ltd.	Korea	Textile and Shoes	Clothing	Woodrow Wilso	http://www.misian.com
140	Nanbabies® Outerwear	Nanbabies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://nanbabies.com
141	Nanbabies® Personal Wear	Nanbabies®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://nanbabies.com
142	NanoHorizons® SmartSilver™	NanoHorizons®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.nanohorizons.com/
143	SmartSilver Anti-Odor Nanotechnology Underwear	Pooghe Laundry	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.nanohorizons.com/
144	PuckSkin™ Odor Eliminator	PuckSkin™	Canada	Textile and Shoes	Clothing	Woodrow Wilso	http://www.puckskin.com
145	Antibacterial Silver Athletic and Lounging Socks	Sharper Image	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.sharperimagebest.com
146	Contour-Foam™ Silver Slippers	Sharper Image®	USA	Textile and Shoes	Clothing	Woodrow Wilso	http://www.sharperimage.com
147	I-Tex "Silver Nano" Anti Bacterial Polo-Shirt	United Textile Mills Co., Ltd.	Thailan	Textile and Shoes	Clothing	Woodrow Wilso	http://www.unitedtextilemills.com
148	Nanbabies® Foot/Shoe Care	Nanbabies®	USA	Textile and Shoes	Other textiles	Woodrow Wilso	http://nanbabies.com
149	Nanbabies® Sleeves and Braces	Nanbabies®	USA	Textile and Shoes	Other textiles	Woodrow Wilso	http://nanbabies.com
150	100% cotton sheet set	AgActive	UK	Textile and Shoes	Other textiles	Woodrow Wilso	http://www.agactive.co.uk
151	Bath and Sports Towels	AgActive	UK	Textile and Shoes	Other textiles	Woodrow Wilso	http://www.agactive.co.uk
152	Benny the Bear Plush Toy	Pure Plushy	USA	Textile and Shoes	Toys	Woodrow Wilso	http://www.pureplushy.com/
153	Donny the Dog Plush Toy	Pure Plushy	USA	Textile and Shoes	Toys	Woodrow Wilso	http://www.pureplushy.com/

Table A1.2. Country of manufacturing and matrix of nanoparticles.

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Country of distributors (abbreviation)	Order via internet (yes/no)	Matrix nanoparicles (fluid, solid, powder, coating, gass, etc.)	size
1	IOGEAR® Germ Free Wireless Laser Mouse	IOGEAR®, Inc.	USA		yes	solid/coatings	
2	IOGEAR® Laser Travel Mouse with Nano Coating Technology	IOGEAR®, Inc.	USA		yes	solid/coatings	
3	IOGEAR® Long Range Wireless Keyboard/Mouse with Nano Tech	IOGEAR®, Inc.	USA		yes	solid/coatings	
4	IOGEAR® Personal Security Mouse with Nano Technology	IOGEAR®, Inc.	USA		yes	solid/coatings	
5	IOGEAR® Wireless Keyboard/Optical Mouse combo w/ Nano Tec	IOGEAR®, Inc.	USA		yes	solid/coatings	
6	Samsung® Notebooks--Q40 and R20	Samsung®	Korea	various countries worldwide	no	coating	
7	Daewoo® Vacuum Cleaner	Daewoo® (UK)	Korea		no	coating	
8	Daewoo® Refrigerator	Daewoo® (Germany)	Korea		no	coating	
9	Daewoo® Washing Machine	Daewoo® (Germany)	Korea		no	coating	
10	LaundryPure™ Cleaning Process	EcoQuest	USA		no	solid	
11	LG® Refrigerator	LG® Electronics	Korea		? (nog zoeken)	solid/coatings	
12	LG® Vacuum Cleaner	LG® Electronics	Korea		? (nog zoeken)	solid/coatings	
13	LG® Washing Machine	LG® Electronics	Korea		? (nog zoeken)	solid/coatings	
14	Samsung® Washing Machine	Samsung®	Korea	various countries worldwide	no	coating	
15	LG® Antibacterial Mobile Phone	LG® Electronics	Korea		? (nog zoeken)	solid/coatings	
16	SAMSUNG Anycall E628 Silver Nano Mobile Phone	Samsung®	Korea	various countries worldwide	no	coating	
17	Nano Dryer	CHI® Cationic Hydration Interlink	USA		no	solid	
18	Helix™ Deep Waver	Hot tools®	USA		no	solid	
19	Helix™ Dryer	Hot tools®	USA		no	solid	
20	Helix™ Flat Irons	Hot tools®	USA		no	solid	
21	Helix™Curling Irons	Hot tools®	USA		no	solid	
22	Ag plus Nano Technology Ionic Dryer	Metropolis	USA		? (product not	solid	
23	S-Nano Ionic Brushes	Metropolis Technology	USA	various countries worldwide	no	solid	
24	S-Nano Ionic Dryer	Metropolis Technology	USA	various countries worldwide	no	solid	
25	S-Nano Ionic Iron	Metropolis Technology	USA	various countries worldwide	no	solid	
26	CleanXchange™ Foil Shaver	Remington	USA		yes	solid	
27	T-Studio Nano Collection	Remington	USA		yes	solid	
28	High Precision™ Personal Grooming Kit	Remington®	USA		yes	solid/coatings	
29	Hair Iron	SE International	Korea		yes	solid	
30	Air Sanitizer	Shenzhen Become Industry & Trade Co., Ltd.	China		yes	fluid/ spray	
31	Air Sanitizer, Nano Silver Photocatalyst	Shenzhen Become Industry & Trade Co., Ltd.	China		yes	fluid	
32	HGT Nano Silver Photocatalyst Aerosol Spray	Daido Corporation	Japan		no	fluid/spray	
33	NANOVER™ Disinfectant Spray	GNS Nanogist	Korea		no	fluid/spray	
34	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® AC filter liquid	Quan Zhou Hu zheng Nano Technology Co.,	China		no	fluid/spray	
35	Nanbabies® Element 47 Moisturizing Spray	Nanbabies®	USA		yes	fluid/ spray	
36	Carrier® Pure Dew Filtration	Carrier	Singapore		no	solid	
37	Germ Guardian™ Digital and Manual Ultrasonic Humidifiers	Germ Guardian™	USA		yes	solid	
38	nanoFresh™	Inspiraz Technology Pte Ltd.	Singapore		no	solid	
39	nanoCotz™ eco-refresh	Inspiraz Technology Pte Ltd.	Singapore		no	fluid/spray	

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Country of distributors (abbreviation)	Order via internet (yes/no)	Matrix nanoparicles (fluid, solid, powder, coating, gass, etc.)	size
40	Plaston™ Ionic Silver Stick	Plaston™	Zwitserland		yes	solid	
41	Samsung® Air Conditioner	Samsung®	Korea	various countries worldwide	no	solid	
42	Nano Air-filter	SongSing Nano Technology Co., Ltd	Taiwan		no	solid	
43	Winix PlasmaWave™ Air Cleaner 9000	Winix Inc.	USA		yes	solid	
44	Nano Silver Spray	SongSing Nano Technology Co., Ltd	Taiwan		no	fluid/spray	
45	Nano Silver Anti-Bacterial Baby Bottle Brush	Sang Shin Industrial Co., Ltd	Korea		no	solid	
46	Nano Silver Cutting Board	A-DO Global	Korea		no	coating	
47	Nano Silver Chopping Board	Fine Polymer Inc	Korea	DU, SI, IT	no	coating	
48	Antibacterial Kitchenware	Nano Care Technology Ltd.	China		no	coating	
49	Antibacterial Table Ware	Nano Care Technology, Ltd.	China		no	coating	
50	Nano Silver Teapot	SongSing Nano Technology Co., Ltd	Taiwan		no	coating	
51	Nano Silver Baby Mug Cup	Baby Dream® Co., Ltd.	Korea		yes	coating	
52	Silver Nano Baby Milk Bottle	Baby Dream® Co., Ltd.	Korea		yes	solid	
53	Food container (NS)	A-DO Global	Korea		no	solid	
54	BlueMoonGoods™ Fresh Box Silver Nanoparticle Food Storage	BlueMoonGoods, LLC	USA		yes	solid	
55	Nano Silver Freshbox®	Fine Polymer Inc	Korea	DU, SI, IT	no	solid	
56	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® Nano-silver St	Quan Zhou Hu zheng Nano Technology Co.,	China		no	solid	
57	FresherLonger™ Miracle Food Storage	Sharper Image®	USA		yes	solid	
58	FresherLonger™ Plastic Storage Bags	Sharper Image®	USA		yes	solid	
59	ASAP Health Max30	Americal Biotech labs	USA		yes	fluid	
60	NanoSil™-10	Greenwood Consumer Products	USA		no	fluid/ powder in H2O	
61	MaatShop™ Crystal Clear Nano Silver	MaatShop™	USA		yes	fluid	
62	MaatShop™ Nano-2+	MaatShop™	USA		yes	fluid	
63	Silvix3®	Natural Care® Products	USA		yes	fluid	
64	Sovereign Silver™	Natural-Immunogenics Corp.	USA		yes	fluid	
65	MesoSilver®	Purest Colloids, Inc.	USA		yes	fluid	0,65
66	Nanoceuticals™ Silver 22	RBC Life Sciences®, Inc	USA		yes	fluid/ powder in H2O	
67	Colloidal Silver Cream	Skybright Natural Health	New Zeeland		no	fluid/creme	
68	Colloidal Silver Liquid	Skybright Natural Health	New Zeeland		no	fluid	
69	Biodream Colloid Plus	Special Health Products VOF	NL		yes	fluid	15
70	Utopia Silver Supplements® Advanced Colloidal Silver	Utopia Silver Supplements®	USA		yes	fluid	
71	NANOVER™ Detergent	GNS Nanogist	Korea		no	fluid	
72	nanoCotz™ Eco-Clean	Inspiraz Technology Pte Ltd.	Singapore		no	fluid	
73	nanoCotz™ Bio Green	Inspiraz Technology Pte Ltd.	Singapore		no	fluid	
74	nanoCotz™ Crystal Clear	Inspiraz Technology Pte Ltd.	Singapore		no	fluid	
75	Lion® Look Kirei no Mist for Bathrooms	Lion® Corporation	Japan		no	fluid/spray	15
76	Lion® Look Kirei no Mist for Kitchens	Lion® Corporation	Japan		no	fluid/spray	15
77	Lion® Look Kirei no Mist for Toilets	Lion® Corporation	Japan		no	fluid/spray	15

Table A1.2. Country of manufacturing and matrix of nanoparticles (continued)

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Country of distributors (abbreviation)	Order via internet (yes/no)	Matrix nanoparieles (fluid, solid, powder, coating, gass, etc.)	size
78	Maha Corp™ Klenz Nano Cleaning Tool	Maha Corp™	Korea		yes	solid	25
79	Fabric Softener IRIN	Aeykung	Korea		no	fluid	
80	nanoCotz™ (glass, ceramic, stone, fabric)	Inspiraz Technology Pte Ltd.	Singapore		no	fluid/spray	
81	Silverex Spray	Inspiraz Technology Pte Ltd.	Singapore		no	fluid/spray	
82	Nano Silver Antimicrobial Paint Supplement	Shanghai Huzheng Nano Technology CO.,LT	China		no	coating	0.2-0.4
83	Antibacterial Pets Products	Nano Care Technology Ltd.	China		no	coating	
84	Contour-Foam™ Silver Back-Support Pillow	Sharper Image®	USA		yes	solid	25
85	Contour-Foam™ Silver Crescent Travel and Nap Pillow	Sharper Image®	USA		yes	solid	25
86	Contour-Foam™ Silver Neck-Support Pillow	Sharper Image®	USA		yes	solid	
87	Silverex showerhead	Inspiraz Technology Pte Ltd.	Singapore		no	coating	
88	Antibacterial Lock	Nano Care Technology Ltd.	China		no	coating	
89	Antibacterial Water Tap	Nano Care Technology, Ltd.	China		no	coating	
90	Nano Silver Teeth Developer	Baby Dream® Co., Ltd	Korea		yes	solid	
91	Nano Pacifier	SongSing Nano Technology Co., Ltd	Taiwan		no	solid	
92	X-SystemTM Scent Eliminating Wipes	ARC Technologies®	USA	various countries worldwide	no	solid	
93	X-SystemTM Scent Elimination Spray	ARC Technologies®	USA	various countries worldwide	no	fluid/spray	
94	Antibacterial Make-up Instrument	Nano Care Technology Ltd.	China		no	coating	
95	Antibacterial Watch Chain	Nano Care Technology, Ltd.	China		no	coating	
96	NANOVER™ Hair Care	GNS Nanogist	Korea		no	fluid	
97	Nanoseal-Hairna essence	NanoPlasma Center Company, Ltd.	Korea		no	solid	
98	Professional Hair Brush	Sang Shin Industrial Co., Ltd.	Korea		no	solid	
99	NANOVER™ Toothpaste	GNS Nanogist	Korea		no	fluid/creme	
100	Nanoseal Toothpaste	NanoPlasma Center Company, Ltd.	Korea		no	fluid/creme	
101	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® Nano-silver To	Quan Zhou Hu zheng Nano Technology Co.,	China		no	fluid/creme	
102	Nano & UV Artificial Teeth Cleaner	Digimax Innovative Products Ltd	Taiwan		?	fluid/creme	
103	Nano Toothbrush	SongSing Nano Technology Co., Ltd.	Taiwan		no	solid	
104	NanoSilver toothbrush	Zerahun Co	Korea		no	solid	
105	Nanometer-Silver Foam Condom	Blue Cross Bio-Medical (Beijing) Co.,Ltd	China		yes	fluid/creme	
106	Platinum Silver Nanocolloid Cream	DHC Skincare	Japan		yes	fluid/creme	
107	Platinum Silver Nanocolloid Milky Essence	DHC Skincare	Japan		yes	fluid/creme	
108	Nano Silver Hand Sanitizer	Fine Polymer Inc	Korea	DU, SI, IT	no	fluid/gel	
109	NANOVER™ Mask Pack	GNS Nanogist	Korea		no	powder	
110	Cyclic Nano Silver Cleanser	NanoCyclic, Inc.	USA		yes	fluid/creme	
111	Cosil Nano Beauty Soap	Natural Korea Company, Ltd	Korea		?	creme	
112	Cosil Whitening Mask	Natural Korea Company, Ltd	Korea		?	fluid/creme	
113	Quan Zhou Hu Zheng Nano Technology Co., Ltd.® Nano-gold Ma	Quan Zhou Hu zheng Nano Technology Co.,	China		no	powder	
114	Susie-K Nano Beauty Soap	Segae-I Pte Ltd	Korea		yes	solid/creme	
115	Susie-K Whitening Mask	Segae-I Pte Ltd	Korea		yes	powder	

Product no.	Name of product	Name of manufacturer	Country of manufacturing	Country of distributors (abbreviation)	Order via internet (yes/no)	Matrix nanopariele s (fluid, solid, powder, coating.	size
116	NANOVER™ Cleansing Soap	GNS Nanogist	Korea		no	solid/creme	
117	Nanbabies® Face Masks	Nanbabies®	USA		yes	solid	
118	NANOVER™ Wet Wipes	GNS Nanogist	Korea		no	solid	
119	Acticoat various wound dressings	Smith & Nephew	USA/UI	various countries worldwide	no	fluid/gel	
120	Business Black Sock	AgActive	UK		yes	solid	
121	Sport Anklet Sock	AgActive	UK		yes	solid	
122	Sport Half Length Sock	AgActive	UK		yes	solid	
123	Sports Long Sock	AgActive	UK		yes	solid	
124	E47 SmartSilver™ Fibers and Fabrics	ARC Technologies®	USA	various countries worldwide	no	solid	
125	X-SystemTM Base Layer Shirts	ARC Technologies®	USA	various countries worldwide	no	solid	
126	X-SystemTM Hats--Balaclava, Head Cover, Hunting Cap, and Rad	ARC Technologies®	USA	various countries worldwide	no	solid	
127	X-SystemTM Plantation Jacket	ARC Technologies®	USA	various countries worldwide	no	solid	
128	X-SystemTM Scent Eliminating Boot Socks	ARC Technologies®	USA	various countries worldwide	no	solid	
129	X-SystemTM Shooters Gloves	ARC Technologies®	USA	various countries worldwide	no	solid	
130	SmartSilver™ and Dri-Lex® Shoe Lining	Faytex Corporation	USA		no	solid	
131	Nano Silver Long Johns	Goodweaver Textiles Co. Ltd.	Taiwan		no	solid	
132	Nano Silver Polo Shirt	Goodweaver Textiles Co. Ltd.	Taiwan		no	solid	
133	Nano Silver Socks	Goodweaver Textiles Co. Ltd.	Taiwan		no	solid	
134	Nano Silver Socks and Shoe Pads	Goodweaver Textiles Co. Ltd.	Taiwan		no	solid	
135	SoleFresh™ Socks	JR Nanotech PLC	UK		yes	solid	
136	Lexon Nano-Silver Sock	Lexon Nanotech Inc..	USA		? (website not found	solid	
137	Nanorama - Nano-silver sock	Lexon Nanotech, Inc	USA		? (website not found	solid	
138	Mipan® Magic Silver Nano	Mipan®	Korea		no	solid	
139	Silver Nano Odor Free Rubber Gloves	Misian Co., Ltd.	Korea		? (website not found	solid	
140	Nanbabies® Outerwear	Nanbabies®	USA		yes	solid	
141	Nanbabies® Personal Wear	Nanbabies®	USA		yes	solid	
142	NanoHorizons® SmartSilver™	NanoHorizons®	USA		no	solid	
143	SmartSilver Anti-Odor Nanotechnology Underwear	Pooghe Laundry	USA		no	solid	
144	PuckSkin™ Odor Eliminator	PuckSkin™	Canad	USA, Canada, Denemarken	no	solid	
145	Antibacterial Silver Athletic and Lounging Socks	Sharper Image	USA	USA, Brazil, Mexico	yes	solid	
146	Contour-Foam™ Silver Slippers	Sharper Image®	USA		yes	solid	
147	I-Tex "Silver Nano" Anti Bacterial Polo-Shirt	United Textile Mills Co., Ltd.	Thailand		yes	solid	
148	Nanbabies® Foot/Shoe Care	Nanbabies®	USA		yes	solid	
149	Nanbabies® Sleeves and Braces	Nanbabies®	USA		yes	solid	
150	100% cotton sheet set	AgActive	UK		yes	solid	25
151	Bath and Sports Towels	AgActive	UK		yes	solid	
152	Benny the Bear Plush Toy	Pure Plushy	USA		yes	solid	
153	Donny the Dog Plush Toy	Pure Plushy	USA		yes	solid	

Appendix 2: Inventory of medical applications containing nano-silver

TableA2.1. Product categories and source.

Product no.	Name of product	Name of manufacturer	Country of manufacturing (abbreviation)	Type product	Subtype product	Source	Website product
1	SilvaSorb® Wound Dressing	AcryMed Inc.	USA	Medical devices	Wound care	internet search	www.acrymed.com
2	SilvaSorb® Cavity Dressing	AcryMed Inc.	USA	Medical devices	Wound care	internet search	www.acrymed.com
3	SilvaSorb® Site Dressing	AcryMed Inc.	USA	Medical devices	Wound care	internet search	www.acrymed.com
4	SilvaSorb® Gel	AcryMed Inc.	USA	Medical devices	Wound care	internet search	www.acrymed.com
5	Silverlon® Calcium Alginate Wound Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
6	Silverlon® Negative Pressure Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
7	Silverlon® Lifesaver™ IV/Catheter Wound Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
8	Silverlon® Island Wound Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
9	Silverlon® Island Wound Dressing (over the counter)	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
10	Silverlon® Wound Pad Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
11	Silverlon® Wound Pad Dressing (over the counter)	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
12	Silverlon® Adhesive Strips	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
13	Silverlon® Adhesive Strips (over the counter)	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
14	Silverlon® Antimicrobial Wound Packaging Strips	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
15	Silverlon® Antimicrobial Wound Contact Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
16	Silverlon® Burn Glove	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
17	Silverlon® Burn Sock	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
18	Silverlon® Burn Contact Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
19	Silverlon® Burn Pad Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
20	Silverlon® Tubular Stretch Knit	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
21	Silverlon® Wrap Dressing	Argentum Medical LLC	USA	Medical devices	Wound care	internet search	www.silverlon.com
22	Modern Medical Antimicrobial Wound Dressing	Modern Medical Equipment Manufacturing Ltd	China	Medical devices	Wound care	internet search	www.fda.org
23	Modern Medical Antimicrobial Burn Dressing	Modern Medical Equipment Manufacturing Ltd	China	Medical devices	Wound care	internet search	www.fda.org
24	Acticoat™ Antimicrobial Barrier Dressing	Smith & Nephew plc	UK	Medical devices	Wound care	internet search	wound.smith-nephew.com.uk
25	Acticoat™ 7 Antimicrobial Barrier dressing	Smith & Nephew plc	UK	Medical devices	Wound care	internet search	wound.smith-nephew.com.uk
26	Acticoat™ Absorbent	Smith & Nephew plc	UK	Medical devices	Wound care	internet search	wound.smith-nephew.com.uk
27	Acticoat™ Moisture Control	Smith & Nephew plc	UK	Medical devices	Wound care	internet search	wound.smith-nephew.com.uk
28	Acticoat™ Site	Smith & Nephew plc	UK	Medical devices	Wound care	internet search	wound.smith-nephew.com.uk
29	Agento™ IC	C.R. Bard Inc.	USA	Medical devices	Anesthetics	internet search	www.bard.com
30	Bardex IC®	C.R. Bard Inc.	USA	Medical devices	Urology	internet search	www.bard.com
31	XpressO Silver™	Spire Corporation	USA	Medical devices	Nephrology	internet search	www.spirecorp.com
32	RetroO Silver™	Spire Corporation	USA	Medical devices	Nephrology	internet search	www.spirecorp.com
33	ON-Q™ SilverSoaker™ Antimicrobial Catheter	I-Flow Corporation	USA	Medical devices	Anesthetics	internet search	www.iflo.com
34	nanoSVO™ battery for cardiac rhythm management	Greatbatch Inc.	USA	Medical devices	Electronics- cardiol	internet search	www.greatbatch.com
35	nanoSVO™ battery for neuromodulation	Greatbatch Inc.	USA	Medical devices	Electronics-urology	internet search	www.greatbatch.com
36	Super G8 Nano Silver Mask	Greenhealthy Australia Pty Ltd	Australia	Medical devices	Textile	internet search	www.tradekey.com
37	HyGentic™ 9000	Bio-Gate AG	Germany	Fibers-various applications		internet search	www.bio-gate.de
38	HyGate™ 9000	Bio-Gate AG	Germany	Fibers-various applications		internet search	www.bio-gate.de

Appendix 3: Study details of published *in vivo* studies on nano-silver

Origin silver particles	Geometric mean (+SD) diameter	AG measurement	Study	Organism	Exposure route	Study setup	Regime	Endpoints (I)	Endpoints (II)/ results	Relevance	Reference
Produced by nanoparticle generator	15,38 ± 1,58	Atomic Absorbance	in vivo	rat (M/F) Sprague-Dawley	Inhalation	28 day	6h/day; 5day/week	Tox: Hematological analysis (20 parameters) ans Biochemical analysis (22 parameters)	Microscopy finding: qualitative distribution (Yes/No) in liver, kidney, adrenals, bladder, spleen, pancreas, thymus, thyroid, trachea, esopagus, tongue, lungs, heart, brain, testes, prostate, seminal vesicles, nasal cavity (male/female)	+++	Ji et al., 2007
	12,6 ± 1,53								Concentration measured in lung, liver, brain, olfactory bulb and blood (male female)		
	12,61 ± 1,53								All endpoints for control, low, middle and high concentration chamber		
Spark dicharging	17.1 ± 1,38	ICP-MS	in vivo	rat (F) Ficher 3444	Inhalation	sacrifice day 0, 1, 4, 7	6h exposure	Distribution of inhaled nanosilver to lungs, liver, kidney, heart, lymph nodes, olfactory, brain, blood	Studie over time: 30 min-2 hours 6h exposure; 1 day, 4 day and 7 day for all estimated organs	+++	Takenaka et al., 2001
Reducing silver perchlorate	11,6 ± 3,5		in vivo	zebrafish	Particles in medium			imaging and transport of AG in embryo		++	Lee et al., 2007
Acticoat	15 nm	ICP-MS	case report	human	Dermal (burned skin)	97 days	acticoat till day 7	Ag in plasma/urine, agyria in skin + 9 biochemical parameters	Reduction to baseline after termination acticoat follow up 90 days	++	Trop et al., 2006
Acticoat	15 nm	ICP-MS	trial	human	Dermal (burned skin)	treatment + follow up		Systemic dermal absorption from acticoat	Although elevated levels of silver in plasma , confirmation that acticoat is safe.	++	Vlachou et al., 2007
Colloidal silver	Unknown		case report	human	Ingestion		daily ingestion	Argyria	AG detection in plasma/urine brain	++	Mirsattari et al 2004
Colloidal silver	Unknown		case report	human	Ingestion			Argyria	Brown black granules in skin were identified	+	Chang et al 2006
Colloidal silver	Unknown	spectral analysis	case report	human	Ingestion		daily ingestion	Argyria	AG was present in Serum / urine and skin granules	+	White et al., 2003
Acticoat	15 nm		in vivo	pig	Dermal (full thickness wounds)	treatment + 7days follow up	several treatments: skin graft, moistured dressing	Graft take, enzyme activity in exudate, apoptosis in wound tissue, histopathology of wound	Promotion of wound healing	++	Wright et al 2002
Acticoat	15 nm		clinical trial	human	Dermal (burn wounds)		daily/twice daily dressing changes	Wound pain, ease of use, antimicrobial	No adverse effects	+	Tredget et al 1998

Appendix 3: Study details of published *in vivo* studies on nano-silver (continued)

Origin silver particles	Geometric mean (+SD) diameter	AG measurement	Study	Organism	Exposure route	Study setup	Regime	Endpoints (I)	Endpoints (II)/ results	Relevance	Reference
Acticoat	15 nm		in vivo	a-thymic mice	Dermal (full thickness wounds grafted cultured skin substitutes)	2-4 week follow up (following graft surgery)	acticoat till day 7	Cytotoxicity, area of wound healing, engraftment, antibactrial effect	No effect on wound healing	++	Supp et al 2005
Acticoat	15 nm		trial	human	Dermal (skin graft on burns)		up to 3 months follow up	Re-epithelisation, bacterial contamination, scar formation	Delayed re-epithelisation	++	Innes 2001
Acticoat	15 nm		trial	human	Dermal (skin graft on burns)			Bacterial contamination, re-epithelisation, wound closure, graft take	Increase re-epithelisation	++	Demling et al 2002
1% nanocrystalline cream (NPI 32101)	96,1% (< 50 nm)		in vivo	mice	Dermal	application on allergic contact dermatitis	once day/4 days	Histological changes, immunochemistry, apoptosis, RNA extraction	Apoptosis of inflammatory cells but not keral	+	Bhol et al 2005
1% nanocrystalline cream (NPI 32101)	96,1% (< 50 nm)		in vivo	pig	Dermal	application on allergic contact dermatitis	once day/5 days	Erythema, oedema, histopathology		+	Bhol et al 2004
Colloidal silver (DAB6)	Unknown		in vivo	rat	Intravenous	single dose toxicity		Death, gross necropsy	Death within 24 hr.	+	Schmal et al 1960
					Subcutaneous	10 months dosing, follow up till end of life	1 weekly dose	Aggria, clinical behaviour (well being), histopathology on observed tumors	Increase in malignant tumors at injection site.	+	
					Intravenous	7 month dosing, follow up till end of life	1 weekly dose	Aggria, clinical behaviour (well being), histopathology on observed tumors		+	
silver powder	Unknown		in vivo	rat	Intramuscular	24 months	1/month	Weight, palpable tumors, complete necropsy	Histopathology on abnormal tissue	+	Furst 1978

N.B. For most of the studies, the used nanoparticles were not characterized in detail (or the characteristics were not reported). In the study of Ji et al. (2007), particles were generated in a high, medium and low concentration chamber with particle concentrations of, respectively, 1,630,000, 160,000 and 16,600 particles.cm^{-3}. The shape of the particles was reported to be spherical in the Takenaka and Lee study; other studies did not mention the particle shape. Aggregation/agglomeration was only reported in a few studies, i.e., Ji et al. (2007): non-agglomerated after production, Takanaka et al. (2001) only for intracheal fraction, and Lee et al. (2007): majority of nanoparticles remain non-aggregated. Apart from the Ag measurement, some reports mention the analysis of the nanoparticles; TEM was used in the Ji and Takanaka study, HR-TEM was used by Lee et al. and EM by White et al. (2003), Chang et al. (2006) used a visible light microscope to analyze NP.