Evaluation of Hazard and Exposure Associated with Nanosilver and Other Nanometal Oxide Pesticide Products

Presented by: Murray J. Height, Ph.D.
Chief Technology Officer
HeiQ Materials
www.heiqmaterials.com

Presented on behalf of the Silver Nanotechnology Working Group (SNWG), an industry effort intended to foster the collection of data on silver and nanotechnology in order to advance the science and public understanding of the beneficial uses of silver nanoparticles in a wide-range of consumer and industrial products.

Also refer to docket submission:
Outline

1. Commercial and regulatory history of nanoscale silver
2. Human health perspective
3. Ecological perspective
4. Policy perspective
Outline

1. Commercial and regulatory history of nanoscale silver

2. Human health perspective

3. Ecological perspective

4. Policy perspective
Nanoscale Silver – Perspective

- Origins of nanoscale silver and terminology
- Uses of nanoscale silver
- Regulatory status for antimicrobial nanosilver products
- Value of nanosilver products as antimicrobials (subject to FIFRA)
Nanoscale Silver - Origins

• Scientific origins of silver nanoparticles buried within *colloidal science*
• Colloidal sols are small solid particles suspended in a solvent

• Colloidal silver produced since 1800s (and earlier)
• Colloidal silver particles are synthesized through many methods¹:
  - Liquid phase reduction reactions
  - Electrolytic methods
  - Vapor methods
  - Mechanical milling
  - etc.

Nanoscale Silver - Origins

- Scientific origins of silver nanoparticles buried within colloidal science
- Colloidal sols are small solid particles suspended in a solvent

- Colloidal silver produced since 1800s (and earlier)
- Colloidal silver particles are synthesized through many methods:\n  - Liquid phase reduction reactions
  - Electrolytic methods
  - Vapor methods
  - Mechanical milling
  - etc.

These methods are also used to produce silver nanoparticles today

---

Nanoscale Silver - Origins

- Scientific origins of silver nanoparticles buried within colloidal science
- Colloidal sols are small solid particles suspended in a solvent

- Colloidal silver produced since 1800s (and earlier)
- Colloidal silver particles are synthesized through many methods\(^1\):
  - Liquid phase reduction reactions
  - Electrolytic methods
  - Vapor methods
  - Mechanical milling
  - etc.

These methods are also used to produce silver nanoparticles today

- Colloidal silver clearly rationally engineered particles of small size
- Are they well characterised?
- What is their size?

Nanoscale Silver - Origins

- Characterisation: Colloidal metals and colloidal silver
- Particle size <100nm accurately determined via a number of historical methods:
Nanoscale Silver - Origins

- Characterisation: Colloidal metals and colloidal silver
- Particle size <100nm accurately determined via a number of historical methods:

<table>
<thead>
<tr>
<th>Year</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>ca.1903</td>
<td>Ultramicroscopes (light scattering optical microscope)(^1,2)</td>
</tr>
<tr>
<td>ca.1907</td>
<td>Dialysis (relative permeability)(^3)</td>
</tr>
<tr>
<td>ca.1917</td>
<td>Electrophoresis (motion in electric field)(^4)</td>
</tr>
<tr>
<td>ca.1923</td>
<td>Ultracentrifuges (sedimentation correlation to particle size)(^5,6)</td>
</tr>
</tbody>
</table>

---

Nanoscale Silver - Origins

- Characterisation: Colloidal metals and colloidal silver
- Particle size <100nm accurately determined via a number of historical methods:
  - ca.1903 Ultramicroscopes (light scattering optical microscope)\(^1,2\)
  - ca.1907 Dialysis (relative permeability)\(^3\)
  - ca.1917 Electrophoresis (motion in electric field)\(^4\)
  - ca.1923 Ultracentrifuges (sedimentation correlation to particle size)\(^5,6\)

---

Nanoscale Silver - Origins

• 1969. Carey Lea colloidal silver produced using same methodology as 1889\(^1\)
• Size determination and characterisation using electron microscopy (TEM) confirms the size from historical characterisation methods\(^2\)
• Carey Lea colloidal silver average size 7 - 10 nm
• Confirmed as metallic silver by X-ray diffraction

• Colloidal silver shown as particles within range of 1 to 100 nm

---


---

Fig. 1. Electron micrograph of a *Carey Lea* silver sol \([2]\)
Nanoscale Silver - Origins

- Silver particles in the nano size range show a yellow/brown color\(^1\)
- This color derives from the surface plasmon effect and is a unique identifier of silver metal particles in the nano size range\(^2\)
- Colloidal silver shares same silver metal properties as silver nanoparticles\(^1,2\)

\(^3\) Photographs and Dynamic light scattering (DLS) data courtesy of *NanoHorizons Inc*
Nanoscale Silver - Origins

- Colloidal silver = silver nanoparticles?

<table>
<thead>
<tr>
<th></th>
<th>Colloidal silver</th>
<th>Silver nanoparticles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engineered?*</td>
<td>Yes. Rationally synthesized</td>
<td>Yes. Rationally synthesized</td>
</tr>
<tr>
<td>Size range?**</td>
<td>1 through 100 nm (µm) ¹</td>
<td>1 through 100 nm ²</td>
</tr>
<tr>
<td>Size distribution?</td>
<td>Wide range possible</td>
<td>Wide range possible</td>
</tr>
<tr>
<td>Character?</td>
<td>Silver metal</td>
<td>Silver metal</td>
</tr>
<tr>
<td>Color?</td>
<td>Brown/yellow color</td>
<td>Brown/yellow color</td>
</tr>
</tbody>
</table>

* Colloidal silver and silver nanoparticles share common synthesis methods.
** Size range is arbitrarily set by convention in both cases. Size range 1 to 100nm expresses a range of conventional interest.
Nanoscale Silver - Origins

- Colloidal silver = silver nanoparticles?

<table>
<thead>
<tr>
<th></th>
<th>Colloidal silver</th>
<th>Silver nanoparticles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engineered?*</td>
<td>Yes. Rationally synthesized</td>
<td>Yes. Rationally synthesized</td>
</tr>
<tr>
<td>Size range?**</td>
<td>1 through 100 nm (µm) ¹</td>
<td>1 through 100 nm ²</td>
</tr>
<tr>
<td>Size distribution?</td>
<td>Wide range possible</td>
<td>Wide range possible</td>
</tr>
<tr>
<td>Character?</td>
<td>Silver metal</td>
<td>Silver metal</td>
</tr>
<tr>
<td>Color?</td>
<td>Brown/yellow color</td>
<td>Brown/yellow color</td>
</tr>
</tbody>
</table>

- Colloidal silver and silver nanoparticles are the same material
- Difference is only terminology used at different points in history
  - colloidal, millimicra, sub-micron, nano etc.

* Colloidal silver and silver nanoparticles share common synthesis methods.
** Size range is arbitrarily set by convention in both cases. Size range 1 to 100nm expresses a range of conventional interest.
Nanoscale Silver – Historical Use

- Example:
- Carey Lea colloidal silver first synthesised in 1880s\(^1\)
  - Metallic silver, typically 5 to 30 nm diameter spheres\(^3\)
- Used widely in photographic film industry throughout 20th century\(^2\)
- Still used today eg. X-ray films\(^3\)

\(^1\) MC. Lea, “On Allotropic Forms of Silver”, American Journal of Science, 37 (1889) 476
Nanoscale Silver – Historical Use

• There are many historic, current and potential applications for silver nanoparticles:
  - Pigments
  - Photography
  - Wound treatments
  - Conductive/antistatic
  - Catalysts
  - Antimicrobial
  - etc.

• Silver nanoparticles as an antimicrobial (FIFRA):
  - Textiles  eg. sportsclothing, socks
  - Medical articles & devices  eg. plasters, wound care
  - Coatings  eg. wall paint
  - Plastics  eg. Keyboards
EPA Registered Nanosilver products

• Many EPA registered nanosilver products over 6 decades\(^1\)

\(^{1}\) NPIRS Public [http://ppis.ceris.purdue.edu/npublic.htm](http://ppis.ceris.purdue.edu/npublic.htm)
EPA Registered Nanosilver products

- Many EPA registered nanosilver products over 6 decades

1 NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
EPA Registered Nanosilver products

- Many EPA registered nanosilver products over 6 decades\(^1\)

1. NPIRS Public [http://ppis.ceris.purdue.edu/npublic.htm](http://ppis.ceris.purdue.edu/npublic.htm)
2. [http://www.epa.gov/history/index.htm](http://www.epa.gov/history/index.htm)
EPA Registered Nanosilver products

- Many EPA registered nanosilver products over 6 decades\(^1\)

EPA Registered Nanosilver Products

\(^1\) NPIRS Public [http://ppis.ceris.purdue.edu/npublic.htm](http://ppis.ceris.purdue.edu/npublic.htm)

\(^2\) [http://www.epa.gov/history/index.htm](http://www.epa.gov/history/index.htm)
EPA Registered Nanosilver products

- Many EPA registered nanosilver products over 6 decades

EPA Registered Nanosilver Products

1954 Colloidal (nano) silver
First silver registration

1970 EPA established

1971 - 1993
All registrations: colloidal (nano) silver or nanosilver-composite

1994 First non-nanosilver registration

1 NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
2 http://www.epa.gov/history/index.htm
Nanosilver Algaecides

EPA-Registered Since 1954*

Product: Silver Algaedyn
Particle size: 20-110 nm
FIFRA Reg # 68161-1
Type: 0.8% Colloidal Silver
First Registered: 12/31/1954¹

¹ NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
² Dynamic light scattering (DLS) data courtesy of NanoHorizons Inc.
* Pre-dating EPA establishment (1970) yet registered in 1954 under FIFRA database¹
Nanosilver Algaecides

EPA-Registered Since 1954*

Product: Silver Algaedyn
Particle size: **20-110 nm**
FIFRA Reg # 68161-1
Type: 0.8% Colloidal Silver
First Registered: 12/31/1954¹

---

1 NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
2 Dynamic light scattering (DLS) data courtesy of NanoHorizons Inc.
3 Pre-dating EPA establishment (1970) yet registered in 1954 under FIFRA database¹

---

**PROCESS OF PRODUCING OLIGODYNAMIC METAL BIOCIDES**

Zdenek Vaclav Moudry, Northfield, Ill., assignor to United States Movidyn Corporation, a corporation of Illinois

Application March 20, 1953, Serial No. 343,705

“...In general, the invention relates to the production of oligodynamic metal microbicides by the reduction of oligodynamic metal salts, through the action of actinic light, in such a manner as to produce a stable dispersion of essentially nonagglomerated microparticles of the elemental metal. By microparticles, I refer to particles which do not exceed a few hundred angstrom units (A.U.) in mean dimension.” [3] < 100nm

Note: 100 angstroms (Å) = 10 nm

---

Nanosilver Algaecides

EPA-Registered Since 1993

Product: nu-clo Silvercide
Particle size: **25-95 nm**
FIFRA Reg # 7124-101
Type: 0.8% Colloidal Silver
First Registered: 6/15/1993

---

1 NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
Dynamic light scattering (DLS) data courtesy of NanoHorizons Inc.
Nanoscale Silver-Impregnated Carbon

EPA-Registered Nanoscale Silver-Impregnated Carbon Filter Media

- Of all EPA silver registrations, 40% (37 of 92) are silver-impregnated filters
- Nanosilver-carbon water filters have been commercial for over 40 years
- Silver particles >50 nm are inefficient; particles 2-15 nm are required

Examples:

<table>
<thead>
<tr>
<th>FIFRA Reg #s</th>
<th>First registered</th>
</tr>
</thead>
<tbody>
<tr>
<td>58295-1</td>
<td>12/01/1988³</td>
</tr>
<tr>
<td>58295-2</td>
<td>11/01/1989³</td>
</tr>
<tr>
<td>58295-3</td>
<td>01/16/1990³</td>
</tr>
</tbody>
</table>

3 NPIRS Public [http://ppis.ceris.purdue.edu/npublic.htm](http://ppis.ceris.purdue.edu/npublic.htm)
Nanosilver Disinfectants

EPA-Registered Nanosilver Disinfectants: American Biotech Labs

“These engineered silver particles currently vary in size between about 10-50 nanometers in diameter…”

William D. Moeller, President, American Biotech Laboratories

“We believe our nano-silver product is an important non-toxic broad-spectrum anti-pathogenic…”

Keith Moeller, VP Marketing, American Biotech Laboratories

Product:  ASAP-AGX
Particle size: 10-50 nm
FIFRA Reg # 73499-1
Type: 0.001% Silver
First Registered: 2/27/2002

Product:  ASAP-AGX-32
Particle size: 10-50 nm
FIFRA Reg # 73499-2
Type: 0.032% Silver
First Registered: 4/23/2003

1 NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
Nanosilver Disinfectants

EPA-Registered Nanosilver Dental Line Cleaners

“The Maintenance Treatment contains a controlled, minute amount of colloidal silver to keep things clean”

Product: H2Pro™ Maintenance Treatment
Particle size: 1-500 nm (est)
FIFRA Reg # 75829 -1
Type: 0.0015% Silver
First Registered: 9/9/2004

1 http://www.garrisonodontal.com/
2 NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
Nanosilver Antimicrobials

EPA-Registered Antimicrobial Additives: Ciba / Bio-Gate

Product: HyGate 4000
Particle size: **50-200 nm**
Agglomerate size: 2-5 µm
FIFRA Reg # 70404-10
Type: 100% Silver
First Registered: 09/05/2008

Product: MicroSilver BG-R
Particle size: **50-200 nm**
Agglomerate size: 2-5 µm
FIFRA Reg # 84146-1
Type: 100% Silver
First Registered: 03/18/2008

Press Release: “Ciba Specialty Chemicals forms marketing cooperation with Bio−Gate for silver antimicrobial technology”

1 NPIRS Public [http://ppis.ceris.purdue.edu/npublic.htm](http://ppis.ceris.purdue.edu/npublic.htm)
Nanosilver Antimicrobials

EPA-Registered Antimicrobial Additives: NanoHorizons

Product: Additive SSB
Particle size: **10 - 20 nm**
FIFRA Reg # 83587-3
Type: 100% Silver
First Registered: 09/28/2007

---


---

1 NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
EPA Registered Nanosilver Products

- Many FIFRA registered nanosilver products over 6 decades\(^1\)

\[\text{EPA Registered Nanosilver Products}\]

\[\text{Registered per year} \quad \text{Total all silver registered} \quad \text{Total nanosilver registered}\]

\[\begin{align*}
\text{Year} & \quad \text{Registered per year} \\
1950-2010 & \\
\end{align*}\]

\[\begin{align*}
\text{Silver Algaedyn} & \quad 20-110 \text{ nm} \quad 68161-1 \\
\text{nu-clo Silvercide} & \quad 25-95 \text{ nm} \quad 7124-101 \\
\text{Silver-carbon} & \quad <25 \text{ nm} \quad 7124-101 \\
\text{ASAP-AGX} & \quad 10-50 \text{ nm} \quad 73499-1 \\
\text{Additive SSB} & \quad 10-20 \text{ nm} \quad 83587-3 \\
\text{HyGate4000} & \quad 50-200 \text{ nm} \quad 70404-10 \\
\end{align*}\]

\[\text{NPIRS Public} \quad \text{http://ppis.ceris.purdue.edu/npublic.htm}\]

\(^1\) NPIRS Public http://ppis.ceris.purdue.edu/npublic.htm
FDA-Approved Nanosilver Products

• Acticoat Wound Care with Nanocrystalline Silver
  - FDA approved in 1998
  - Clinically proven to reduce wound infection

• I-Flow SilverSoaker Nanosilver Catheters
  - FDA approved in 2005
  - Recommended by NGOs to reduce hospital acquired infections

• Other FDA approved nanosilver products:
  - Baxter Needless IV Connectors
  - SilverSol Nanosilver Wound Care Gel
  - Bard Silver-coated Endotracheal Tubes
FDA-Approved Nanosilver Products

- The low risk of human toxicity and the benefits of nanoscale silver and are widely recognised by many regulatory and scientific leaders.

**ENGINEERING MATERIALS ACHIEVEMENT AWARD**

**NANOSILVER WOUND DRESSING**

Robert Burrell
University of Alberta
Edmonton, Alberta

Dr. Robert Burrell developed what is believed to be the first commercial application of nanotechnology through a silver particle-infused bandage in which silver nanoparticles act as an anti-microbial.

Bourious, 14-hour process based on physical vapor deposition. In the process, high-density polyethylene is fed through a pressure vessel whose vacuum chamber is filled with electrically charged argon gas. This binds the ionized silver particles to the material in a one-micron-thick layer. The polyethylene material is ultrasonically bonded to a laminate backing, then packaged and sterilized with radiation.

Silver has long been used as an anti-microbial. [1]

---

EPA registered Copper Nanomaterial

EPA-Registered Nanomaterials: NanoCopper Wood Preservatives

Product: ORD-X372 / MicroPro 200
Particle size: **50-700 nm**
FIFRA Reg # 3008 -90
Type: 35% Copper (as carbonate)
First Registered: **5/12/2005**

“…Micronized copper wood preservatives are the latest generation wood preservative systems in which very small (sub-micron) particles of solid copper”

The copper particle size used in the micronized copper products average about 300 nm. Particles <80 nm penetrate the wood.

Cited in EPA Green Chemistry Awards.

---

Nanoscale Silver: Regulatory History

1954:
Nanosilver colloidal algaecides (~70 nm) first registered under FIFRA

1960s-90s:
EPA-registered silver-impregnated carbon filters (2-15 nm) widely used to protect municipal water supply

1998:
First FDA approved nanocrystalline silver wound care devices are approved

2002:
First nanosilver spray disinfectant approved by EPA (~50 nm)

Present:
Estimated 82% (75 of 92) of EPA-registered products contain nanoscale particles or ionic (picoscale) silver
Nanoscale Silver: Regulatory History

1954:
Nanosilver colloidal algaecides (~70 nm) first registered by EPA

1960s-90s:
EPA-registered silver-impregnated carbon filters (2-15 nm) widely used to protect municipal water supply

1998:
First FDA approved nanocrystalline silver wound care devices are approved

2002:
First nanosilver spray disinfectant approved by EPA (~50 nm)

Present:
Estimated 82% (75 of 92) of EPA-registered products contain nanoscale particles or ionic (picoscale) silver
How Do Silver-based Antimicrobials Work?

• All silver-based antimicrobials act against bacteria through the action of silver ions (Ag⁺)

• The effect of silver ions against microorganisms is well established and is referred to as the oligodynamic effect [1]

• Silver ions interact with bacteria cells through 3 mechanisms (see Figure):
  1. Damage bacteria cell membrane [2]
  2. Displace Ca²⁺ and Zn²⁺ ions [2]
  3. Interact with sulphur, oxygen or nitrogen [3]

• Silver ions are active against a broad range of gram-positive and gram-negative bacteria

• Unique qualities of silver ions:
  - Low risk for bacteria resistance [5]
  - Effective in very low concentrations [4]
  - No human toxicity

Silver Additives Deliver Silver Ions

Antimicrobial effect solely from Ag⁺
Threshold concentration of Ag⁺ required to give antimicrobial effect

Liberation of Ag⁺ from source antimicrobial additive

Bacteria

Ag⁺
Ca²⁺, Zn²⁺
Ag⁺
Ag⁺

Silver zirconium phosphate
Silver zeolite
Silver glass
Silver chloride
Nanosilver

Silver Additives Deliver Silver Ions

Silver ion exchangers
Silver salts
Silver metal
HeiQ silver metal microcomposite
EPA registration numbers
Silver Additives Deliver Silver Ions

Antimicrobial effect solely from Ag⁺
Threshold concentration of Ag⁺ required to give antimicrobial effect

Liberation of Ag⁺ from source antimicrobial additive

All silver-based antimicrobials “Store” silver ions

Silver ion exchangers
Silver salts
Silver metal
Silver salt microcomposite

Silver zirconium phosphate
Silver zeolite
Silver glass
Silver chloride
Nanosilver metal
Silver metal

EPA registration numbers
EPA 11631-2
EPA 11631-3
EPA 74079-1
EPA 71227-1
EPA 72854-1
EPA 40810-18
EPA 82415-3
EPA 73148-1
EPA 59441-7
EPA 49403-34
EPA 70404-10
EPA 84146-1
EPA 83587-3
EPA 58295-1
EPA 58295-2
EPA 58295-3

0-hypothesis (Wijnhoven et al.)

Silver as an Antimicrobial

General advantages of silver antimicrobials:
- Can be directly integrated into polymers, coatings and formulations
- Easily processable - robust and temperature resistant
- Replace synthetic chemical antimicrobials
- Can be used in low concentrations to protect substrates from action of microorganisms

Example application - Textiles:
- Unpleasant odours from synthetic fibers
- Discoloration and stains
- Reduced service lifetime of textile
- Silver provides straightforward way to provide antimicrobial effect
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag⁺)
- Extent of Ag⁺ release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of Ag⁺ release
  - Silver sulfide is totally insoluble - lowest possible extent of Ag⁺ release
  - Various silver antimicrobials lay in-between these extremes

![Diagram showing the spectrum of Ag⁺ release from silver sulfide to silver nitrate](image)
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag⁺)
- Extent of Ag⁺ release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of Ag⁺ release
  - Silver sulfide is totally insoluble - lowest possible extent of Ag⁺ release
  - Various silver antimicrobials lay in-between these extremes
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag\(^+\))
- Extent of Ag\(^+\) release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of Ag\(^+\) release
  - Silver sulfide is totally insoluble - lowest possible extent of Ag\(^+\) release
  - Various silver antimicrobials lay in-between these extremes
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag\(^+\))
- Extent of Ag\(^+\) release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of Ag\(^+\) release
  - Silver sulfide is totally insoluble - lowest possible extent of Ag\(^+\) release
  - Various silver antimicrobials lay in-between these extremes
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag\(^+\))
- Extent of Ag\(^+\) release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of Ag\(^+\) release
  - Silver sulfide is totally insoluble - lowest possible extent of Ag\(^+\) release
  - Various silver antimicrobials lay in-between these extremes
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions ($\text{Ag}^+$)
- Extent of $\text{Ag}^+$ release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of $\text{Ag}^+$ release
  - Silver sulfide is totally insoluble - lowest possible extent of $\text{Ag}^+$ release
  - Various silver antimicrobials lay in-between these extremes

- Because of the higher surface area per mass of silver, nanosilvers have a higher release capability than bulk silver metal
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag\(^+\))
- Extent of Ag\(^+\) release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of Ag\(^+\) release
  - Silver sulfide is totally insoluble - lowest possible extent of Ag\(^+\) release
  - Various silver antimicrobials lay in-between these extremes

Because of the higher surface area per mass of silver, nanosilvers have a higher release capability than bulk silver metal
Silver Additives in Use

Silver metal particles (CASRN: 7440-22-4)

- Silver metal (bulk)
- Silver metal (micro)
- Silver metal (nano)

Ag$^+$ release

Ag$^+$
Silver Metal – Why go smaller?

- Antimicrobial effect from ionic silver (Ag\(^+\))
- Efficient silver use considers Ag\(^+\) release per mass of silver used
- Ag\(^+\) release only from surface of metal on contact with water
- Efficiency is based on proportion of surface to volume (mass) of the particle

<table>
<thead>
<tr>
<th>Diameter</th>
<th>1</th>
<th>4</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface to volume ratio</td>
<td>10</td>
<td>2.5</td>
<td>1</td>
</tr>
</tbody>
</table>
Silver Metal – Why go smaller?

- Ag⁺ release proportional to surface to volume (mass) of the particle

Availability of Ag⁺ ions per mass of silver is higher for smaller particles
Silver Metal – Why go smaller?

- Ag⁺ release proportional to surface to volume (mass) of the particle

**Smaller particles allow much lower mass of silver to achieve a given Ag⁺ dosing**

**Example:**
For equivalent Ag⁺ dosing

- 1µm particles: 10’000 ppm Ag required
- 10 nm particles: 100 ppm Ag required
Silver Additives in Use

- Silver antimicrobials derive activity from release of silver ions (Ag\(^+\))
- Extent of Ag\(^+\) release varies over a wide range
  - Can be roughly considered as having different “solubilities”
  - Silver nitrate is totally soluble in water - highest possible extent of Ag\(^+\) release
  - Silver sulfide is totally insoluble - lowest possible extent of Ag\(^+\) release
  - Various silver antimicrobials lay in-between these extremes

Silver metal particles (CASRN: 7440-22-4)

- Because of the higher surface area per mass of silver, nanosilvers have a higher release capability than bulk silver metal
Silver Additives in Use

- A key factor in use of silver additives is the required durability which in turn dictates the amount of antimicrobial additive required.
- In general:
  - High $\text{Ag}^+$ release rate $\rightarrow$ low durability $\rightarrow$ high dosing levels required to give durability
  - Low $\text{Ag}^+$ release rate $\rightarrow$ high durability $\rightarrow$ high dosing levels to give required activity
  - Moderate release rate $\rightarrow$ good durability at low loadings
Silver Additives in Use

- A key factor in use of silver additives is the required durability which in turn dictates the amount of antimicrobial additive required.
- In general:
  - High $\text{Ag}^+$ release rate → low durability → high dosing levels required to give durability
  - Low $\text{Ag}^+$ release rate → high durability → high dosing levels to give required activity
  - Moderate release rate → good durability at low loadings
Silver Additives in Use

- A key factor in use of silver additives is the required durability of silver ion release which in turn dictates the amount of antimicrobial additive required.
- In general:
  - High Ag$^+$ release rate → low durability → high dosing levels required to give durability
  - Low Ag$^+$ release rate → high durability → high dosing levels to give required activity
  - Moderate release rate → good durability at low loadings

Amount of silver required in end-use

Ag$^+$ release

Silver sulfide
Silver metal (bulk)
Silver metal (micro)
Silver metal (nano)
Silver chloride
Silver zeolite
Silver zirconium phosphate
Silver glass
Silver nitrate
Silver Additives in Use

- A key factor in use of silver additives is the required durability of silver ion release which in turn dictates the amount of antimicrobial additive required.
- In general:
  - High Ag$^+$ release rate $\rightarrow$ low durability $\rightarrow$ high dosing levels required to give durability
  - Low Ag$^+$ release rate $\rightarrow$ high durability $\rightarrow$ high dosing levels to give required activity
  - Moderate release rate $\rightarrow$ good durability at low loadings

Sustainable Technologies:
- Less silver needed
- Less silver loss over lifetime
- Highest durability
Nanosilver versus Conventional Silver Materials

Compared to other silver additives, silver nanoparticles generally have:

- Lower antimicrobial activity
- Longer durability
- Less silver needed in a treated article - combination of durability and activity is achieved at lower concentrations
Nanosilver versus Conventional Silver Materials

Compared to other silver additives, silver nanoparticles generally have:

- Lower antimicrobial activity\(^1\)
- Longer durability
- Less silver needed in a treated article - combination of durability and activity is achieved at lower concentrations

### TABLE 1. Comparison of the antimicrobial activities of silver nanocomposite powder, silver nitrate, and silver zeolite \([1]\)

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Silver nanocomposite</th>
<th></th>
<th>Silver nitrate</th>
<th></th>
<th>Silver zeolite</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (µg/ml)(^a)</td>
<td>MBC or MFC (µg/ml)(^b)</td>
<td>MIC (µg/ml)(^a)</td>
<td>MBC or MFC (µg/ml)(^b)</td>
<td>MIC (µg/ml)(^a)</td>
<td>MBC or MFC (µg/ml)(^b)</td>
</tr>
<tr>
<td><em>Escherichia coli</em> ATCC 2732(^c)</td>
<td>62.5</td>
<td>125</td>
<td>7.8</td>
<td>15.6</td>
<td>3.9</td>
<td>15.6</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> ATCC 4352(^c)</td>
<td>62.5</td>
<td>125</td>
<td>7.8</td>
<td>7.8</td>
<td>7.8</td>
<td>31.2</td>
</tr>
<tr>
<td><em>Pseudomonas fluorescens</em> LME 2333(^d)</td>
<td>62.5</td>
<td>250</td>
<td>7.8</td>
<td>7.8</td>
<td>15.6</td>
<td>31.2</td>
</tr>
<tr>
<td><em>Salmonella enterica</em> serovar Enteritidis D1(^c)</td>
<td>62.5</td>
<td>250</td>
<td>7.8</td>
<td>7.8</td>
<td>15.6</td>
<td>62.5</td>
</tr>
<tr>
<td><em>Salmonella enterica</em> serovar Typhimurium DB 7155(^c)</td>
<td>62.5</td>
<td>250</td>
<td>7.8</td>
<td>7.8</td>
<td>15.6</td>
<td>31.2</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> ATCC 19433(^d)</td>
<td>62.5</td>
<td>250</td>
<td>7.8</td>
<td>7.8</td>
<td>15.6</td>
<td>31.2</td>
</tr>
<tr>
<td><em>Bacillus cereus</em> ATCC 14579(^f)</td>
<td>250</td>
<td>500</td>
<td>31.2</td>
<td>31.2</td>
<td>62.5</td>
<td>250</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em> Scott A(^f)</td>
<td>500</td>
<td>1,000</td>
<td>31.2</td>
<td>31.2</td>
<td>31.2</td>
<td>62.5</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> ATCC 29213(^f)</td>
<td>250</td>
<td>1,000</td>
<td>15.6</td>
<td>15.6</td>
<td>15.6</td>
<td>125</td>
</tr>
<tr>
<td><em>Candida albicans</em> ATCC 10259(^k)</td>
<td>125</td>
<td>2,000</td>
<td>31.2</td>
<td>250</td>
<td>62.5</td>
<td>250</td>
</tr>
<tr>
<td><em>Aspergillus niger</em> ATCC 9642(^b)</td>
<td>2,000</td>
<td>ND(^f)</td>
<td>15.6</td>
<td>ND</td>
<td>125</td>
<td>ND</td>
</tr>
</tbody>
</table>

Nanosilver versus Conventional Silver Materials

Compared to other silver additives, silver nanoparticles generally have:

- Lower antimicrobial activity\(^1\)
- Longer durability
- Less silver needed in a treated article - combination of durability and activity is achieved at lower concentrations

Nanosilver versus Conventional Silver Materials

Compared to other silver additives, silver nanoparticles generally have:

- Lower antimicrobial activity\(^1\)
- Longer durability
- Less silver needed in a treated article - combination of durability and activity is achieved at lower concentrations


Rationale for using nanoscale silver is NOT because of any higher activity! - the reason is longer durability achieved with less silver (sustainability)
Nanoscale Silver – Perspective

- Origins of nanoscale silver and terminology
  - Colloidal silver = nanoscale silver

- Uses of nanoscale silver
  - Used for over 100 years in many areas, many not antimicrobial

- Regulatory status for antimicrobial nanosilver products
  - >50% of EPA registered silver products are based on nanoscale silver

- Value of nanosilver products as antimicrobials (subject to FIFRA)
  - Nanoscale silver has environmental and in-use advantages compared to other silver products
  - Lower absolute antimicrobial activity than other silver forms
Outline

1. Commercial and regulatory history of nanoscale silver

2. Human health perspective

3. Ecological perspective

4. Policy perspective
Human Health Perspective

Two assumptions drive the nanosilver risk narrative:

- Assumption #1: Nanoscale silver is a new material.

- Assumption #2: The current dataset is derived from conventional ‘bulk’ silver (and therefore not applicable to nanoscale silver)
Human Health Perspective

Two assumptions drive the nanosilver risk narrative:

• Assumption #1: Nanoscale silver is a new material.

• Assumption #2: The current dataset is derived from conventional ‘bulk’ silver (and therefore not applicable to nanoscale silver)

Are these assumptions valid?
Human Health Perspective

- Nanoscale silver colloids (Collargol, Argyrol, etc.) have been sold continuously since early 1900s
  - An extensive database of toxicological data is available

- All major ‘conventional’ silver toxicology limits are in fact based on nanoscale silver colloids or ionic silver:
  - EPA drinking water limit
  - OSHA 8 hr inhalation limit
  - Dietary exposure EPA IRIS
Human Health Perspective

• Nanoscale silver colloids (Collargol, Argyrol, etc.) have been sold continuously since early 1900s
  - An extensive database of toxicological data is available

Assumption #1: Nanoscale silver is a new material.

• All major ‘conventional’ silver toxicology limits are in fact based on nanoscale silver colloids or ionic silver:
  - EPA drinking water limit
  - OSHA 8 hr inhalation limit
  - Dietary exposure EPA IRIS

Assumption #2: The current dataset is derived from conventional ‘bulk’ silver (and therefore not applicable to nanoscale silver)
Human Health Perspective

• Nanoscale silver colloids (Collargol, Argyrol, etc.) have been sold continuously since early 1900s
  - An extensive database of toxicological data is available

Assumption #1: Nanoscale silver is a new material.

• All major ‘conventional’ silver toxicology limits are in fact based on nanoscale silver colloids or ionic silver:
  - EPA drinking water limit
  - OSHA 8 hr inhalation limit
  - Dietary exposure EPA IRIS

Assumption #2: The current dataset is derived from conventional ‘bulk’ silver (and therefore not applicable to nanoscale silver)

• Challenge: How well characterized?
## Human Health Perspective

### Particle Sizes of Common Colloidal Silver Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Use</th>
<th>Particle Size (nm)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argyrol</td>
<td>Anti-Infective (early 1900s)</td>
<td>35 nm</td>
<td>DLS Study, NanoHorizons, 2009.</td>
</tr>
<tr>
<td>Collargol</td>
<td>Anti-Infective (early 1900s)</td>
<td>10-20 nm</td>
<td>Muller, 1926 (1). Bogdanchikova, 1992 (2).</td>
</tr>
<tr>
<td>Protargol</td>
<td>Anti-Infective (early 1900s)</td>
<td>2 nm</td>
<td>Bogdanchikova, 1992 (2).</td>
</tr>
</tbody>
</table>


Human Health Perspective

Nanotoxicology in 1926:
Bone Marrow Reactions with Nanoscale Silver


The collargol or colloidal silver employed is said to contain 78 per cent of metallic silver and a small percentage of egg albumin and its oxidation product (11). It is manufactured by the Heyden Chemical Works, and distributed by Schering and Glatz, New York. The size of the particles has been determined by Bechhold (12) to average 20 millimicra (μ), the individual particle consisting of aggregates of metallic silver and the protective colloid. The concentration of the colloidal suspension, which was made up in small doses in sterile distilled water and filtered immediately before use, varied between 0.1 and 2 per cent. Physiological saline as a solvent was tried, but a white precipitate was formed on stand-

“IV administration of small amounts of collargol [20 nm metallic silver particles] produced a stimulation of the endothelium. The animal’s health remained unimpaired and the blood counts were normal.”
Human Health Perspective

Review of Silver Threshold Limits: Inhalation

• All silver exposure limits are based on argyria which is considered a cosmetic condition, not toxic.

• Not all forms of silver have the same propensity to cause argyria.
Human Health Perspective

Review of Silver Threshold Limits: Inhalation

- All silver exposure limits are based on argyria which is considered a cosmetic condition, not toxic.

- Not all forms of silver have the same propensity to cause argyria.

- American Conference of Governmental Industrial Hygienists (ACGIH) has established separate threshold limit values (TLVs) for metallic silver and soluble compounds of silver.

  Dust or fume of metallic silver .......... 0.1 mg/m³

  Soluble silver salts (silver nitrate) ...... 0.01 mg/m³

- “The available data on soluble compounds of silver demonstrate that silver salts have a greater propensity to cause argyria than does the dust or fume of metallic silver.” (ACGIH, 1991).
Human Health Perspective

Nanotoxicology in 1974:
Relative toxicity of nanoscale silver to silver nitrate

• Silver nitrate is 20 times more toxic than colloidal silver when given intraperitoneally.\(^1\)


• “Based on total Ag concentration, toxicity was 18 times higher for \(\text{AgNO}_3\) than for AgNP [silver nanoparticles].”\(^2\)


The historical risk assessment data bridges to present day silver nanoparticles
Human Health Perspective

Review of Silver Threshold Limits: Inhalation

- Question: The ACGIH inhalation TLV of 0.1 mg/m³ applies to silver dust and fumes, but does it adequately reflect the argyria hazard for nanoscale silver?
Review of Silver Threshold Limits: Inhalation

• Question: The ACGIH inhalation TLV of 0.1 mg/m$^3$ applies to silver dust and fumes, but does it adequately reflect the argyria hazard for nanoscale silver?

• Answer: Yes. Ninety-day subchronic inhalation toxicity of 18-19 nm silver nanoparticles was studied in Sprague-Dawley rats and a no observable adverse effect level of 0.1 mg/m$^3$ was determined – in full agreement with existing ACGIH TLV.\(^1\)

The data bridges…. Why?

Human Health Perspective

Inhalation: The data bridges. Why?

Reason #1. Silver dust and fumes are composed largely nanosilver.
Inhalation: The data bridges. Why?

Reason #1. Silver dust and fumes are composed largely nanosilver.

Reason #2. The ACGIH TLV is based on two extensive reviews of argyria from exposure to silver nitrate or nanoscale silver colloid.


(2) Gaul and Staud (1935) Seventy cases of generalized argyria following organic and colloidal silver medication, including biospectrometric analysis of ten cases. AMA 104:1387-1390.
What datasets have EPA and OSHA used to set current exposure limits?

• Referring to Gaul and Staud (1935): “One in 70 [patients] developed argyria after receiving an intravenous dose of 1 gram. This intravenous dose was converted to an oral dose of 0.014 mg/kg/day and was considered a lowest observed effect level. Other patients did not develop argyria until doses five times higher were administered.”

• Referring to Hill and Pillsbury (1939): “Both of the US standards for silver in drinking water and in workplace air have been based on a presumed 1 g minimum dose of silver that has caused argyria.”

2 EPA-440/5-80-071 or PB81-117822 “Ambient water quality criteria for silver” U.S. EPA. 1980.
Summary: Seventy cases of argyria from nanosilver colloidal were reviewed. Data was derived primarily from Argyrol (35 nm) and Collargol (10-20 nm).

Gaul & Staud (1935) is the primary reference for all EPA documents on silver toxicity.
Human Health Perspective

Nanosilver Toxicology: Exposure Summary

The Gaul and Staud (1935) and Hill and Pillsbury (1939) argyria 1 gram threshold value is the basis¹⁻³ for:
- ACGIH’s Inhalation Threshold Limit Value (TLV)
- OSHA Inhalation Permissible Exposure Limit (PEL)
- Mine Safety and Health Administration PEL
- EPA IRIS oral reference dose (RfD)
- EPA Office of Water’s Secondary Maximum Contamination Level

Every major exposure limit set over the last 50 years is based on these 2 reviews of argyria (a non-toxic effect) from nanosilver colloids or soluble silver compounds.

No studies on micron-sized silver powders were referenced. Very little is known about the toxicity of micron-sized silver particles.

² EPA-440/5-80-071 or PB81-117822 “Ambient water quality criteria for silver” U.S. EPA. 1980.
Human Health Perspective

Occupational Exposure:

• Occupational exposure limits for silver are already based on nanosilver materials

• Do more modern studies confirm the earlier limits? .............. YES

• Argyria (non-toxic condition) end-point and exposure limits confirmed by extensive review of silver exposure by NIOSH

Due to improved work conditions, more emphasis on safety and health in the workplace, and better engineering controls, future cases of occupational argyria or argyrosis will be extremely rare. Although the number of occupational epidemiological studies evaluating workers’ exposure to all forms of silver is limited, the fact that silver has been in use for thousands of years and the most notable adverse health effect is argyria and/or argyrosis, additional studies would most likely come to the same conclusions, i.e. metallic silver has minimal effect on the human body and soluble silver compounds are more likely to produce argyria and argyrosis; therefore, separate PELs should be established.

The body’s uptake of silver is often much higher when taken orally as medication, as opposed to occupational exposure, which is predominantly through inhalation. The majority of occupational exposure reports involve soluble silver compounds, which seem to cause toxic effects at lower concentrations than metallic silver and insoluble silver compounds.

For example, silver concentrations in skin biopsies found by Wolbling et al. (1988) and blood-silver concentrations found by Williams and Gardner (1995) and Armitage et al. (1996) were considerably higher in workers exposed to soluble silver compounds than in workers exposed to metallic silver or insoluble silver compounds.

### Human Health Perspective

**Table 2. Health effects associated with various forms of silver**

<table>
<thead>
<tr>
<th>Source of silver</th>
<th>Outcome and/or health effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Silver nitrate—oral ulceraions</td>
<td>Argyria</td>
<td>Auseth et al., 1981; Lee and Lee, 1994</td>
</tr>
<tr>
<td>Silver nitrate—topical for gingival bleeding</td>
<td>Argyria, silver deposits in organs², and abdominal pain</td>
<td>Marshall and Schneider, 1977</td>
</tr>
<tr>
<td>Silver nitrate solution—venous veins</td>
<td>Argyria</td>
<td>Shelley et al., 1987</td>
</tr>
<tr>
<td>Silver acetate—antismoking gum, lozenges, and tablets</td>
<td>Argyria</td>
<td>Jensen et al., 1988; Meclntyre, 1978; Van Garsse and Versieck, 1995</td>
</tr>
<tr>
<td>Colloidal silver protein—allergy and cold mediated</td>
<td>Argyria</td>
<td>Guibranoson et al., 2000</td>
</tr>
<tr>
<td>Colloidal silver protein—treatment of ailments</td>
<td>Argyria</td>
<td>White et al., 2003</td>
</tr>
<tr>
<td>Silver protein—nose drops</td>
<td>Argyria</td>
<td>Jacobs, 1998</td>
</tr>
<tr>
<td>Colloidal protein—eye drops</td>
<td>Argyrosis</td>
<td>Loeffer and Lee, 1987</td>
</tr>
<tr>
<td>Colloidal silver and silver compounds</td>
<td>Argyria, argyrosis</td>
<td>Hill and Pillsby, 1939</td>
</tr>
<tr>
<td>Silver coated pills—mouth freshener</td>
<td>Argyrosis</td>
<td>Sato et al., 1999 (case 1)</td>
</tr>
<tr>
<td>Silver coated acupuncture needles</td>
<td>Argyrosis</td>
<td>Sato et al., 1999 (case 2)</td>
</tr>
<tr>
<td>Silver in water—hemodialysis therapy</td>
<td>Argyria</td>
<td>Sue et al., 2001</td>
</tr>
<tr>
<td><strong>Occupational</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soluble</td>
<td>Elevated blood-silver levels</td>
<td>Armitage et al., 1996</td>
</tr>
<tr>
<td>Soluble</td>
<td>Argyrosis, elevated blood-silver levels</td>
<td>Williams, 1999</td>
</tr>
<tr>
<td>Soluble</td>
<td>Argyrosis, abdominal pain</td>
<td>Rosenman et al., 1979</td>
</tr>
<tr>
<td>Soluble</td>
<td>Argyrosis, abdominal pain², nonbleed³, respiratory irritation, allergic response</td>
<td>Rosenman et al., 1979</td>
</tr>
<tr>
<td>Soluble</td>
<td>Argyria, ocular argyrosis</td>
<td>Moss et al., 1979</td>
</tr>
<tr>
<td>Soluble</td>
<td>Argyria, argyrosis</td>
<td>Wobling et al., 1988 (soluble group)</td>
</tr>
<tr>
<td>Soluble</td>
<td>Argyrosis</td>
<td>Williams and Gardner, 1995 (case 2)</td>
</tr>
<tr>
<td>Soluble</td>
<td>Argyrosis</td>
<td>Buckley, 1963</td>
</tr>
<tr>
<td>Metallic</td>
<td>Argyrosis-sclerotic of the lungs</td>
<td>Barrie and Hurding, 1947</td>
</tr>
<tr>
<td>Metallic</td>
<td>No health effects</td>
<td>Limet and Bradford, 1986</td>
</tr>
<tr>
<td>Insoluble</td>
<td>Severe circulatory and respiratory symptoms²</td>
<td>Forzycki et al., 1983</td>
</tr>
<tr>
<td>Insoluble</td>
<td>Argyrosis</td>
<td>Pifer et al., 1989</td>
</tr>
<tr>
<td>Insoluble</td>
<td>No health effects</td>
<td>DiVincenzo et al., 1985</td>
</tr>
<tr>
<td>Insoluble</td>
<td>No health effects</td>
<td>Bonesdach, 1995</td>
</tr>
<tr>
<td>Insoluble</td>
<td>No health effects</td>
<td>Williams and Gardner, 1995 (case 1)</td>
</tr>
<tr>
<td>Insoluble</td>
<td></td>
<td>Wobling et al., 1998 (insoluble group)</td>
</tr>
</tbody>
</table>

¹ Organs involved were liver, spleen, intestines and pancreas.
² Effects thought to be caused by cadmium, not silver.
³ Injuries appeared to be due to inadequate ventilation, not the toxic effects of metallic silver vapors.

---

- Data over period of 8 decades
- Nanoscale silver materials were encountered in both medicinal and occupational (inhalation) settings.
  - Colloidal (nano) silver
  - Metallic dusts & fumes (nano)
- End-point is argyria
- Soluble silver salts as worst-case scenario

---

Human Health Perspective

Summary:

- EPA has registered silver nanoparticles over a period of 6 decades
  - Colloidal silver algacides
  - Silver-carbon water filters
  - Nanosilver disinfectants
  - Antimicrobial additives

- This long history of regulated use in a wide range of applications, coupled with the extraordinarily low rate of recorded incidents, suggests that EPA and other regulatory bodies have adequately managed risks associated with commercial applications of silver nanoparticles.

- Newer studies on ‘nanosilver’ reveal no significant new risks because the database used for the last 50+ years is derived from studies of ionic or nanoscale silver. Data is not derived from conventional silver.
Outline

1. Commercial and regulatory history of nanoscale silver
2. Human health perspective
3. Ecological perspective
4. Policy perspective
Ecological Perspective

- Two primary aspects regarding ecological risk assessment for silver nanoparticles:
  - Eco-Exposure
  - Eco-Toxicity
Ecological Perspective

• Two primary aspects regarding ecological risk assessment for silver nanoparticles:
  - Eco-Exposure
  - Eco-Toxicity
Eco-Exposure

- Textiles functionalized with silver bring many benefits
- Are silver nanoparticles released from functionalized textiles during laundry?
- 3 studies have characterised the potential for release from textiles:
  - Benn & Westerhof (2008)
  - Geranio, Heuberger & Nowack (2009)
  - Delattre & Height (2009)
Eco-Exposure: Benn & Westerhoff

- Seven commercially available silver socks were washed under aggressive conditions\(^1\)
- Silver particle and ionic silver release was measured

<table>
<thead>
<tr>
<th>Sock Style</th>
<th>EPA Reg</th>
<th>Silver in Sock</th>
<th>Silver Nanoparticle Released?</th>
<th>Silver Ion Conc (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lounge Sock (Green)</td>
<td>?</td>
<td>ü</td>
<td>Yes</td>
<td>836</td>
</tr>
<tr>
<td>Lounge Sock (Blue)</td>
<td>?</td>
<td>ü</td>
<td>No</td>
<td>1845</td>
</tr>
<tr>
<td>Athletic Sock (White)</td>
<td>?</td>
<td>ü</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>FoxRiver / X-Static</td>
<td># 70927-1</td>
<td>ü</td>
<td>Yes</td>
<td>165</td>
</tr>
<tr>
<td>Arctic Shield / Additive SSB</td>
<td># 83587-3</td>
<td>ü</td>
<td>No</td>
<td>below detection</td>
</tr>
<tr>
<td>Basketball Sock</td>
<td>?</td>
<td>ü</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Casual Black Sock</td>
<td>?</td>
<td>ü</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

- Silver nanoparticle socks (Additive SSB EPA 83587-3) no nanoparticle release
- “conventional bulk silver” (X-Static EPA 70927-1) released nanoparticles

Silver functionalized socks were washed with mechanically aggressive washing method with and without presence of bleaching agents. Silver particle and ionic silver release was measured.

“A conventional silver textile did not show any significant difference in the size distribution of the released silver compared to many of the textiles containing nano-Ag.”

“These results have important implications for the risk assessment of Ag-textiles and also for environmental fate studies of nano-Ag, because they show that under conditions relevant to washing, primarily coarse (>450nm) Ag-containing particles are released.”

Mechanical stress abrades textile (normal wear)
Released silver particles are contained within larger (non-nano) matrix
No difference between conventional and nano silver textiles

---

Eco-Exposure: Delattre & Height

- Investigation of silver nanoparticle leaching from textile substrates during laundry\(^1\)
- Method based on Benn et al.\(^2\), suggested by EPA as suitable basis for assessing release potential

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Description</th>
<th>Silver functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Polyester reference fabric</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Polyester with silver inside coating layer</td>
<td>HeiQ AGS-20 TF</td>
</tr>
<tr>
<td>3</td>
<td>Polyester with silver inside fibers</td>
<td>HeiQ AGS-20 MB</td>
</tr>
<tr>
<td>4</td>
<td>Arctic Shield sock (used in Benn et al paper(^3))</td>
<td>NanoHorizons Additive SSB**</td>
</tr>
</tbody>
</table>

** NanoHorizons Additive SSB is a nanosilver material registered by EPA under registration number 83587-3.

- No release of silver nanoparticles
- All 3 treated fabrics also tested in the Geranio et al.\(^3\) study with same finding
- NanoHorizons fabric also tested in Benn et al.\(^2\) study with same finding

---


Eco-Exposure: Textiles

- Textile laundry studies have examined the potential for release of silver nanoparticles during laundering of functionalized textiles
  - No difference in silver particle release between textiles treated with conventional or nanoscale silver
  - Mechanical abrasion (wear) from washing typically abrades large (>450nm) portions of textile matrix. Silver particles are integrated in this larger matrix.
  - Particle release behavior not influenced by washing agents such as bleach
  - Results consistent for 3 fabrics tested between 2 peer reviewed papers

- Best practice textile functionalization gives very high securing of silver nanoparticles
- Data supports a very low risk of eco-exposure from silver nanoparticle functionalized textiles
Ecological Perspective

- Two primary aspects regarding ecological risk assessment for silver nanoparticles:
  - Eco-Exposure
  - Eco-Toxicity
Eco-Toxicity

- Silver is well known to be strongly passivated by natural environmental complexing agents such as sulfur, chlorides, phosphate and dust\textsuperscript{1,2}.

"Silver from products used for swimming pool and human drinking water systems is discharged into the municipal wastewater effluent and treated in municipal water treatment plants. In these sewage treatment plants, microorganisms convert silver (I) into insoluble silver sulfides…"\textsuperscript{2}


- Recent research shows same phenomena holds for silver nanoparticles.

"Silver nanoparticles may continuously changes their forms/sizes in the sewer pipes and the WWTPs through oxidation, dissolution and complexation…Nanosilver may complex with sulfide in the pipe to reduce its toxicity."\textsuperscript{3}


- New findings agree with 1993 Silver RED

\textsuperscript{2} EPA Re-registration Eligibility Document for Silver, Case 4082 (1993).
Eco-Toxicity

- Silver is well known to be strongly passivated by natural environmental complexing agents such as sulfur, chlorides, phosphate and dust\(^1,2\).

“Silver from products used for swimming pool and human drinking water systems is discharged into the municipal wastewater effluent and treated in municipal water treatment plants. In these sewage treatment plants, microorganisms convert silver (I) into insoluble silver sulfides…”\(^2\)


- Recent research shows same phenomena holds for silver nanoparticles.

“Silver nanoparticles may continuously changes their forms/sizes in the sewer pipes and the WWTPs through oxidation, dissolution and complexation...Nanosilver may complex with sulfide in the pipe to reduce its toxicity.”\(^3\)


- New findings agree with 1993 Silver RED

---

Eco-Toxicity

• Silver is well known to be strongly passivated by natural environmental complexing agents such as sulfur, chlorides, phosphate and dust\(^1,2\).

“Silver that does manage to make its way to a WWTP from Ag-containing materials will most likely be in the form of AgCl.... This is important because AgCl is one of the most insoluble chloride salts known and much less reactive than elemental Ag.”

U.S. EPA, National Risk Management Research Lab (C. Impellitteri et al.\(^1\))

“recent research suggests that the environmental risk from nanoscale Ag particles is low”\(^1\)

U.S. EPA, National Risk Management Research Lab (C. Impellitteri et al.\(^1\))

• Real environmental conditions of complexing and speciation is fundamental to the low eco-toxicity of silver
• Research suggests silver nanoparticles behave in same way as conventional silver

Eco-Toxicity

- Historical perspective is available
- Nanoscale silver has been used in direct fresh and wastewater contact for decades:
  - Algaecides for swimming pools
  - Drinking water filters
Eco-Toxicity

- Historical perspective is available
- Nanoscale silver has been used in direct fresh and wastewater contact for decades:
  - Algaecides for swimming pools
  - Drinking water filters

“Silver from products used for swimming pool and human drinking water systems is discharged into the municipal wastewater effluent and treated in municipal water treatment plants. In these sewage treatment plants, microorganisms convert silver (I) into insoluble silver sulfides…”


- EPA has examined the real-life impact of these nanosilvers in detail (even though nano terminology was not used at the time)
- Treated products such as textiles logically have far lower potential to cause harm than these established water-contact products that have in-fact been used safely for decades

\(^1\) EPA Re-registration Eligibility Document for Silver, Case 4082 (1993).
Outline

1. Commercial and regulatory history of nanoscale silver
2. Human health perspective
3. Ecological perspective
4. Policy perspective
Policy Perspective

- Objective of all stakeholders:
  - Ensure products pose no “unreasonable adverse effects to human health or the environment”\(^1\).

- How to rationally assess risk for nanoscale silver?

\(^1\) EPA, “FIFRA Scientific Advisory Panel Background Paper”, (2009)
Policy Perspective

- Objective of all stakeholders:
  - Ensure products pose no “unreasonable adverse effects to human health or the environment”\(^1\).

- How to rationally assess risk for nanoscale silver?

- Key considerations:
  1. Nanoscale silver is not a new material
  2. Nanoscale silver offers real benefits to many applications
  3. Nanoscale silver has lower antimicrobial activity compared to many silver forms
  4. Nanoscale silver has been registered and used in real-life for decades
  5. Established data on key toxicity parameters exists

\(^1\) EPA, “FIFRA Scientific Advisory Panel Background Paper”, (2009)
Policy Perspective

• Objective of all stakeholders:
  – Ensure products pose no “unreasonable adverse effects to human health or the environment”\(^1\).

• How to rationally assess risk for nanoscale silver?

• Key considerations:
  1. Nanoscale silver is not a new material
  2. Nanoscale silver offers real benefits to many applications
  3. Nanoscale silver has lower antimicrobial activity compared to many silver forms
  4. Nanoscale silver has been registered and used in real-life for decades
  5. Established data on key toxicity parameters exists

• Terminology has changed to nano, the material involved is the same (for over a century!)
• Where are the real data gaps if any?

\(^1\) EPA, “FIFRA Scientific Advisory Panel Background Paper”, (2009)
Policy Perspective

• SNWG member companies have generated independent data:
  – Acute toxicity (GLP, OECD methods)
    • No oral, dermal, inhalation toxicity
    • No skin or eye irritation
    • No skin sensitization
  – Environmental fate and life cycle analysis studies
  – Textile exposure studies
  – Wastewater treatment compatibility studies
  – Occupational exposure studies
  – etc.

• All submitted to EPA to aid in risk assessment efforts

• Independent expert assessments (eg. Oekotex)

• Industry has been and continues to be pro-active in stewardship on human health and environment
Policy Perspective

• How is EPA able to manage risk?

• EPA has many robust risk mitigation capabilities for silver:
  - Mandatory reporting of product production and inventory
  - Requirement to report incidents or health effects (EPA OPP IDS)
  - Strict label requirements eg. “Do not discharge into estuaries”
  - Re-registration review process to update and evaluate risk through data generation by all registrants
Policy Perspective

• How is EPA able to manage risk?

• EPA has many robust risk mitigation capabilities for silver:
  - Mandatory reporting of product production and inventory
  - Requirement to report incidents or health effects (EPA OPP IDS)
  - Strict label requirements eg. “Do not discharge into estuaries”
  - Re-registration review process to update and evaluate risk through data generation by all registrants

• Nanoscale silver is best considered under existing re-registration framework of all silver registrants:
  - Opportunity for equitable market access
  - Distribution of costs for data generation
  - Restrict any animal testing to absolute minimum

• Best path for achieving reasonable outcome for all stakeholders
EPA Submission & Charge Questions

• The Silver Nanotechnology Working Group (SNWG) has provided a written submission\(^1\) to the SAP docket that addresses the following areas:

1. A detailed analysis of the EPA background paper and cited documents\(^2\)
2. A detailed response to each of the 4 charge questions posed to the SAP

• The SNWG invites the panel members to consider the above documents in tandem with this presentation when advising the EPA on how to proceed

---


The Silver Nanotechnology Working Group (SNWG) has provided a written submission\(^1\) to the SAP docket that addresses the following areas:

1. A detailed analysis of the EPA background paper and cited documents\(^2\)

2. A detailed response to each of the 4 charge questions posed to the SAP

The SNWG invites the panel members to consider the above documents in tandem with this presentation when advising the EPA on how to proceed.

The SNWG thanks the Scientific Advisory Panel and the EPA for the opportunity to make this presentation and contribute to the process of achieving a rational risk assessment of nanoscale silver.

---


Contact

Silver Nanotechnology Working Group (SNWG)

Rosalind Volpe, D.PH
Executive Director

1822 E NC Hwy 54
Suite 120
Durham, NC 27713
Phone: (919) 361-4647 ext. 3023
Email: rvolpe@caa.columbia.edu
www.silverinstitute.org