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

S N W G
Silver Nanotechnology
Working Group

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.*

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN CONSULTATION MEETING
November 3 - 6, 2009
Arlington VA

Also refer to docket submission:

JL.Delattre, R.Volpe, "Comments of The Silver Nanotechnology Working Group for Review by The FIFRA Scientific Advisory Panel", SNWG (2009).

Outline

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

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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 methods[1]:
  - Liquid phase reduction reactions
  - Electrolytic methods
  - Vapor methods
  - Mechanical milling
  - etc.

[1] A.Ede,"The rise and decline of colloid science in North America, 1900-1935. The neglected dimension", *Science, Technology and Culture 1700-1945 series,* Ashgate Publishing (2007).

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

[1] A.Ede,"The rise and decline of colloid science in North America, 1900-1935. The neglected dimension", *Science, Technology and Culture 1700-1945 series,* Ashgate Publishing (2007).

Nanoscale Silver - Origins

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ca.1907	Dialysis (relative permeability)[3]
ca.1917	Electrophoresis (motion in electric field)[4]
ca.1923	Ultracentrifuges (sedimentation correlation to particle size)[5,6]

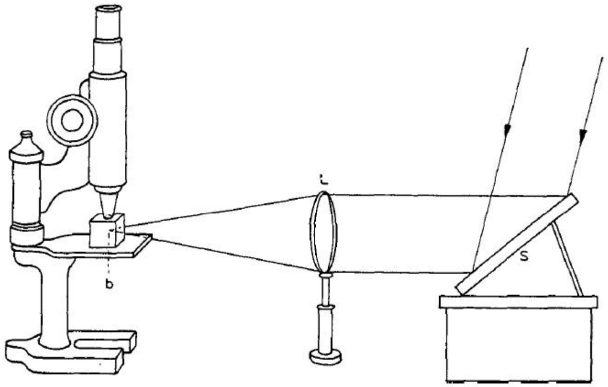

Fig. I. The first arrangement for making ultramicroscopic particles visible. **[2]**

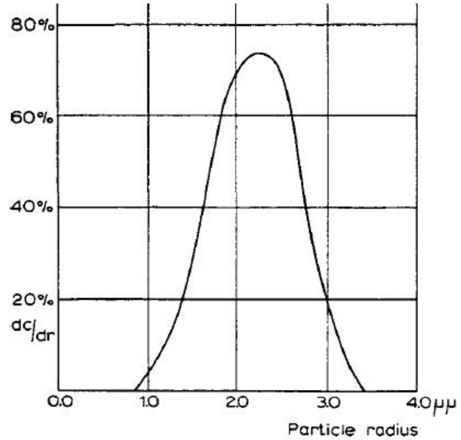

Fig. 9. The particle distribution in a highly disperse gold colloid, calculated from the graph in Fig. 8 (according to H. Rinde). **[6]**

[1] H.Siedentopf, R.Zsigmondy, „Über Sichtbarmachung und Grössenbestimmung ultramikroskopischer Teilchen, mit besonderer Anwendung auf Goldrubingläser“, *Annalen der Physik* 10 (1903) pp1-10.
[2] R.Zsigmondy, “Properties of colloids”, *Nobel Lecture*, December 11 (1926).
[3] H.Bechhold, “Die Gallertfiltration”, *Zeitschrift für Chemie und Industrie der Kolloide*, 2(1) (1907) pp3-9.
[4] TR, Briggs, “Electrical endosmose I”, *Journal of Physical Chemistry*, 21(3) (1917) pp198–237.
[5] T.Svedberg, JB.Nichols, “Determination of size and distribution of size of particles by centrifugal methods”, *Journal American Chemistry Society*, 45 (1923) pp2910-17.
[6] T.Svedberg, “The ultracentrifuge”, *Nobel Lecture*, May 19 (1927).

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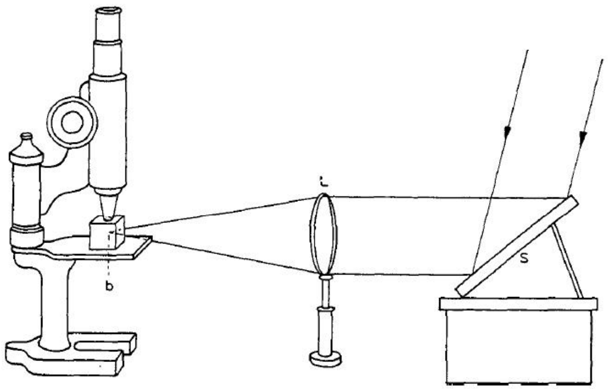

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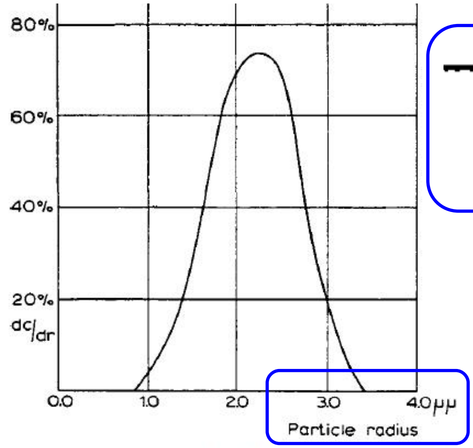

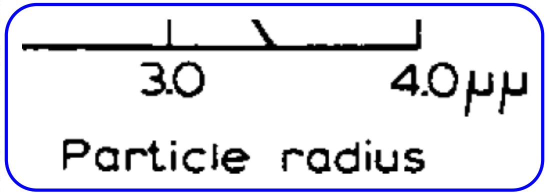

4 μμ = 4 x10^{-9} m
= 4 nm
Millimicron (μμ) = nanometer (nm)

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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 100nm

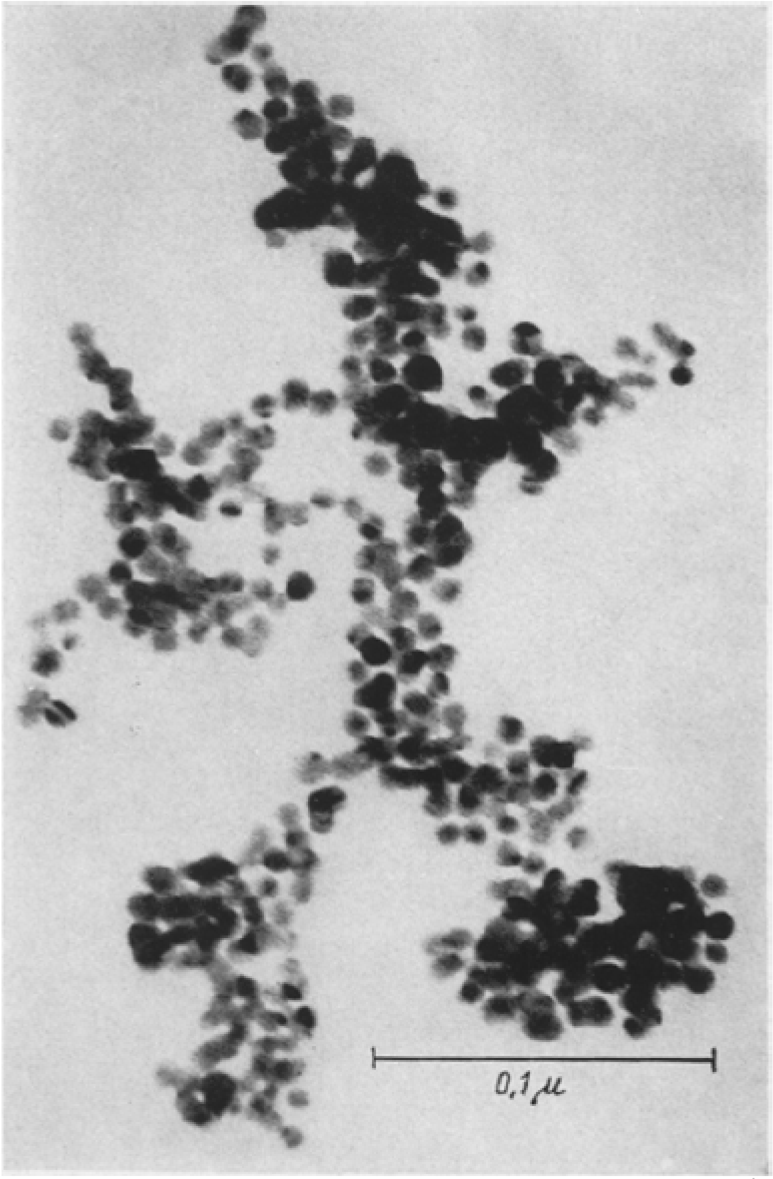

Fig. 1. Electron micrograph of a *Carey Lea* silver sol **[2]**

[1] MC. Lea, "On Allotropic Forms of Silver", *American Journal of Science*, 37 (1889) 476.

[2] G.Frens, J.Th.G.Overbeek, "Carey Lea's colloidal silver", *Kolloid-Zeitschrift und Zeitschrift für Polymere*, 233(1-2) (1969) pp922-929.

Nanoscale Silver - Origins

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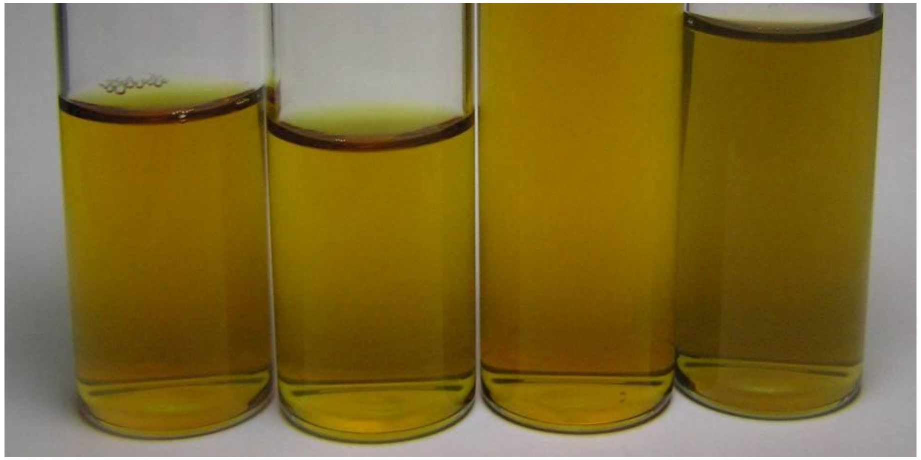
- Silver particles in the nano size range show a yellow/brown color[1]
- This color derives from the surface plasmon effect and is a unique identifier of silver metal particles in the nano size range[2]
- Colloidal silver shares same silver metal properties as silver nanoparticles[1,2]

4 different colloidal silver commerical products



Yellow/brown color is a scientifically well-established characteristic of silver nanoparticles

Size (DLS)[3]	**35 nm**	**20–110 nm**	**25-95 nm**	**2 nm**

All show nano size range

[1] A.Moores, F.Goettmann "The plasmon band in noble metal nanoparticles: an introduction to theory and applications", *New Journal of Chemistry*, 30 (2006) pp1121-1132.
[2] VK.Sharma, RA.Yngard, Y.Lin, "Silver nanoparticles: green synthesis and their antimicrobial activites", *Advances in Colloid Science and Interface Science*, 145 (2009) pp83-96.
[3] Photographs and Dynamic light scattering (DLS) data courtesy of *NanoHorizons Inc*

Nanoscale Silver - Origins

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- Colloidal silver = silver nanoparticles?

	Colloidal silver	Silver nanoparticles
*Engineered?**	Yes. Rationally synthesized	Yes. Rationally synthesized
*Size range?***	1 through 100 nm (μμ) [1]	1 through 100 nm [2]
Size distribution?	Wide range possible	Wide range possible
Character?	Silver metal	Silver metal
Color?	Brown/yellow color	Brown/yellow color

[1] A.Ede,"The rise and decline of colloid science in North America, 1900-1935. The neglected dimension", *Science, Technology and Culture 1700-1945 series,* Ashgate Publishing (2007).
[2] EPA," Nanotechnology White Paper", (2007).
* 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.

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- 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.

[1] A.Ede,"The rise and decline of colloid science in North America, 1900-1935. The neglected dimension", *Science, Technology and Culture 1700-1945 series,* Ashgate Publishing (2007).
[2] EPA," Nanotechnology White Paper", (2007).
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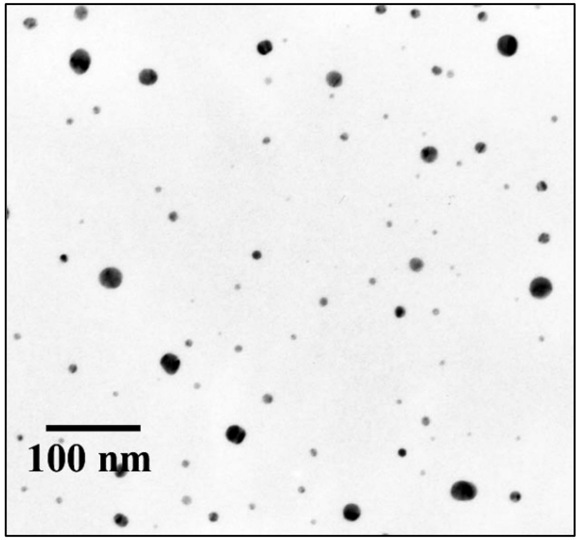
Nanoscale Silver – Historical Use

- 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]



Carey Lea colloidal silver **[3]**

[1] MC. Lea, "On Allotropic Forms of Silver", *American Journal of Science*, 37 (1889) 476
[2] D.Whitcomb, "Mathew Carey Lea: Chemist, photographic scientist", *Chemical Heritage Newsmagazine*, 24(4) (2006/7).
[3] DR.Whitcomb, "Nanosilver Particles in Medical X-ray Diagnostic Films", Eastman Kodak Company (2005). www.particlesociety.org/Whitcomb.pdf

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

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- Many EPA registered nanosilver products over 6 decades[1]

[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

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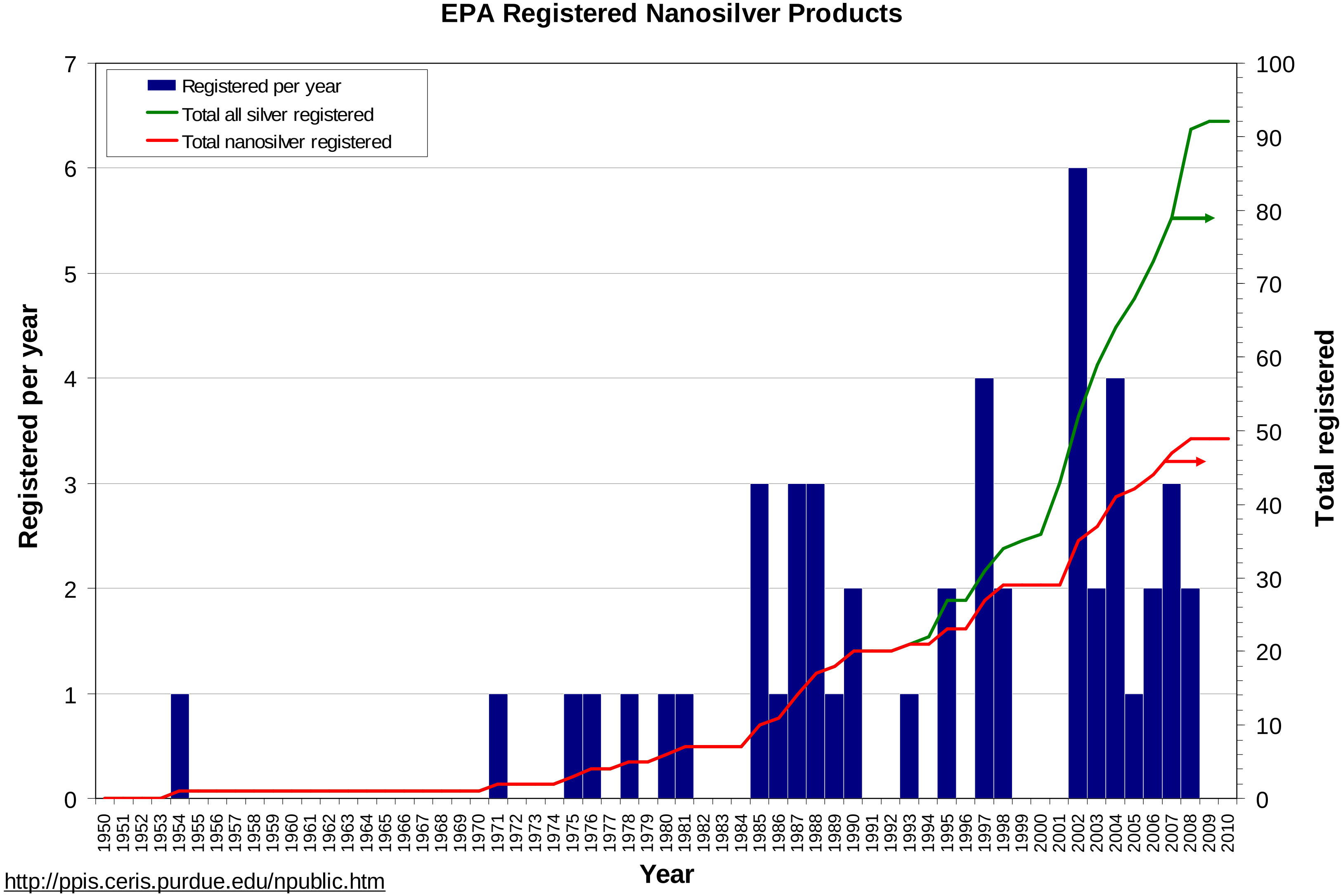

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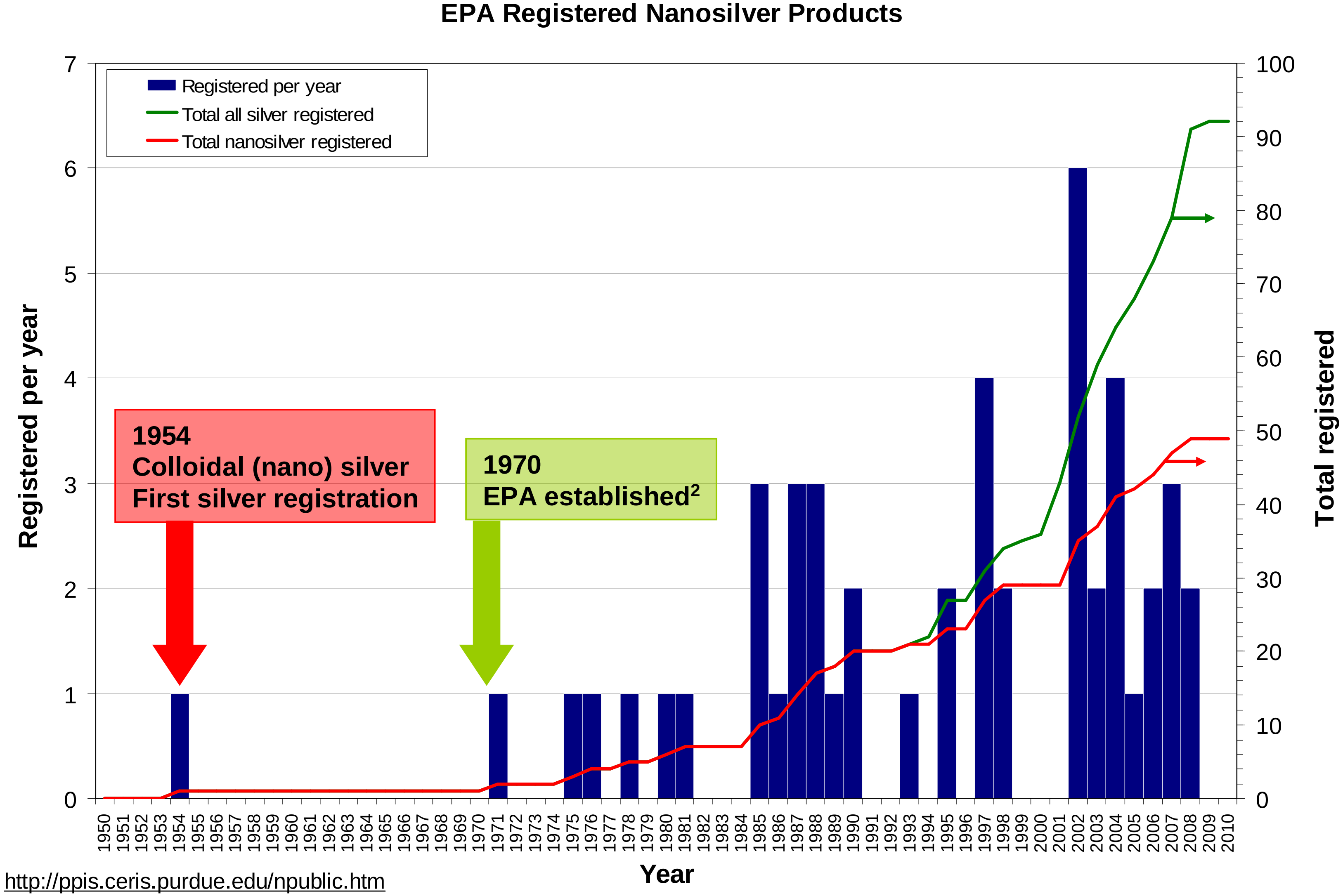

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[2] http://www.epa.gov/history/index.htm

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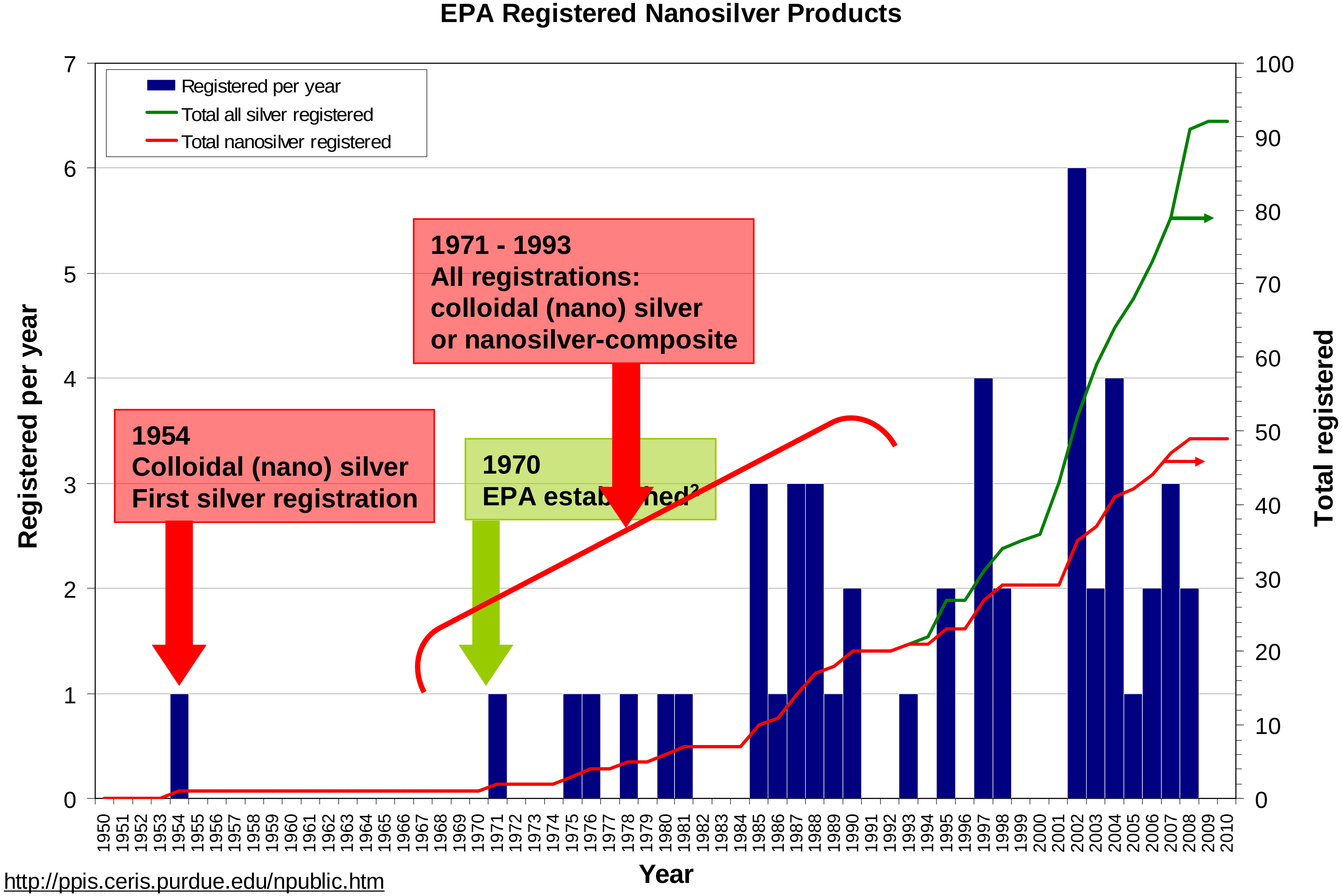

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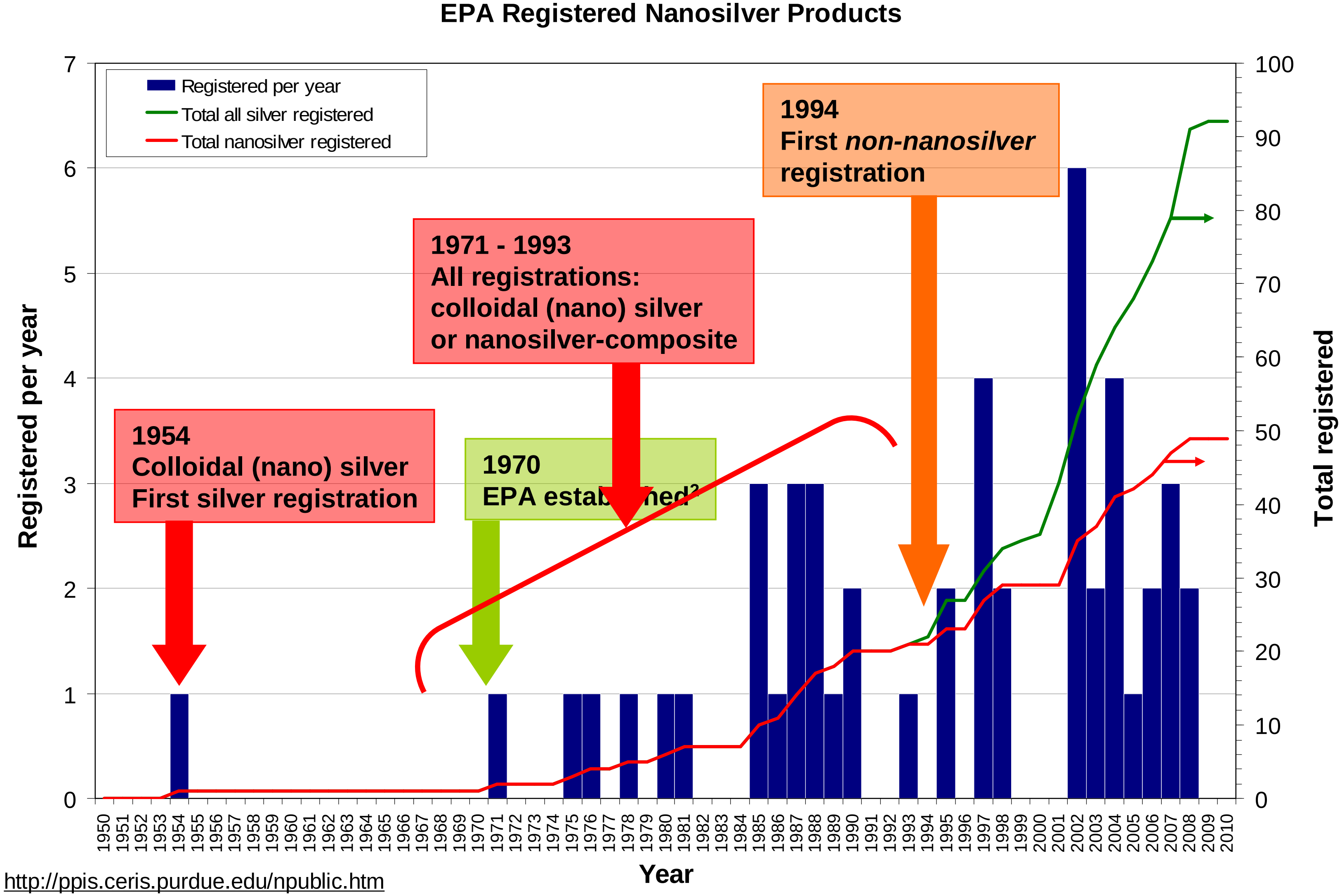

[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm
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Nanosilver Algaecides

EPA-Registered Since 1954*

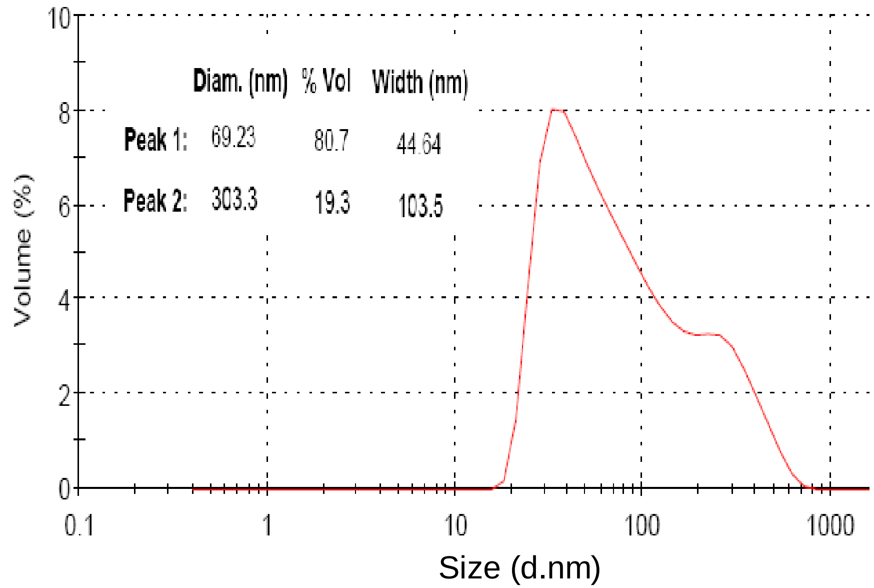
Product: Silver Algaedyn

Particle size: **20-110 nm**

FIFRA Reg # 68161-1

Type: 0.8% Colloidal Silver

First Registered: 12/31/**1954**[1]



[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 database[1]

Nanosilver Algaecides

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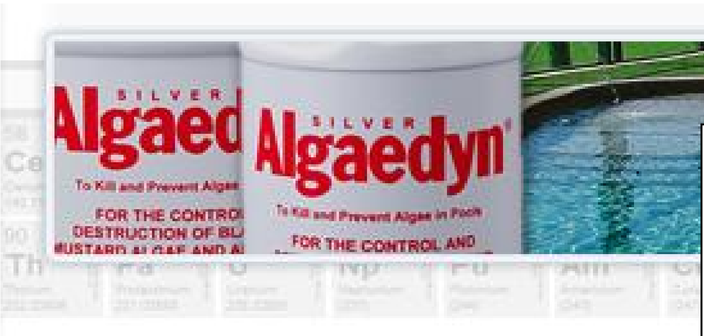

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FIFRA Reg # 68161-1

Type: 0.8% Colloidal Silver

First Registered: 12/31/**1954**[1]

2,927,052

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

[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 database[1]

[3] ZV.Moudry, "Process of Producing Oligodynamic Metal Biocides", United States Patent, **US2927052** (Application date 1953).

Nanosilver Algaecides

EPA-Registered Since 1993

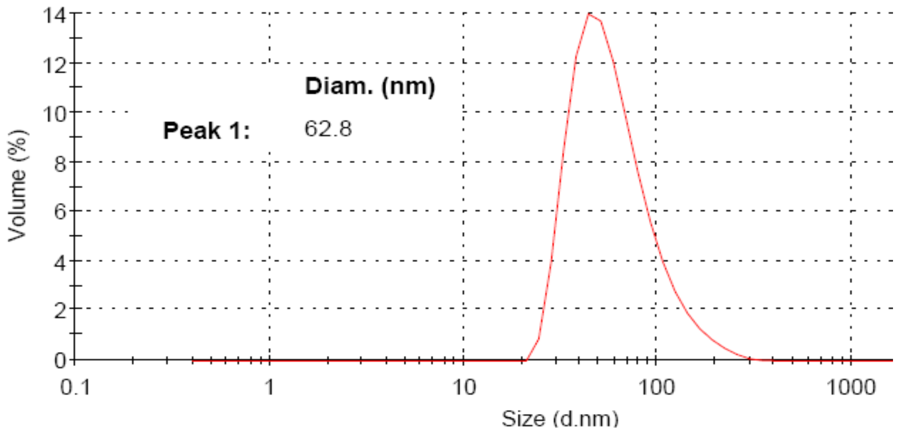
Product: nu-clo Silvercide

Particle size: **25-95 nm**

FIFRA Reg # 7124-101

Type: 0.8% Colloidal Silver

First Registered: 6/15/**1993**[1]



[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm
Dynamic light scattering (DLS) data courtesy of *NanoHorizons Inc*.

Nanoscale Silver-Impregnated Carbon

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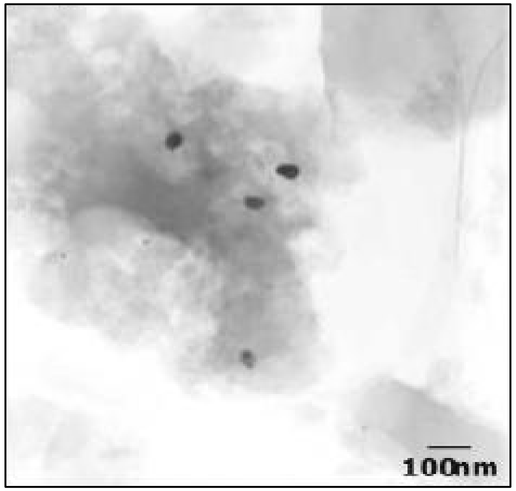
EPA-Registered Nanoscale Silver-Impregnated Carbon Filter Media

- 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



Ryu et al.[2]

"…for proper efficiency, the silver must be dispersed as particles of colloidal size (less than 250 Å [25 nm] in crystallite size…)"[1]

Examples:

FIFRA Reg #s	First registered
58295-1	12/01/**1988**[3]
58295-2	11/01/**1989**[3]
58295-3	01/16/**1990**[3]

[1] U.S. Patent #3,374,608 **(1968).** "*Silver Impregnated Carbon*", Assigned to Pittsburgh Activated Carbon Co. (now Calgon Carbon)
[2] S.K.Ryu, S.Y.Eom, T.H.Cho, D.D.Edie, "*Distribution of Silver Particles in Silver-containing Activated Carbon Fibers*", *Carbon Science*, 4(4), 168-174 (**2003**).
[3] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

Nanosilver Disinfectants

EPA-Registered Nanosilver Disinfectants: American Biotech Labs

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

Product: ASAP-AGX-32
Particle size: **10-50 nm**
FIFRA Reg # 73499-2
Type: 0.032% Silver
First Registered: 4/23/**2003**[1]

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

William D. Moeller, President, American Biotech Laboratories
*Testimony on Malaria before the U.S. House of Representatives, International Relations Committee, Subcommittee on Africa, Global Human Rights, and International Operations, April 26, **2005**.*

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

Keith Moeller, VP Marketing, American Biotech Laboratories
*ABL press release, Tuesday November 28, **2006***.
http://www.azom.com/news.asp?newsID=14717

[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"[1]

Product: H2Pro™ Maintenance Treatment
Particle size: **1- 500 nm** (est)
FIFRA Reg # 75829 -1
Type: 0.0015% Silver
First Registered: 9/9/**2004**[2]

[1] http://www.garrisondental.com/

[2] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

Nanosilver Antimicrobials

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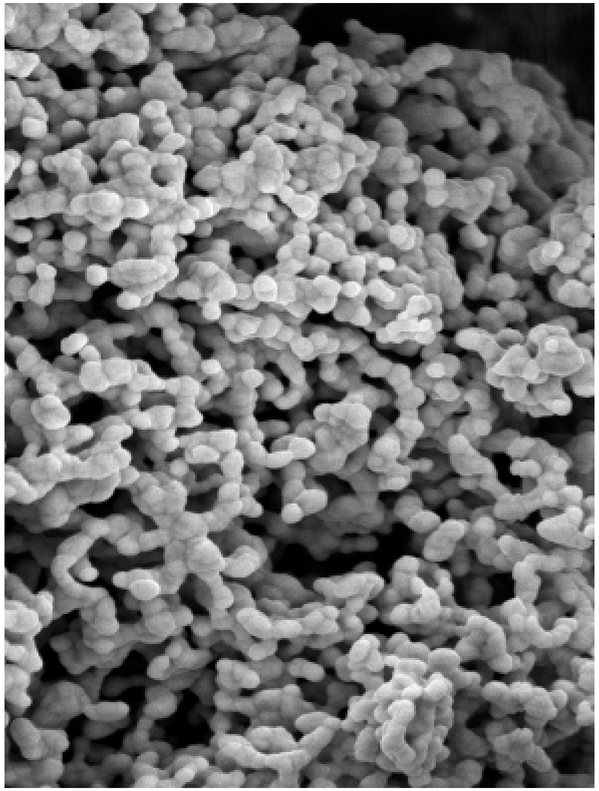
EPA-Registered Antimicrobial Additives: Ciba / Bio-Gate

Ciba

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**[1]

Bio Gate

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**[1]



Press Release: "Ciba Specialty Chemicals forms marketing cooperation with Bio−Gate for silver antimicrobial technology" 14.12.2005, Basel, Switzerland.

[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

Nanosilver Antimicrobials

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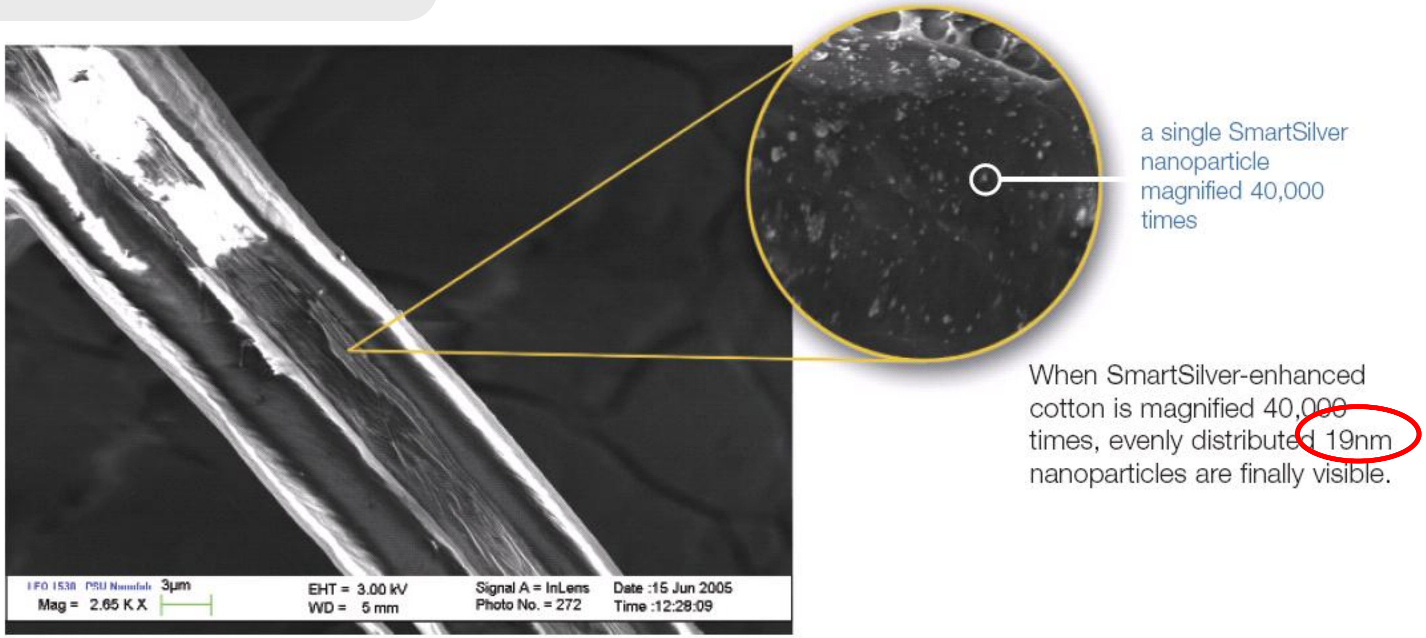
EPA-Registered Antimicrobial Additives: NanoHorizons

Product: Additive SSB
Particle size: **10 - 20 nm**
FIFRA Reg # 83587-3
Type: 100% Silver
First Registered: 09/28/**2007**[1]

NanoHorizons

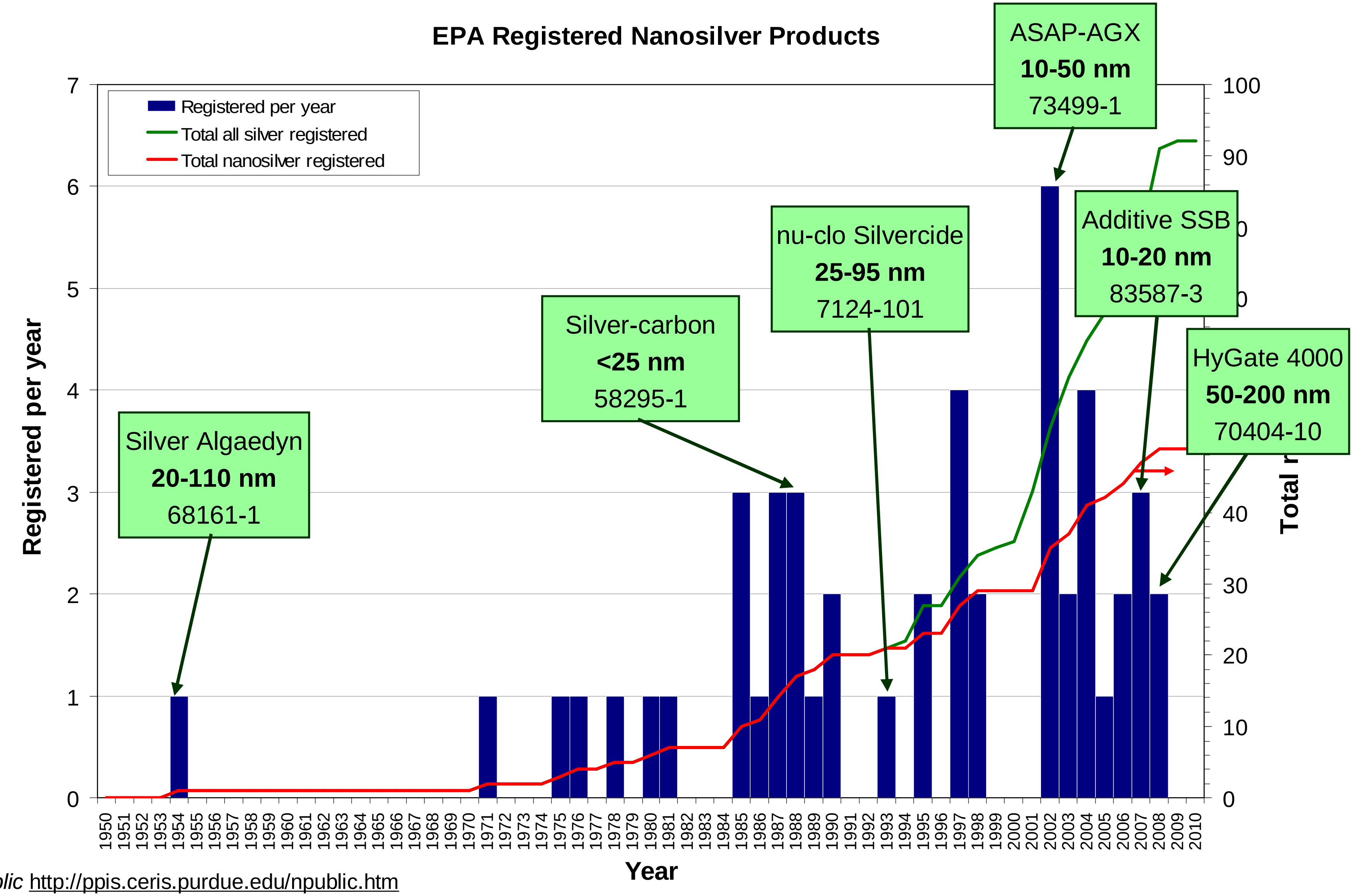


NanoHorizons brochure (2006).

[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

EPA Registered Nanosilver products

- Many FIFRA registered nanosilver products over 6 decades[1]



[1] *NPIRS Public* http://ppis.ceris.purdue.edu/npublic.htm

FDA-Approved Nanosilver Products

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- 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

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- The low risk of human toxicity and the benefits of nanoscale silver and are widely recogised 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.

borious, 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.

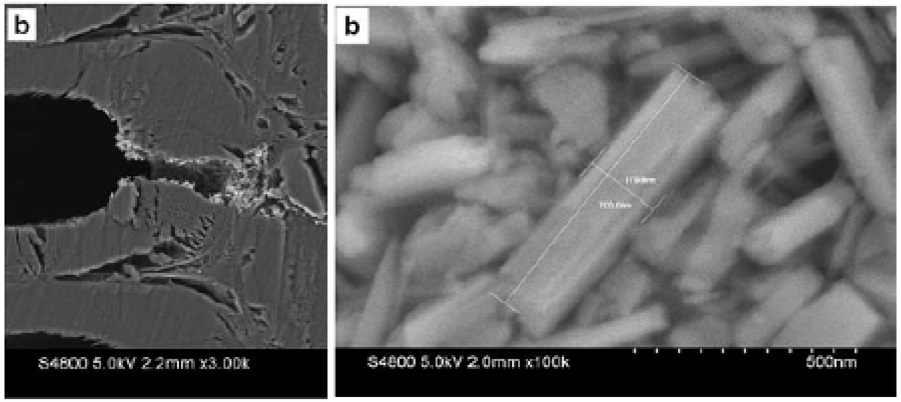
Silver has long been used as an anti-microbial **[1]**

[1] R.Burrell, "Engineering Materials Achievement Award Nanosilver Wound Dressing", *Advanced Materials & Processes*, Volume 167, Issue 10 (October 2009) p24.

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**[1]



"…Micronized copper wood preservatives are the latest generation wood preservative systems in which very small (sub-micron) particles of solid copper"[1]

The copper particle size used in the micronized copper products average about 300 nm. Particles <80 nm penetrate the wood.[2]

Cited in EPA Green Chemistry Awards.[3]

1 http://www.treatedwoodtruth.com/Treated-Wood-Information-on-Osmose-MicroPro-Lumber.php
2 "Microdistribution of copper-carbonate and iron oxide nanoparticles in treated wood." H. Matsunaga, M. Kiguchi, P. Evans. J Nanopart Res. 11,5. 1087-1098 (2009).
3 http://www.epa.gov/greenchemistry/pubs/docs/award_entries_and_recipients2007.pdf

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:

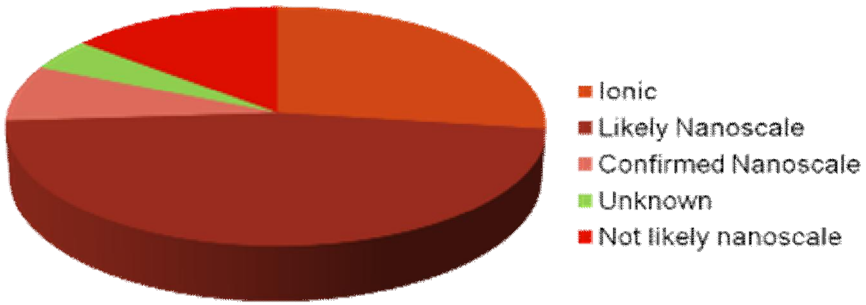
First FDA approved nanocrystalline silver wound care devices are approved

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



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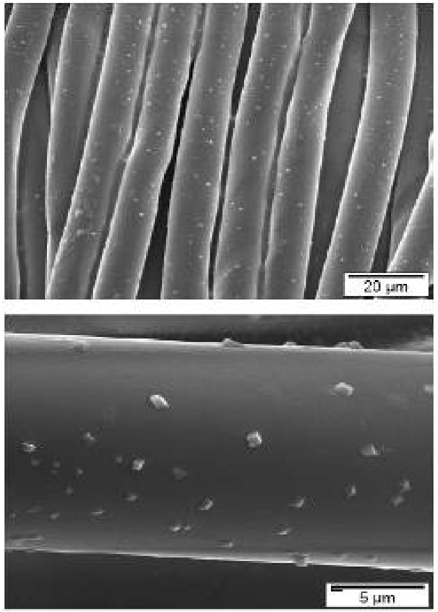
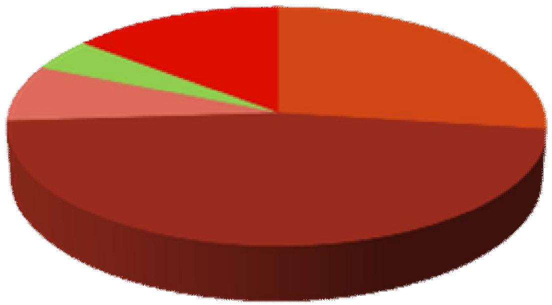
Kodak AGPET08 (FIFRA# 59441-9)
Particle size: 50-500 nm
Photo: KODAK Publication **No. G2.1-2007**



Many EPA registered silver salts also fall within the nano size range

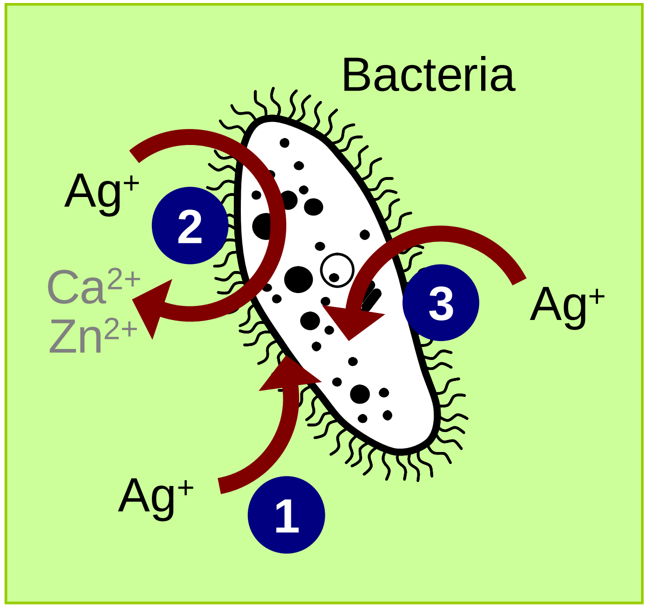


How Do Silver-based Antimicrobials Work?

- 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 Ca^{2+} and Zn^{2+} 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

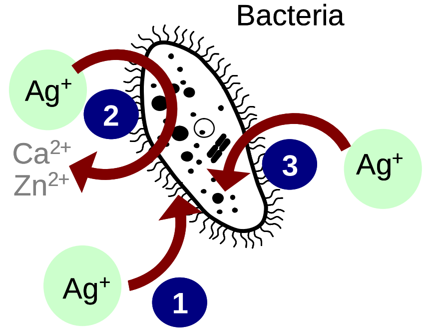
- Unique qualities of silver ions:
  - Low risk for bacteria resistance [5]
  - Effective in very low concentrations [4]
  - No human toxicity

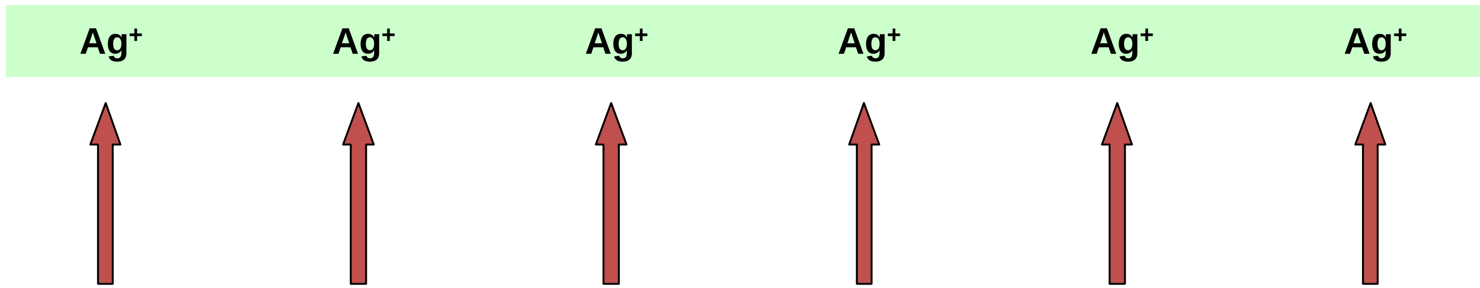
1. US. EPA, "R:E:D. Facts – Silver", 1993.
2. Sondi I, et al. Journal of Colloid Interface Science, 2004, 275: 177-182.
3. Dowling DP, et al., Thin Solid Films, 2001, 398: 602-606.
4. Gilchrist T, et al., Biomaterials, 1991, 12: 76-78.
5. Damm, C. et al., Soft materials, 2006, 3:71-88.

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

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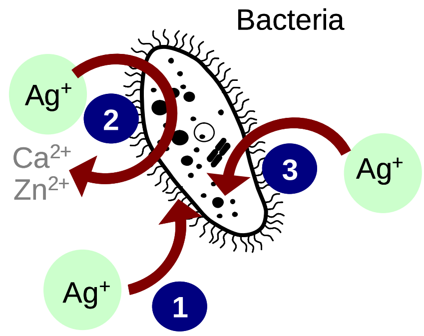
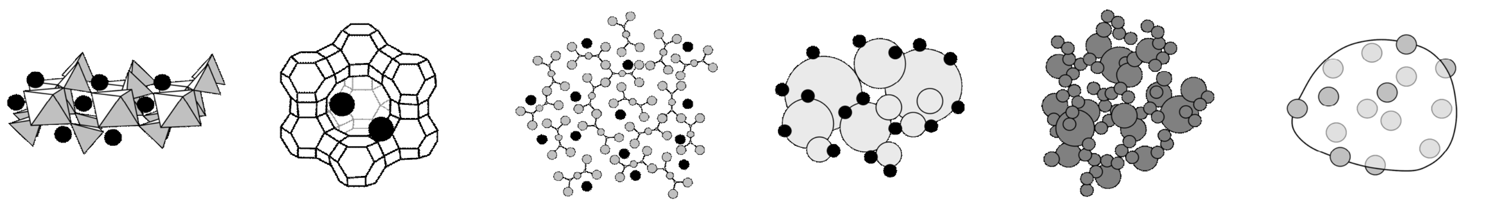


0-hypothesis (Wijnhoven et al.[1])

Ag^+	Ag^+	Ag^+	Ag^+	Ag^+	Ag^+

Liberation of Ag^+ from source antimicrobial additive

All silver-based antimicrobials "Store" silver ions



Silver ion exchangers — *Silver salts* — *Silver metal*

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

[1] SWP. Wijnhoven, WJGM. Peijnenburg, CA. Herberts, WI. Hagens, AG. Oomen, EHW. Heugens, B. Roszek, J. Bisschops, I. Gosens, D. Van De Meent, S. Dekkers, WH. De Jong, M. van Zijverden, AJAM. Sips, RE. Geertsma, "Nano-silver - a review of available data and knowledge gaps in human and environmental risk assessment", *Nanotoxicology*, 3:2 (2009) p109 — 138.

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

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- 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

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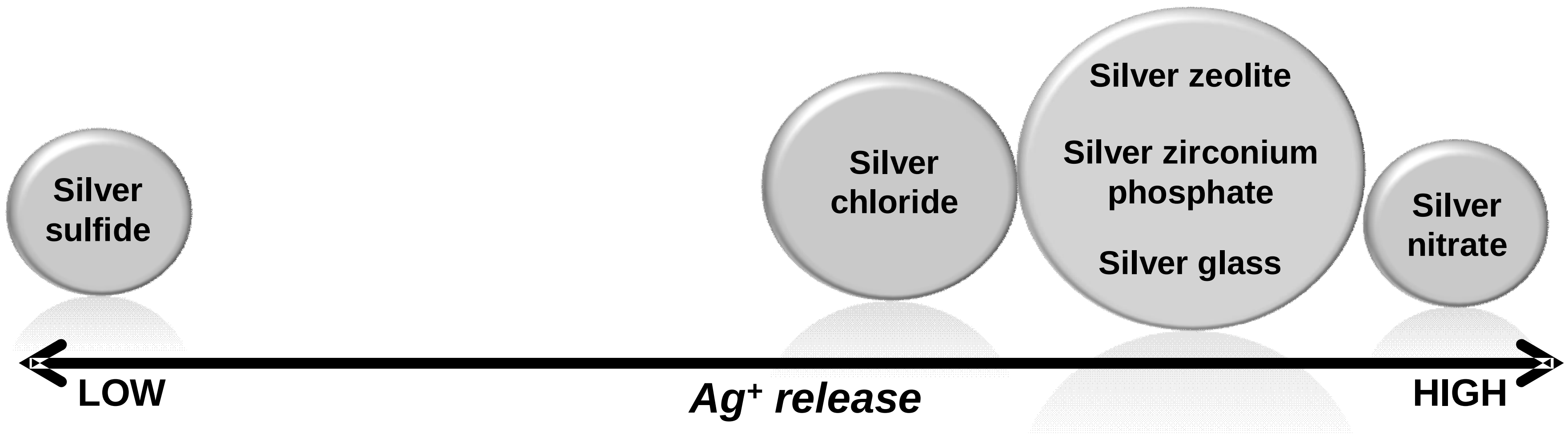

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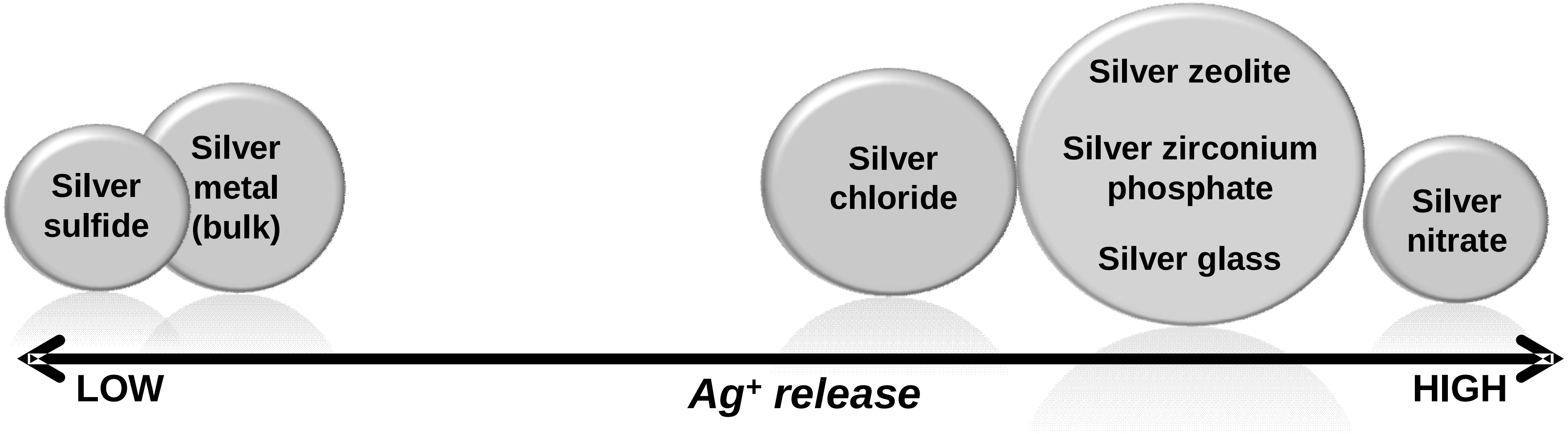

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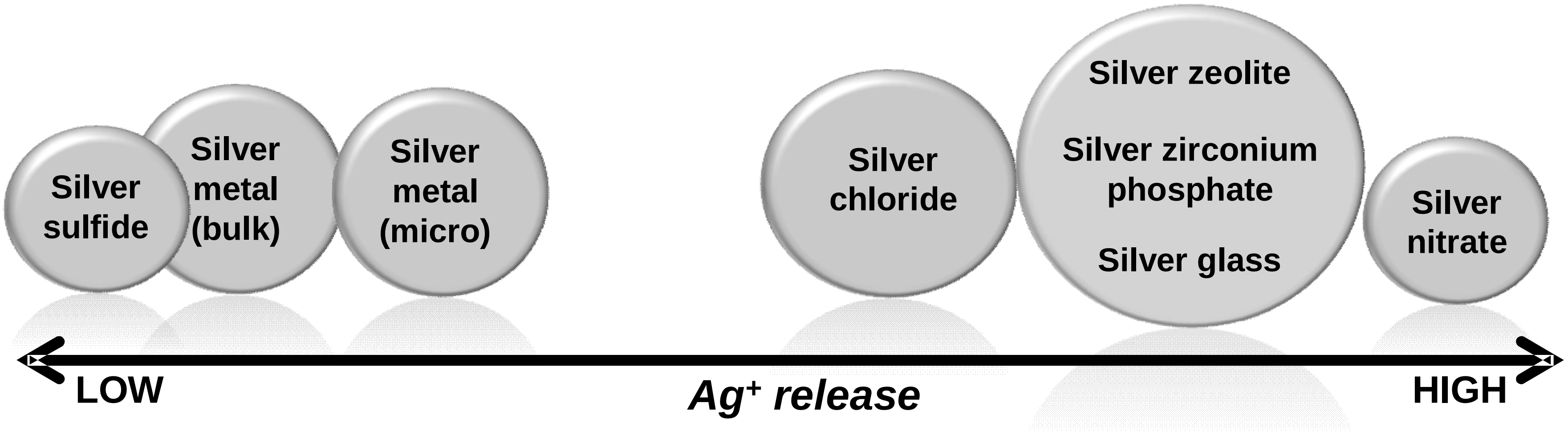

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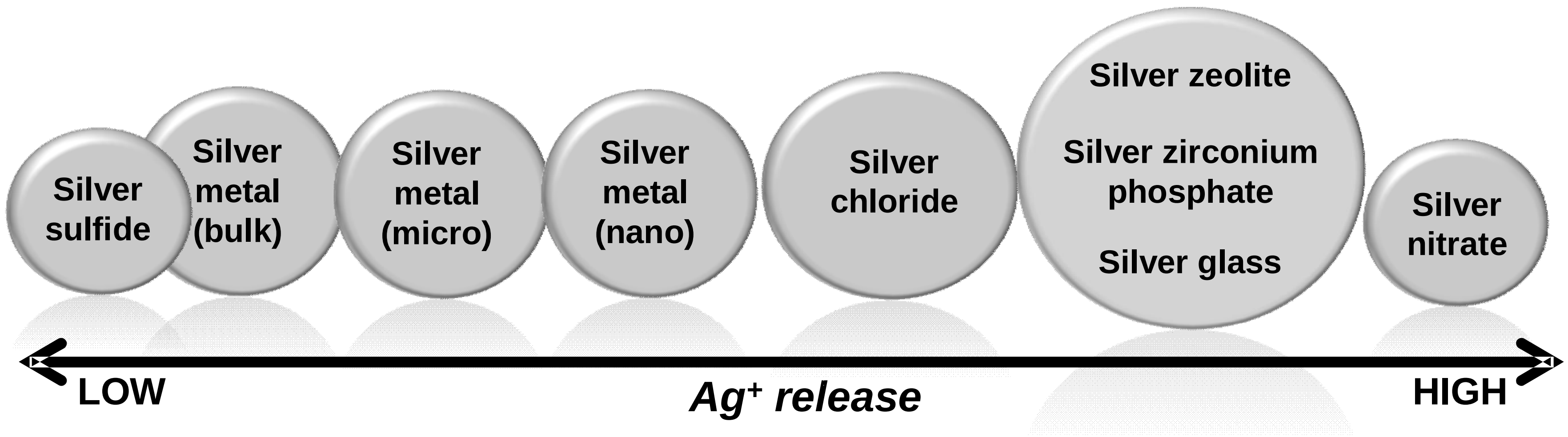

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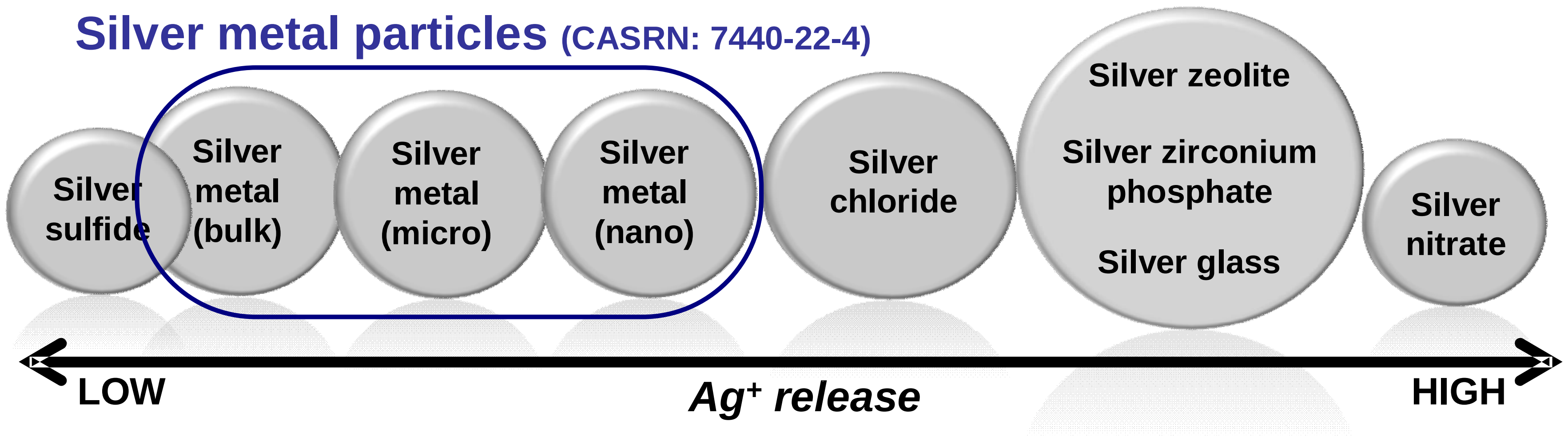

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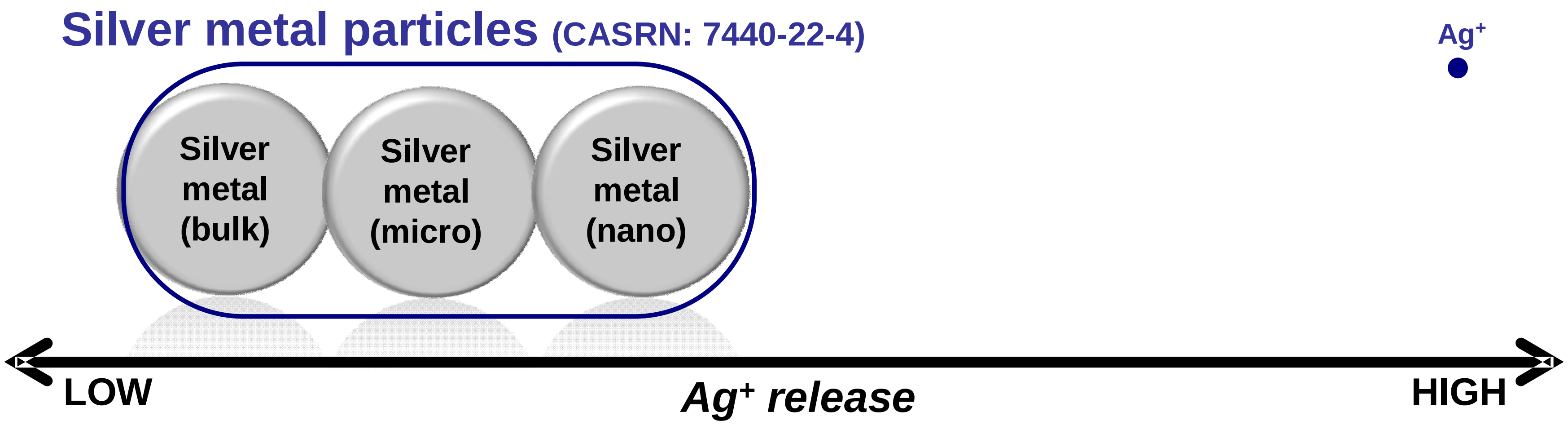
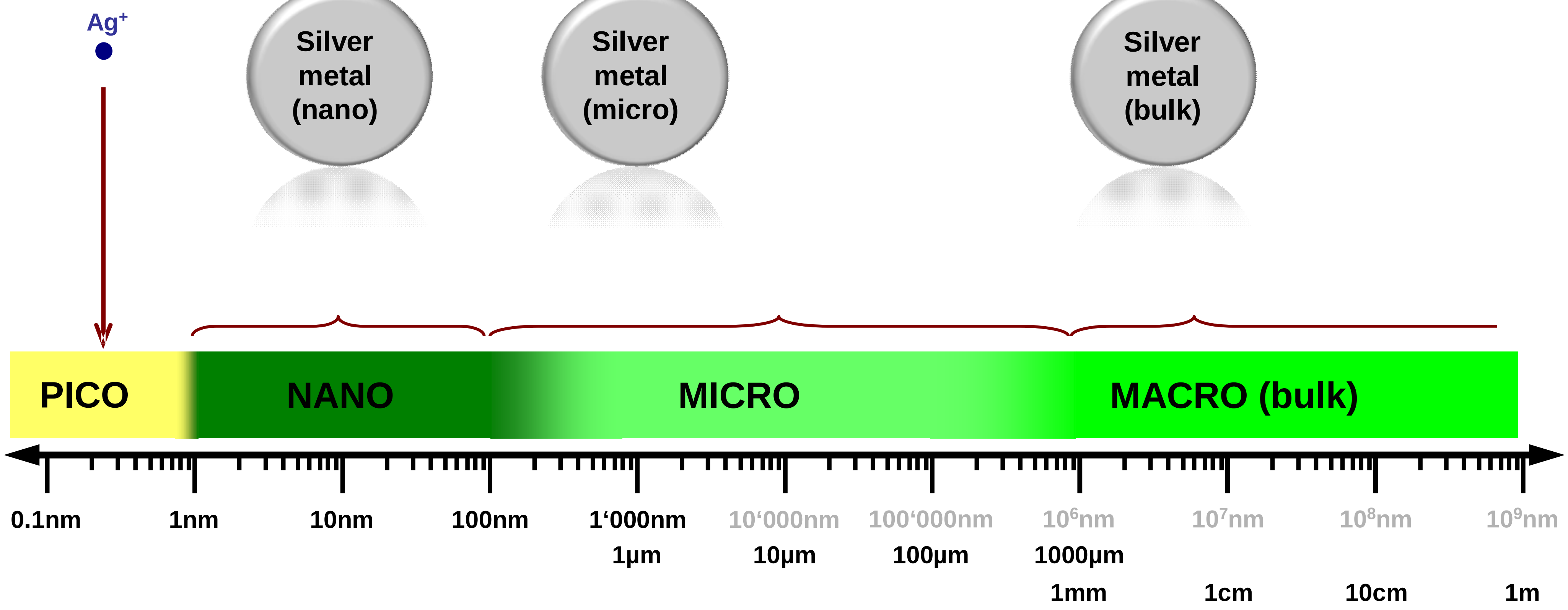
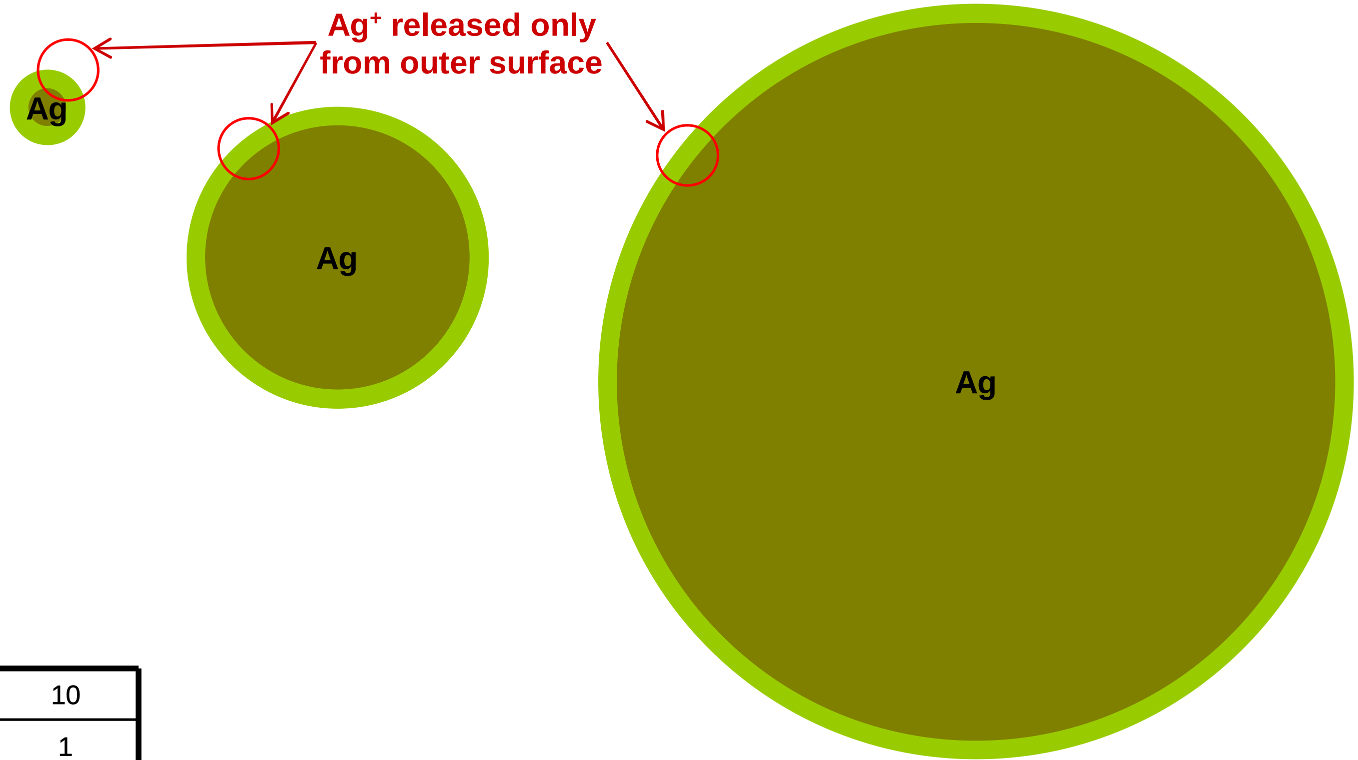


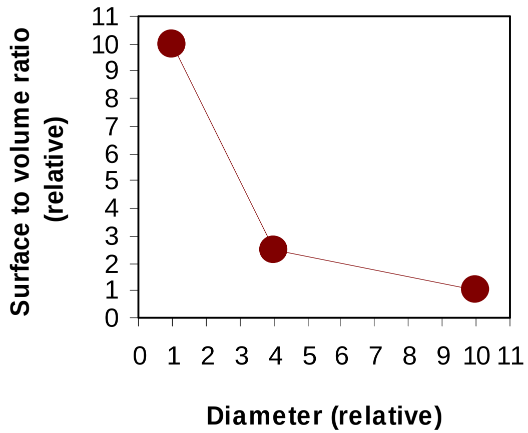
Silver Metal Antimicrobials – Size continuum



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

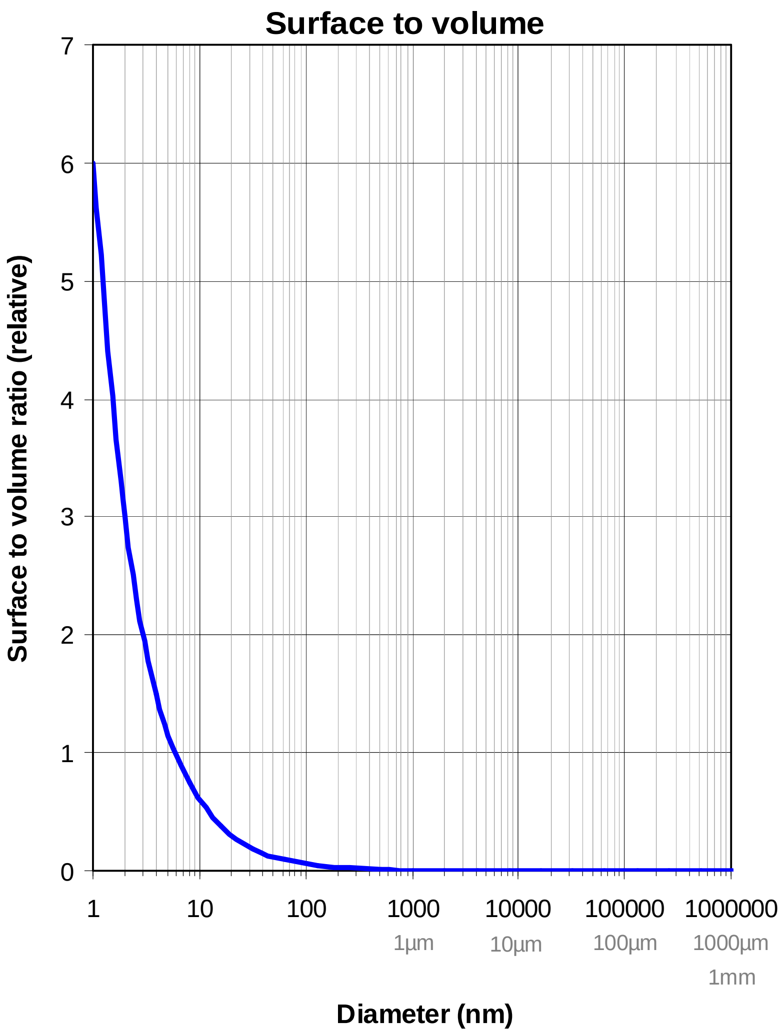




Diameter	1	4	10
Surface to volume ratio	10	2.5	1

Silver Metal – Why go smaller?

- Ag^+ release proportional to <u>surface to volume (mass) of the particle</u>



Availability of Ag^+ ions per mass of silver is higher for smaller particles

Silver Metal – Why go smaller?

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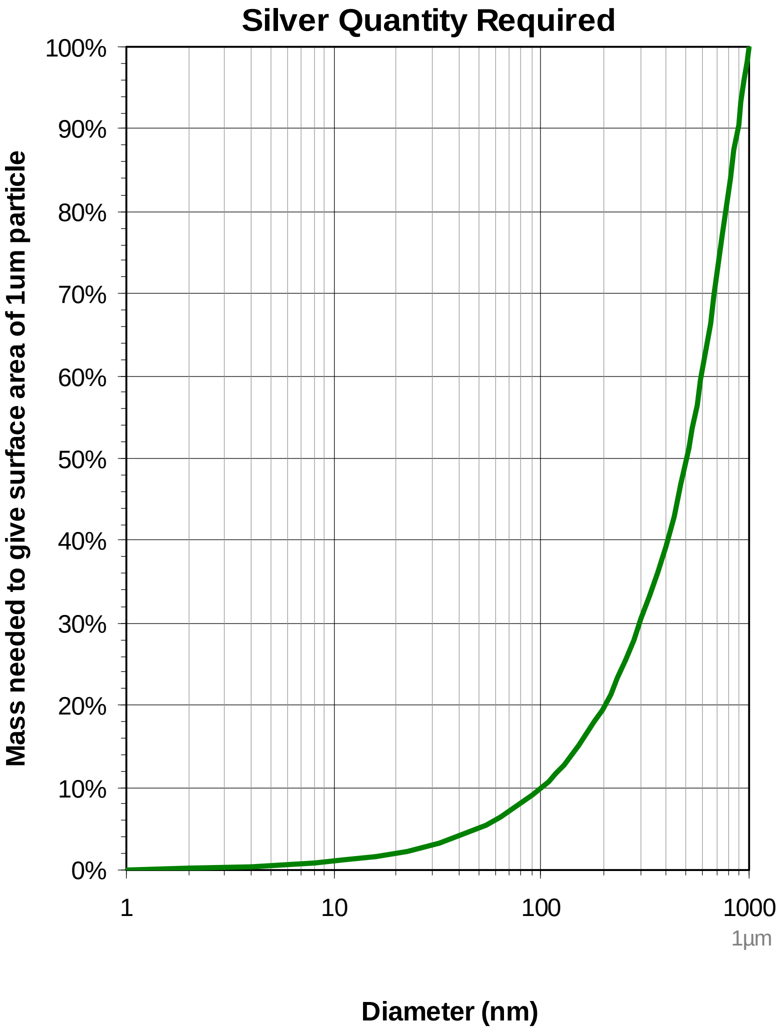

Smaller particles allow much lower mass of silver to achieve a given Ag^+ dosing

Example:
For equivalent Ag^+ dosing

1µm particles	10‘000 ppm Ag required
10 nm particles	100 ppm Ag required

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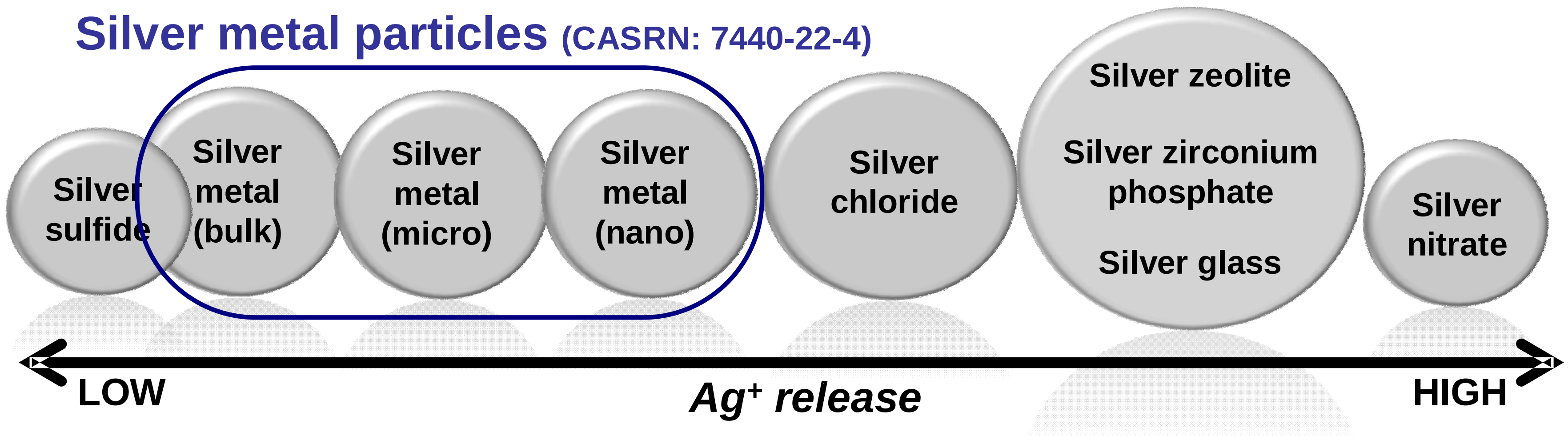

- Because of the higher surface area per mass of silver, nanosilvers have a higher release capability than bulk silver metal

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 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

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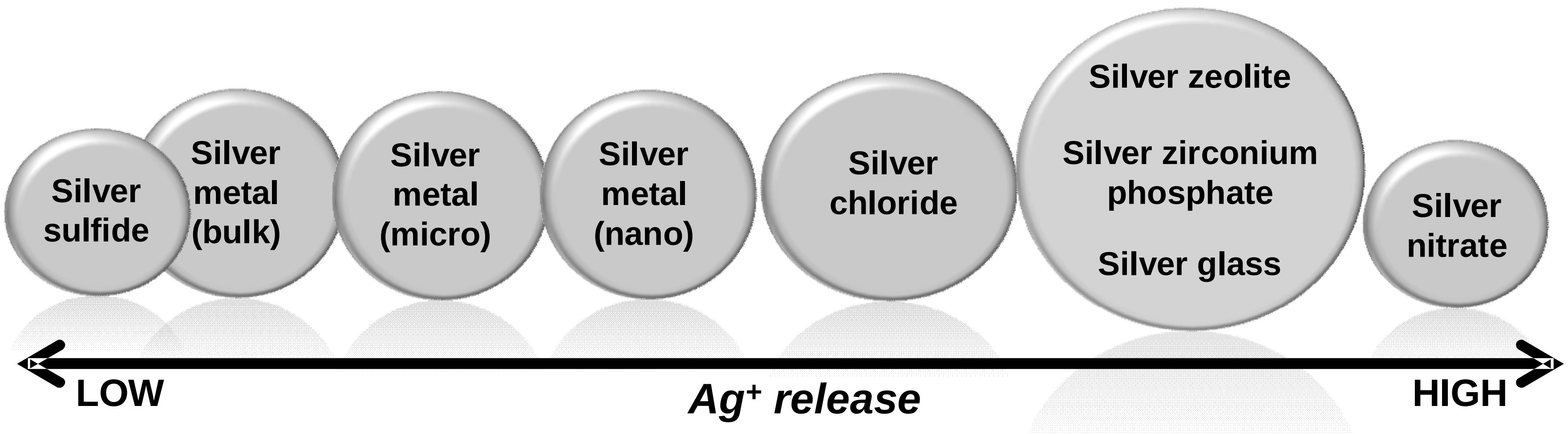

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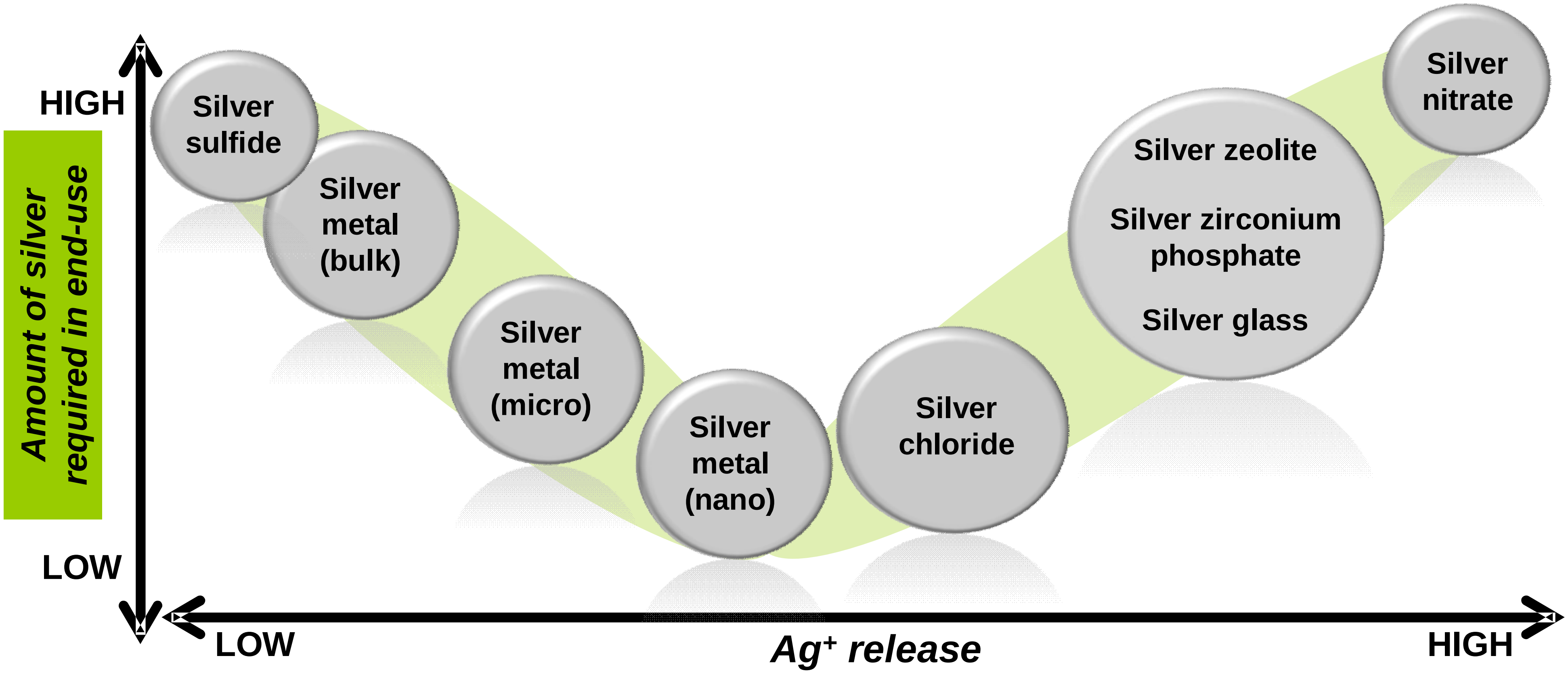

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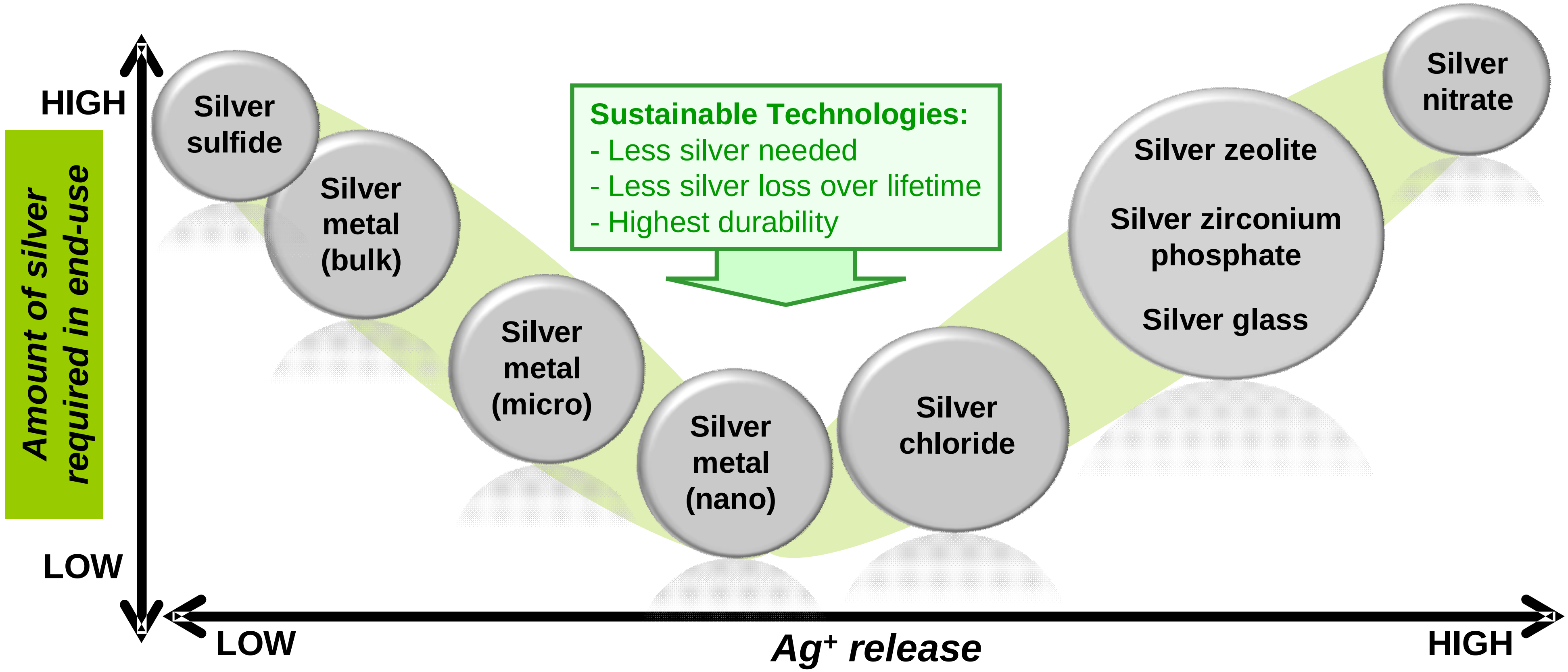

Nanosilver versus Conventional Silver Materials

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

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TABLE 1. Comparison of the antimicrobial activities of silver nanocomposite powder, silver nitrate, and silver zeolite **[1]**

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	MIC (μg/ml)[a]	MBC or MFC (μg/ml)[b]	MIC (μg/ml)[a]	MBC or MFC (μg/ml)[b]	MIC (μg/ml)[a]	MBC or MFC (μg/ml)[b]
Escherichia coli ATCC 2732[c]	62.5	125	7.8	15.6	3.9	15.6
Klebsiella pneumoniae ATCC 4352[c]	62.5	125	3.9	7.8	7.8	31.2
Pseudomonas fluorescens LME 2333[d]	62.5	250	7.8	7.8	15.6	31.2
Salmonella enterica serovar Enteritidis D1[c]	62.5	250	3.9	7.8	15.6	62.5
Salmonella enterica serovar Typhimurium DB 7155[c]	62.5	250	3.9	15.6	15.6	31.2
Enterococcus faecalis ATCC 19433[e]	62.5	250	3.9	7.8	7.8	7.8
Bacillus cereus ATCC 14579[e]	250	500	31.2	31.2	62.5	250
Listeria monocytogenes Scott A[f]	500	1,000	31.2	31.2	31.2	62.5
Staphylococcus aureus ATCC 29213[f]	250	1,000	15.6	15.6	15.6	125
Candida albicans ATCC 10259[g]	125	2,000	31.2	250	62.5	250
Aspergillus niger ATCC 9642[h]	2,000	ND[i]	15.6	ND	125	ND

[1] S.Egger, RP.Lehmann, MJ.Height, MJ.Loessner and M.Schuppler, „Antimicrobial Properties of a Novel Silver-Silica Nanocomposite Material", *Applied and Environmental Microbiology*, 75(9), 2973–2976, (2009).

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Highest activity	**$AgNO_3$**
Medium activity	**Ag zeolite**
Lowest activity	**Silver nano**

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Rationale for using nanoscale silver is <u>NOT because of any higher activity!</u>
- the reason is *longer durability* achieved with *less silver* (sustainability)

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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

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Are these assumptions valid?

Human Health Perspective

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- 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

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- Challenge: How well characterized?

Human Health Perspective

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Particle Sizes of Common Colloidal Silver Products

Product	Use	Particle Size (nm)	Reference
Argyrol	Anti-Infective (early 1900s)	35 nm	DLS Study, NanoHorizons, 2009.
Collargol	Anti-Infective (early 1900s)	10-20 nm	Muller, 1926 (1). Bogdanchikova, 1992 (2).
Mesosilver	“Dietary Supplement”	2 nm	DLS Study, NanoHorizons, 2009.
Protargol	Anti-Infective (early 1900s)	2 nm	Bogdanchikova, 1992 (2).

(1) Experimental Bone Marrow Reactions: I. Anemia Produced by Collargol. Muller, G.L. The Journal of Experimental Medicine, Vol 43, 533-553, (1926).

(2) Activity of colloidal silver preparations towards smallpox virus, Pharmaceutical Chemistry Journal, N. E. Bogdanchikova, A. V. Kurbatov, V. V. Tretyakov, P. P. Rodionov. 26, 9-10, 778 (1992).

Human Health Perspective

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Nanotoxicology in 1926:
Bone Marrow Reactions with Nanoscale Silver

Experimental Bone Marrow Reactions: I. Anemia Produced by Collargol. by Muller, G.L. *The Journal of Experimental Medicine*, Vol 43, 533-553, **1926**.

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 ($\mu\mu$), 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. Physio-

"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.

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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/m^3

Soluble silver salts (silver nitrate) …… 0.01 mg/m^3

- "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]

[1] Dequidt, J., P. Vasseur, and J. Gromez-Potentier. **1974.** Experimental toxicological study of some silver derivatives. Bull. de la Soc. de Pharm. de Lille. 1: 23-35.

- "Based on total Ag concentration, toxicity was 18 times higher for $AgNO_3$ than for AgNP [silver nanoparticles]."[2]

[2] Navarro et al. **"**Toxicity of Silver Nanoparticles to Chlamydomonas reinhardtii", *Environ. Sci. Technol*. 42 (**2008**) 8959–8964.

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/m^3 applies to silver dust and fumes, but does it adequately reflect the argyria hazard for nanoscale silver?

Human Health Perspective

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]

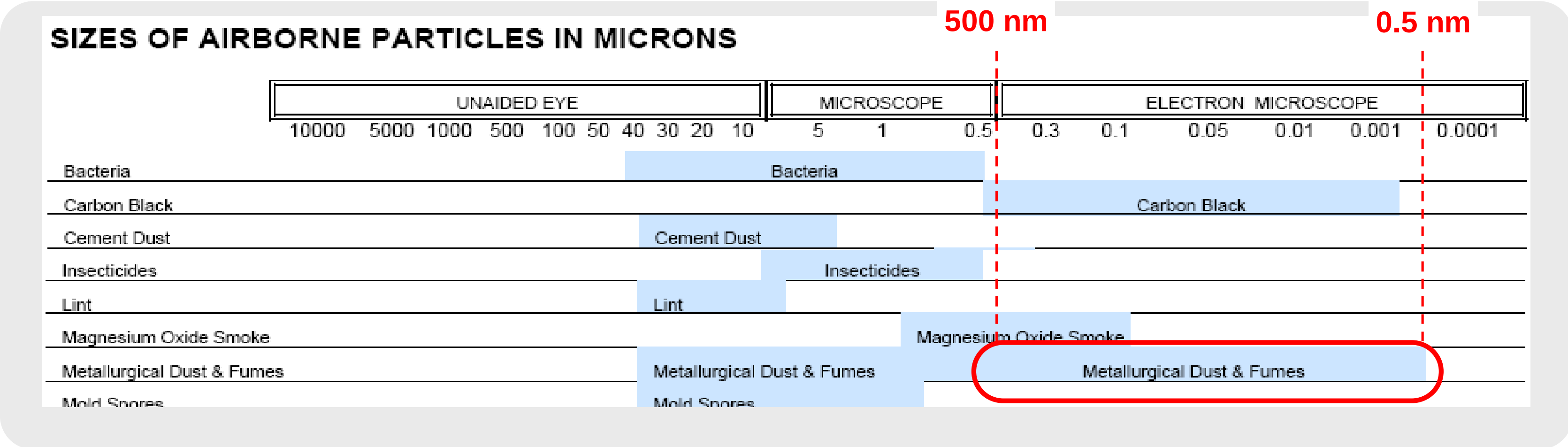
The data bridges…. Why?

[1] Sung, et al. "Subchronic Inhalation Toxicity of Silver Nanoparticles", *Toxicological Sciences* 108(2), 452–461 (2009).

Human Health Perspective

Inhalation: The data bridges. Why?

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



Human Health Perspective

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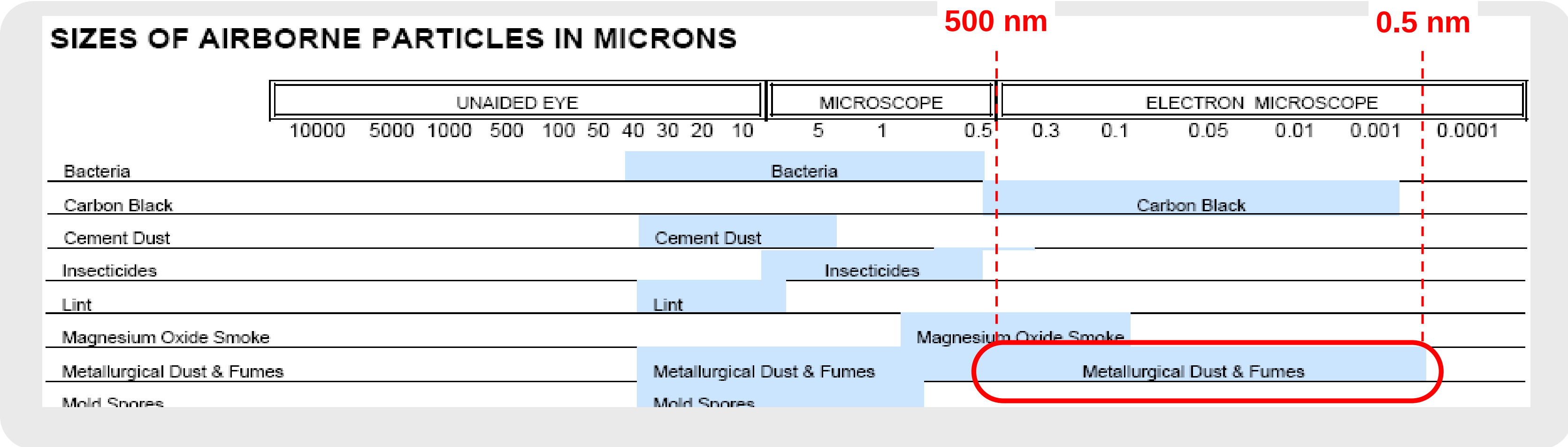

Reason #2. The ACGIH TLV is based on two extensive reviews of argyria from exposure to silver nitrate or <u>nanoscale silver colloid</u>.

(1) Hill and Pillsbury (1939) Argyria: the pharmacology of silver. Baltimore, MD: Williams & Wilkins Company.

(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.

Human Health Perspective

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."[1]

- 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]

[1] EPA–HQ–OPP–2007–0395 Federal Register / Vol. 74, No. 110 / June 10, 2009

[2] EPA-440/5-80-071 or PB81-117822 "Ambient water quality criteria for silver" U.S. EPA. 1980.

Human Health Perspective

Nanosilver Toxicology: Gaul and Staud (1935)

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Summary: Seventy cases of argyria from nanosilver colloidals were reviewed.
Data was derived primarily from Argyrol (35 nm) and Collargol (10-20 nm).

Table 1.—*Generalized Argyria Cases Following Peroral, Nasal and Pharyngeal Medication with Organic and Colloidal Silver Compounds*

Crispin, A. M.: J. A. M. A. [illegible]	......	..	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Tobler, T.: Schweiz. med. Wchnschr. **52**: 774, 1922	......	54	♀	Peroral	1 month	10 years ago	Collargol
Gernez, Houcke and Cuvelier: Ann. de méd.lég. **12**: 251, 1932	7 cases	..	..	Peroral	2-4 years	1 year ago	Collargol
Goldstein, H. I.: J. A. M. A. **77**: 1514, 1921	T. R.	..	♂	Pharyngeal	1 year	8 years ago	Argyrol
Zacks, M. A.: Laryngoscope **43**: 680, 1933	E. C.	10	♀	Intranasal	6 years	2 years ago	Argyrol
Freilick, E. B., and Dorne, M.: Illinois M. J. **51**: 467, 1927	A. M.	33	♂	Peroral	5 years	2 years ago	Argyrol
Odell, A. G.: Clifton M. Bull. **15**: 4, 1929	(a)	..	♀	Intranasal	Several years	Not known	Argyrol
	(b)	65	♂	Intranasal pharyngeal	2 years	Several years ago	Argyrol
	(c)	..	♀	Peroral	Not known	Not known	Argyrol
Davis, T. D.: Virginia M. Monthly **51**: 154, 1924	(a)	63	♂	Intranasal	Not known	Not known	Argyrol
	(b)	49	♀	Gums	11 years	Not known	Argyrol
Jones, M.: Laryngoscope **35**: 38, 1925	(a)	42	♂	Intranasal	8 years	3 years ago	Argyrol
Stillians, A. W., and Lawless, T. K.: Arch. Dermat. & Syph. **17**: 153, 1928	(a)	..	♀	Peroral	1 year	13 years ago	Argyrol
Jamieson, R. C.: Arch. Dermat. & Syph. **14**: 493, 1926	B. M.	55	♀	Intranasal pharyngeal	10 months	Not known	Argyrol Neo-Silvol
Chargin: Arch. Dermat. & Syph. **11**: 400, 1925	O. S.	39	♂	Pharyngeal	Several years	3 years ago	Argyrol
Kelly, I. D., cited by Weiss, R. S.: Arch. Dermat. & Syph. **8**: 244, 1923	(a)	..	♀	Pharyngeal	Several years	Not known	Argyrol
Fox, Howard: Arch. Dermat. & Syph. **22**: 584, 1930	H. N.	28	♀	Intranasal pharyngeal	1 year	3 years ago	Argyrol
Willims: Arch. Dermat. & Syph. **14**: 484, 1926	B. G.	49	♀	Intranasal	5 years	3 years ago	Argyrol
Wise, Fred: Arch. Dermat. & Syph. **29**: 624, 1934	W. F.	39	♀	Intranasal	5 years	3 years ago	Argyrol
Klauder, J. V.: Arch. Dermat. & Syph. **27**: 718, 1933	M. G.	51	♀	Mouth	5 years	4 years ago	Argyrol
	A. E.	57	♂	Pharyngeal	Many years	10 years ago	Argyrol
	H. E.	38	♀	Pharyngeal	Many years	5 years ago	Argyrol
Schwartz, H. J.: Personal communication to the authors	M. L.	57	♂	Intranasal	6 months	Not known	Argyrol
MacKee, G. M.: Private patient	E. K.	26	♂	Pharyngeal	Not known	Not known	Argyrol
Patek, A. J.: J. A. M. A. **102**: 787, 1934	(a)	60	♀	Pharyngeal	Many years	Not known	Argyrol
	(b)	Mentioned another similar case					
	V. L.	7	♀	Intranasal	3 years	1 year ago	Argyrol

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 basis[1-3] 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.

[1] EPA–HQ–OPP–2007–0395 Federal Register / Vol. 74, No. 110 / June 10, 2009

[2] EPA-440/5-80-071 or PB81-117822 "Ambient water quality criteria for silver" U.S. EPA. 1980.

[3] Drake and Hazelwood: "Exposure-Related Health Effects of Silver and Silver Compounds: A Review" - Annals of Occupational Hygiene, vol. 49, p. 575-58-, 2005.

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[1]

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. **[1]**

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. **[1]**

[1] PL.Drake, KJ.Hazelwood, "Exposure-related health effects of silver and silver compounds: A review", *The Annals of Occupational Hygiene*, 49 (**2005**), pp. 575–585.

Human Health Perspective

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Table 2. Health effects associated with various forms of silver [1]

Source of silver	Outcome and/or health effects	References
Medicinal		
Silver nitrate—oral ulcerations	Argyria	Aaseth *et al.*, 1981; Lee and Lee, 1994
Silver nitrate—topical for gingival bleeding	Argyria, silver deposits in organs[a], and abdominal pain	Marshall and Schneider, 1977
Silver nitrate solution—varicose veins	Argyria	Shelley *et al.*, 1987
Silver acetate—antismoking gum, lozenges, and tablets	Argyria	Jensen *et al.*, 1988; MacIntyre, 1978; Van Garsse and Versieck, 1995
Colloidal silver protein—allergy and cold med.	Argyria and high blood-silver levels	Gulbranson *et al.*, 2000
Colloidal silver protein—treatment of ailments	Argyria	White *et al.*, 2003
Silver protein—nose drops	Argyria	Jacobs, 1998
Colloidal protein—eye drops	Argyrosis	Loeffler and Lee, 1987
Colloidal silver and silver compounds	Argyria, argyrosis	Hill and Pillsbury, 1939
Silver coated pills—mouth freshener	Argyria	Sato *et al.*, 1999 (case 1)
Silver coated acupuncture needles	Argyria	Sato *et al.*, 1999 (case 2)
Silver in water—hemodialysis therapy	Argyria	Sue *et al.*, 2001
Occupational		
Soluble	Elevated blood-silver levels	Armitage *et al.*, 1996
Soluble	Argyrosis, elevated blood-silver levels	Williams, 1999
Soluble	Argyria, argyrosis, abdominal pain	Rosenman *et al.*, 1979
Soluble	Argyrosis, abdominal pain[b], nosebleed[b], respiratory irritation, allergic response	Rosenman *et al.*, 1987
Soluble	Argyria, ocular argyrosis	Moss *et al.*, 1979
Soluble	Argyria, argyrosis	Wobling *et al.*, 1988 (soluble group)
Soluble	Argyrosis	Williams and Gardner, 1995 (case 2)
Soluble	Argyria	Buckley, 1963
Metallic	Argyro-siderosis of the lungs	Barrie and Harding, 1947
Metallic	No health effects	Linnett and Bradford, 1996
Insoluble	Severe circulatory and respiratory symptoms[c]	Forycki *et al.*, 1983
Insoluble	Argyrosis	Pifer *et al.*, 1989
Insoluble	No health effects	DiVincenzo *et al.*, 1985
Insoluble	No health effects	Breitstadt, 1995
Insoluble	No health effects	Williams and Gardner, 1995 (case 1)
Insoluble	No health effects	Wobling *et al.*, 1988 (insoluble group)

[a]Organs involved were liver, spleen, intestines and pancreas.
[b]Effects thought to be caused by cadmium, not silver.
[c]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

[1] PL.Drake, KJ.Hazelwood, “Exposure-related health effects of silver and silver compounds: A review”, *The Annals of Occupational Hygiene*, 49 (**2005**), pp. 575–585.

Human Health Perspective

Summary:

- EPA has registered silver nanoparticles over a period of 6 decades
  - Colloidal silver algaecides
  - 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

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

Ecological Perspective

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- Two primary aspects regarding ecological risk assessment for silver nanoparticles:
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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 & Westerhof

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- Seven commercially available silver socks were washed under aggressive conditions[1]
- Silver particle and ionic silver release was measured

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

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

[1] TM. Benn and P. Westerhoff, “Nanoparticle Silver Released into Water from Commercially Available Sock Fabrics”, *Environmental Science and Technology*, 42 (2008) 4133–4139.

Eco-Exposure: Geranio, Heuberger & Nowack

- Silver functionalized socks were washed with mechanically aggressive washing method with and without presence of bleaching agents[1]
- 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

[1] L.Geranio, M.Heuberger, B.Nowack, "The Behavior of Silver Nanotextiles during Washing", *Environmental Science and Technology*, Accepted (2009).

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

Sample ID	Description	Silver functionality
1	Polyester reference fabric	None
2	Polyester with silver inside coating layer	HeiQ AGS-20 TF
3	Polyester with silver inside fibers	HeiQ AGS-20 MB
4	ArcticShield sock (used in Benn et al paper[1])	NanoHorizons Additive SSB**

** 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

[1] JL.Delattre, MJ.Height, "Risk Assessement Case Study: Silver Nanoparticles", Silver Nanotechnology Working Group, *OECD Workshop on Risk Assessment of Manufactured Nanomaterial in a Regulatory Context*, Washington DC (2009).

[2] TM.Benn, P.Westerhoff, "Nanoparticle Silver Released into Water from Commercially Available Sock Fabrics", *Environmental Science and Technology*, 42 (2008) 4133–4139.

[3] L.Geranio, M.Heuberger, B.Nowack, "The Behavior of Silver Nanotextiles during Washing", *Environmental Science and Technology*, Accepted (2009).

Eco-Exposure: Textiles

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- 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

S N W G
Silver Nanotechnology Working Group

- 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[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]

EPA Re-registration Eligibility Document for Silver (1993).

- 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]

O.Choi and Z.Hu, Water Sci. Technol. 59(9):1699-702 (2009).

- New findings agree with 1993 Silver RED

[1] J.Wang, CP.Huang, D.Pirestani, "Interactions of silver with wastewater constituents.", *Water Research,* 37 (2003) pp4444-4452.
[2] EPA Re-registration Eligibility Document for Silver, Case 4082 (1993).
[3] O.Choi, Z.Hu, "Nitrification inhibition by silver nanoparticles", *Water Science and Technology*, 59(9) (2009) pp1699-702.

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Colloidal (nano) silver
FIFRA # 68161-1, 7124-101 etc.

Nanosilver-composites
FIFRA #s 58295-1, 58295-2, 58295-3 etc.

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"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

[1] C.Impellitteri, T.Tolaymat, K.Scheckel, "The speciation of silver nanoparticles in antimicrobial fabric before and after exposure to a Hypochlorite/Detergent solution", *Journal of Environmental Quality*, 38(4) (2009) pp1528-30.

Eco-Toxicity

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- 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

S N W G
Silver Nanotechnology Working Group

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Colloidal (nano) silver	Nanosilver-composites
FIFRA # 68161-1, 7124-101 etc.	FIFRA #s 58295-1, 58295-2, 58295-3 etc.

- EPA has examined the real-life impact of these nanosilvers in detail[1] (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
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Policy Perspective

- Objective of all stakeholders:
  - Ensure products pose no “unreasonable adverse effects to human health or the environment”[1].

- How to rationally asses risk for nanoscale silver?

[1] EPA, “FIFRA Scientific Advisory Panel Background Paper”, (2009)

Policy Perspective

- Objective of all stakeholders:
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- How to rationally asses 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

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- *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 compatability 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

S N W G
Silver Nanotechnology
Working Group

- 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”
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- 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

SNWG
Silver Nanotechnology Working Group

- 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

[1] JL.Delattre, R.Volpe, "Comments of The Silver Nanotechnology Working Group for Review by The FIFRA Scientific Advisory Panel", SNWG (2009)
[2] EPA, "FIFRA Scientific Advisory Panel Background Paper", (2009)

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- 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

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