

Pesticide Registration of Nanosilver

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Issues and Presentation Overview

First US pesticide registration known to contain nanosilver

- EPA used available data and conservative assumptions to evaluate the risk from exposure to textiles treated with nanosilver
- EPA granted registration for nanosilver as a textile preservative while requiring generation of new data and occupational protection measures
- Potential to reduce amount of silver in textiles



FIFRA Regulatory Framework

- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires:
 - All pesticides to be “registered” (licensed) before they may be sold or distributed in US
 - Applicants for registration to provide information showing proposed use of the pesticide will not “cause unreasonable adverse effects on the environment” – the safety determination.
 - EPA to weigh the potential risks and benefits of use when deciding whether to register a pesticide



Nanosilver Registration

- First Application to Register Nanosilver in US
 - September 2008, HeiQ Materials AG submits to register AGS-20, a product containing nanosilver
 - HeiQ points to other currently registered products in US that contain nanosilver (See Nowack et al., 120 Years of Nanosilver History: Implications for Policy Makers, *Environ. Sci. Technol.* 45:1177, 2011)
 - EPA unknowingly registered nanosilver using subchronic toxicity data for ionic silver
- HeiQ submitted same basic data as other nanosilver registrants
 - Animal data for acute oral, dermal, inhalation, and eye toxicity of AGS-20
 - Additional studies characterizing the potential for human and environmental exposure to AGS-20



Nanosilver Pesticide Products in the US Marketplace

- Nowack et al. (2011) report that of the registered silver-based pesticides in US:
 - 7 are confirmed to contain nanosilver
 - 42 are likely to contain nanosilver
- EPA sent letter of inquiry asking whether registered silver-based pesticide contains any amount of nanosilver
 - 4 admit their product contains nanosilver (see table below)

Company/Registrant	Use	Registered
1. Nanohorizons	Materials Preservative	2007
2. Garrison Dental	Dental Line Cleaner	2004
3. American Biotech Labs	Disinfectant	2002
4. Pool Products Packaging	Swimming Pools	1954



Risk Assessment Evaluation

- Nanomaterials in pesticides not previously evaluated by EPA
 - Data requirements and risk assessment present unique challenges
 - Science for assessing hazard and risk of nanosilver still developing and data is limited
 - EPA convenes external peer review through Scientific Advisory Panel (SAP)
 - Panel members from Academic (US, IT, KR) and US National Research Institutes
 - Presentations from EPA, Businesses, Non-Governmental Organizations, and Silver Nanotechnology Working Group

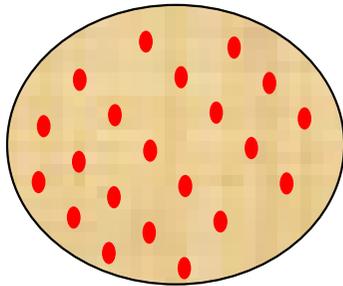


2009 FIFRA Science Advisory Panel

- SAP Conclusions on the Evaluation of Hazard and Exposure Associated with Nanosilver
 - EPA must have data to evaluate hazard, exposure, and risk of nanosilver, similar to other pesticides
 - Cannot assume data for macroscale or ionic silver appropriate to assess nanosilver
 - Determine data needs for nanosilver on a case-by-case basis
 - Panel majority: unsupportive of bridging among silver-based materials with different properties
 - Panel minority: some bridging appropriate for materials of similar size and with essentially identical physical properties

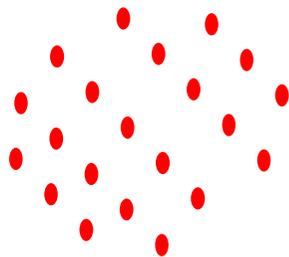


AGS-20 Exposures



Nanosilver-Silica Composite

- Nanosilver sintered to SiO_2
- 1,000 nm overall diameter



Nanosilver – 1 to 10 nm (avg)
and in the 50 nm range



Ionic silver

Required New
Risk Assessment

Existing Risk
Assessment

(See Egger et al. *Appl. Environ. Micro.* 75:2973 2009 for AGS-20 details)



Exposure Scenarios

Occupational and Consumer Exposures to AGS-20

1. Composite acts like nanosilver

Occupational risk from *inhalation* and *dermal* exposure to mixing, loading, and applying AGS-20 powder



2. AGS-20 Treated Textile Release Nanosilver

Residential risk from incidental *oral* and *dermal* exposure to 3 year old toddler wearing a new jumpsuit each day



Available Mammalian Toxicity Data

Exposure Route	NOAEL	Basis
Inhalation	133 $\mu\text{g}/\text{m}^3$	Based on the observed effects in rats after inhaling nanosilver for 13 weeks (Sung et al., 2009)
Incidental Oral	0.5 mg/kg/day	Based on the observed effects in mice after ingesting nanosilver for 28 days (Park et al., 2010).
Dermal	0.5 mg/kg/day	No subchronic studies are available for dermal toxicity of nanosilver. Because of this, a NOAEL was chosen by route-to-route extrapolation from the oral toxicity study with a NOAEL of 0.5 mg/kg/day (Park et al., 2010).

Sung, J.H., Ji, J.H., Park, J. D., et al. 2009. Subchronic Inhalation Toxicity of Silver Nanoparticles. *Toxicol. Sci.* 108:452-461.

Park, E.J., Bae, E., Yi, J., et al. 2010. Repeated-Dose Toxicity and Inflammatory Responses in Mice by Oral Administration of Silver Nanoparticles. *Environ. Toxicol. Pharm.* 30: 162-168.



Incomplete Mammalian Tox Data I

- Neurotoxicity of Nanosilver
 - Little evidence that silver enters CNS or causes neurotoxic damage (Lansdown *Crit. Rev. Toxicol.* 37:237, 2007)
 - However, *in vivo* studies indicate silver increase in olfactory bulb and brain after inhalation (Sung et al. *Toxicol. Sci.* 108:452, 2009) and oral administration of nanosilver (Kim et al. *Part. Fib. Toxicol.* 7:20, 2010, Kim et al. *Inhal. Toxicol.* 20:575 2008).
 - *In vitro* studies indicate nanosilver can cause neuronal toxicity (Hussain et al. *Toxicol. Sci.* 92:456, 2006; Liu et al. *ACS Nano* 4:6903, 2009)
 - Unknown if the doses used in the *in vitro* studies would approximate *in vivo* levels



Incomplete Mammalian Tox Data II

- Reproductive and Developmental Toxicity
 - No studies available on repro. or develop. tox. in mammals
 - One study showed significant, dose-dependent increases of silver in the testes of rats (Kim et al., *Inhal. Toxicol.* 20:575-583 2008)
- Mutagenicity of Nanosilver
 - Genotoxic potential investigated *in vivo* by measuring micronucleated polychromatic erythrocytes (MN PCEs) in rats (Kim et al. *Inhal. Toxicol.* 20:575 2008)
 - No statistically significant treatment-related increase of MN PCEs in the male and female rats when compared to negative control
 - Study indicates that nanosilver is not genotoxic *in vivo*, although was not demonstrated that nanosilver reached the bone marrow



Accounting for Incomplete Data

- EPA used an uncertainty factor (UF_D) to account for the incomplete characterization of nanosilver toxicity
 - Sufficient inhalation and oral toxicity data for nanosilver which can be used to determine the potential health effects caused by nanosilver released from AGS-20
 - However, the database is incomplete with respect to neurotoxicity, reproductive and developmental toxicity, and mutagenicity
 - EPA used the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the incomplete toxicity dataset (US EPA, 2002)
 - EPA is requiring HeiQ to investigate these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles



Daily-Dose of Nanosilver

1. Occupational Exposure – Textile Manufacturing

- Mixing, loading, and applying AGS-20 powder during the treatment of textiles
- Dose based on unit exposures for mixing and loading of wettable powders (Matthews, Pesticide Application Methods, 2000)

2. Residential Exposure – Wearing Textiles

- Incidental oral and dermal exposure while wearing or working treated fabrics
- Dose based on silver found in ISO color fastness test by Geranio et al. (*Environ. Sci. Technol.* 43:8113 2009)
- Inhalation exposure during laundry drying – wettable powder

3. Environmental Exposure – Laundering of textiles



Risk Assessment and Risk Mitigation

1. Occupational Risk – Textile Manufacturing

- Expected inhalation and dermal exposures exceed level of concern for workers who mix, load, and apply AGS-20 powder

2. Residential Risk – Wearing Textiles

- Expected incidental oral and dermal exposures to AGS-20 treated textiles for 3-year old toddler are below level of concern for short, intermediate, and long-term exposures

3. Ecological risk assessment for surface water indicates no concern for aquatic species



EPA Grants HeiQ Registration

- Conditional Registration Granted December 2011
 - Workers must wear full-face respirators and use engineering controls, gloves and coveralls when handling AGS-20 powder
 - Enforceable four year schedule for developing AGS-20 toxicity data used to confirm risk assessment based on nanosilver analogs; tiered evaluations during the four years
 - If HeiQ fails to initiate or submit required studies, EPA will issue notice to cancel under FIFRA section 6(e)
- Public Interest/Benefit
 - Reduction in amount of silver in textiles from 22 mg/g using conventional silver-salts to 0.1 mg/g for AGS-20
 - Potential for decrease in amount of silver entering the environment and wastewater treatment plants
 - Reduces market disparity and uncertainty in regulatory process



Required Tier I Data for AGS-20

Physical Characteristics

- Particle Size Distribution
- Surface Area

Release Characteristics

- Dissolution Kinetics
- Leaching Test of Textile
- Dermal Exposure
- Inhalation Exposure
- Laundry Exposure

Health Effects

- 90 Day Inhalation
- 90 Day Dermal Tox
- Modified
Repro/Developmental Tox
Screening Test
- *In vitro* Micronucleus Assay

Ecological Effects

- Avian Acute Oral Tox
- Aquatic Invertebrate Acute Tox
- Fish Acute Tox



Tier II Data if Nanosilver Released from AGS-20

Physical Characteristics

- Particle Size Distribution
- Surface Area
- Zeta Potential
- UV-Vis

Ecological Effects

- Modified Aquatic Food Chain Transfer
- Terrestrial Plant Tox
- Aquatic Plant Growth
- Algal Tox
- Chronic Effects on Sediment Dwellers

Health Effects

- 90 Day Inhalation
- 90 Day Dermal Tox
- Modified
Repro/Developmental Tox
Screening Test
- *In vitro* Micronucleus Assay

Environmental Fate

- Rate of Deposition
- Activated Sludge Isotherm
- Adsorption/Desorption
- Soil Column Test
- Sludge Respiration Inhibition Test



Antimicrobial Resistance

- Increasing use of silver may result in bacteria developing resistance to silver and limit its use as an antibiotic agent for wound care (Gupta and Silver, *Nature Biotech.* 16:887, 1998)
 - Chopra (*J. Anti. Chemo.* 59:587 2007) concluded there is a low threat of bacterial resistance to silver in the clinical setting
- 30 day dosing of 1 mg/L nanosilver to estuarine sediment cores
 - No impact to microbial community and no increase in antibiotic resistance to the bacterial population in sediment (Bradford et al. *Environ. Sci. Technol.* 43:4530, 2009; Mühling et al. *Mar. Environ. Res.* 68:278 2010)
 - Lack of antimicrobial effect in the microcosm expected given bacterial proteins efficiently bind nanosilver (Wigginton et al. *Environ. Sci. Technol.* 44:2163 2010)



Follow-on Actions

- Natural Resources Defense Council filed a petition in US Court of Appeals seeking judicial review of EPA's conditional registration for HeiQ AGS-20
 - EPA's policy is not to comment on pending litigation
- Unequal Registration Conditions
 - EPA unknowingly registered nanosilver prior to 2007
 - HeiQ AGS-20 registered with more data requirements and use restrictions than for previously registered nanosilver products
 - EPA issuing Data Call-Ins requiring all nanosilver registrants to produce similar types of data based on use pattern



Further Information

- Thanks to Dr. Andrea Haas, Dr. Astrid Epp, and BfR!
- For Decision Documentation Please visit:
<http://www.regulations.gov>
 - Decision Document EPA-HQ-OPP-2009-1012-0064
 - Response to Public Comments EPA-HQ-OPP-2009-1012-0065
- US EPA Nano Science Team
 - Jonathan Chen, PhD, Toxicologist
 - Jessica Ryman-Rasmussen, PhD, DABT, Toxicologist
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 - Earl Goad, Biologist
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 - Rochelle Bohaty, PhD, Chemist
 - Donna Randall, Environmental Toxicology

