

Registration of HeiQ AGS-20

EPA Response to Comments Received on
Proposed Decision Document for the Registration of HeiQ AGS-20
as a Materials Preservative in Textiles
Docket: EPA-HQ-OPP-2009-1012

The public comment period was open from August 12 until September 13, 2010 and a total of 45 total comments were received as of October 8, 2010. The comments were listed in order received and each assigned a docket number. All comments are contained in this document but have been grouped and appear as follows:

- A. Citizens - 27 from Citizens
- B. POTWs -3 from POTW Operators (Tri-TAC and Hampton Roads, NACWA)
- C. Trade Association - 1 from Trade Association (Copper Development)
- D. States - 2 from State Agencies (Wisconsin DHS, Cal DPR)
- E. Industry - 3 from industry (DOW, BASF, HeiQ)
- F. NGOs - 9 from NGOs (ICTA, NanoCEO, EWG, NRDC, Humane Society, Center for Environmental Health, Food and Water Watch, CLF Ventures, and Anonymous)

A. Citizens

Comment 3: J. Ferro (8/19/2010 [EPA-HQ-OPP-2009-1012-0021](#))

Do not approve use of nanosilver in textiles. When the day of Armagedon comes, and there won't be electricity or water to wash our clothes or take baths, we might need the stuff. Not now. We have enough illnesses and diseases to deal with and enough things causing the illnesses and diseases.

Response: HeiQ submitted short-term acute animal toxicity testing data for AGS-20 as detailed in the Decision Document. These data demonstrated that AGS-20 did not cause mortalities or abnormalities in test animals after administration by oral, dermal, and inhalation routes, was moderately to non-irritating in skin and eye testing, and was not a skin sensitizer based on dermal testing. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed. Thus, given the available information and

using sound scientific risk assessment methods, the Agency believes that use of HeiQ's AGS-20 will not likely cause illness or disease during the period when data are being generated.

EPA has already registered a number of silver-based antimicrobial products for use as materials preservatives in textiles. Most antimicrobial silver-based pesticide products currently contain a silver salt, [e.g., AgCl or AgNO₃]. Compared to the amount of silver in HeiQ's product, most currently registered silver-based materials preservatives require larger amounts of silver to be added to textiles in order to provide a sufficient lifetime of activity for antimicrobial treatment. Therefore, the overall potential environmental loading of silver resulting from the lower-volume use of the HeiQ product should be smaller than from a comparable use of currently registered silver-based pesticides. For example, Geranio et al. (2009) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. As a result of this information, with this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives.

Comment 4: K. Mego (8/19/2010 [EPA-HQ-OPP-2009-1012-0022](#))

I strongly oppose the conditional registration of this pesticide. We should require additional product chemistry, toxicology, exposure, and environmental data BEFORE it is allowed to enter the stream of commerce, not 4 years earlier than that. The adverse effects cannot yet be determined nor measured at this time, and therefore the reasonableness of the exposure cannot be determined.

The levels of human and environmental exposure and risks have not yet been measured, therefore the likelihood that those levels will be low is false reasoning. Pass-through of nanosilver in fabrics into the environment is only one issue. The exposure level created by direct contact with the skin is also something of concern. Again, that level of exposure has not been measured, so it cannot yet be determined what level is reasonable or likely. Complete studies should be conducted before any determination is made regarding this substance.

Response: EPA typically uses "leaching studies" to estimate the amount and form of silver that consumers wearing and chewing on AGS-20 treated textiles could potentially be exposed to. These studies typically involve immersing textiles in biological fluids such as simulated sweat and saliva solutions for extended periods of time at physiological temperatures (i.e., 98.6 °F or 37 °C) and measuring the amount and form of silver released to those fluids. HeiQ submitted two "leaching studies" one of which used a standard test for the color fastness of textiles during laundering to determine the effect of pH, surfactants, and bleaching agents on the rate of silver release. The leaching study performed by Geranio et al. (2009) did not use biological fluids and does not directly simulate the release of silver in saliva or perspiration. However, the ISO color fastness test involved the use of detergent, alkaline conditions, steel balls, and physiologic temperature (40 °C) to determine the persistence of color in textiles during laundering. EPA concludes that while this ISO color-fastness test does not exactly simulate wearing or chewing on textiles, because it involved aggressive conditions potentially resulting in greater release than might otherwise occur during chewing on or wearing

textiles, it does provide a reasonable first estimate for the amount silver transferred to the mouth while chewing on and transferred to skin while wearing textiles treated with AGS-20.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed. The purpose of requiring additional leaching studies is to confirm the results from the submitted studies regarding the low rate of nanosilver release from AGS-20 treated textiles.

Comment 5: M. May (8/19/2010 [EPA-HQ-OPP-2009-1012-0023](#))

I cannot believe that the EPA would approve of this chemical to be used in clothing. One of the advertized "benefits" is that such clothing would smell "fresh". There are many people, myself included, who have become very chemically sensitive and become sick when exposed to scents used in perfumes, fabric softeners, and other things. I have experienced many times being out on a bike path or other place where I encounter people whose clothing is permeated with heavy scents and the entire air surrounding them makes it difficult for others to enjoy the outdoors. A few years ago I ordered a swimsuit from L.L. Bean and it had a "fresh" scent which I tried to wash out. Nothing worked to remove the scent and I had to return the suit. I'm afraid of any more chemicals being introduced into our lives and the lives of our children and grandchildren who at younger ages suffer from allergies and other health problems. You are the watchdog for a clean environment. Do your duty!

Response: AGS-20 has no odor or scent; it is not a perfume or chemical with an odor. Instead it is intended to reduce the number of odor causing bacteria.

Comment 6: E. Vrabel (8/19/2010 [EPA-HQ-OPP-2009-1012-0024](#))

HeiQ AGS-20 should not be approved. No chemical or material should be approved unless there is irrefutable evidence that the chemical or material will cause no harm to the environment. The burden of proof should be on the *manufacturer* not the regulating agency. It is also important to note that *everything* ends up in the environment eventually. The only question is what the impact will be.

Response: The scientific consensus is that nanosilver is harmful to bacteria, which is why it is being used as an antibacterial agent. EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the

Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 8: C. Genung (8/19/2010 [EPA-HQ-OPP-2009-1012-0026](#))

We do not need this product and it's unknown effects on our environment. There is already evidence that it is washed out of fabric and enters the environment, in teeny tiny particles that will be very difficult to remove or prevent from entering into places we don't want it to go. Four years approval is four years too many! We already have soap and water....wash your fabric and yourselves and this is a totally unnecessary unknown to add to our already struggling environment!

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 9: M. Loomis (8/19/2010 [EPA-HQ-OPP-2009-1012-0027](#))

As a member of the medical community as well as a private citizen and parent, I respectfully request the EPA not allow the use of nanosilver in the United States. The long term consequences of nanosilver on the many beneficial bacteria necessary for the health of our environment and bodies are potentially catastrophic. The potential benefits of nanosilver pesticide do not in any way outweigh the risks of harm. Please protect us.

Response: Silver is currently used as a broad spectrum antibiotic in wound dressings and thus will impact beneficial bacteria. However, the present concern is regarding the increase use of silver, such as silver nanoparticles for preserving textiles, which may result in more bacteria developing resistance to silver and limit its use as an antibiotic agent for wound care. In the wound care setting, a recent review by Chopra (2007) concluded that the threat of bacterial resistance to silver in the clinical setting is low.

In terms of environmental impact, a recent study involved releasing 1 mg/L of silver nanoparticles into microcosms containing estuary water overlying estuarine sediment cores (Bradford et al., 2009). The study found no impact to the microbial community over a 30 day monitoring period. Evidence for antibacterial resistance was also evaluated during this study and no increase in antibiotic resistance to

the bacterial population in the sediment was found (Mühling et al. 2010). Wigginton et al. (2010) suggested that the lack of antimicrobial effect in the microcosm was expected given that bacterial proteins efficiently bind to silver nanoparticles.

The Agency concludes that while development of antibacterial resistance due to the use of silver nanoparticles in AGS-20 is possible, the likelihood is low that the levels used in AGS-20 treated textiles will lead to the development of widespread bacterial resistance to silver.

Comment 10: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0028](#))

Please reconsider giving conditional approval to the use of nanosilver in consumer products. I am a supporter of the precautionary principle that states we should prove that something is safe before we allow its use - not the other way around as is being done here.

There are already tens of thousands of toxic chemicals on the market that have never been tested for human safety - we don't need to add to that list. In this case there is a genuine concern and question over the potential negative environmental and human health impacts of nanosilver. Please don't allow its use in the United States until it is proven safe. Thank you.

Response: The scientific consensus is that nanosilver is harmful to bacteria, which is why it is being used as an antibacterial agent. EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. HeiQ submitted results from testing of AGS-20 to determine the product identity and composition, physical and chemical properties, and acute health effects. EPA reviewed the 24 submitted test results and determined that 17 were acceptable. HeiQ also submitted five additional studies covering the amount of silver released from and the efficacy of AGS-20 treated textiles, the occupational exposures to AGS-20, and potential impacts to wastewater treatment.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 11: M. McGuire [EPA-HQ-OPP-2009-1012-0029](#))

I am very concerned with the proposed application to textiles as this will allow massive amounts into the environment without knowing what this product can actually do once introduced to the environment. I would expect a new technology such as this to be required to undergo stringent testing PRIOR to being used massive quantities. The unknown impact on sewage processing plants and the treatment of the water should be vigorously tested.

Response: The maximum amount of AGS-20 that can be used in textiles is limited to 0.01% silver by weight. As to the total volume of nanosilver that will enter the market place as a result of registering AGS-20, this value is unknown at this time. However, based on Agency confidential records, the total mass of silver distributed as a material preservative in the United States during 2009 was less than 6,800 kg. The Agency estimated that 4,500 kg/yr of AGS-20 nanosilver may be used in the unlikely event that every person in America was to purchase one t-shirt treated with AGS-20. While this volume is not insignificant, it is small relative to the approximately 500,000 kg of silver that was released into the environment from other industry sectors during 2008 according to the EPA's Toxic Release Inventory.

There is the potential for silver nanoparticles released from AGS-20 treated textiles to reach publically owned wastewater treatment and privately owned septic systems where they will most likely complex with sulfide and partition to biosolids. Once entrained in the biosolids, the silver nanoparticles could serve as a long term source of ionic silver which may adversely affect microorganisms that are vital to the wastewater treatment process. To evaluate this potential, HeiQ submitted test results on the impact of AGS-20 to wastewater treatment bacteria. This test involved introducing AGS-20 powder and an AGS-20 liquid formulation used to surface treat textiles (AGS-20 TF) into bottles containing biosolids obtained from a wastewater treatment plant. Based on the similarity between the biological oxygen demand (BOD) caused by introducing glucose into bottles with AGS-20 and those without, there was no impact to the microorganisms in these bottles for AGS-20 loadings from 3.8 to 188 mg/L (0.76 to 37.6 mg/L as silver) or the AGS-20 TF liquid at loadings from 1 to 50 g/L over the 26 day test period. Although this result suggests that the silver in AGS-20 would not be expected to negatively impact wastewater treatment systems, it is unclear if the 26 day test period was sufficient time to evaluate this impact given that the rate of ionic silver released from AGS-20 is unknown.

There are contradictory reports in the scientific literature regarding the impact of silver nanoparticles on wastewater treatment systems. For example, nanosilver was reported to inhibit nitrification in the range of 50% (Choi and Hu, 2009a) to 84% (Choi and Hu, 2009b) based on a reduction in oxygen uptake rate. However, Burkhardt et al. (2010) found no impact to nitrification at nanosilver dosages of 1 mg/L, the same dosage that Choi and Hu (2009a and 2009b) reported as inhibitory. These two research groups are reporting different findings with the Burkhardt group suggesting little impact of nanosilver to nitrification and the Hu group suggesting that an impact to wastewater treatment systems from nanosilver is expected.

While there are reports suggesting the potential for nanosilver to impact wastewater treatment operations, the Agency does not anticipate that registering AGS-20 will lead to negative impacts to wastewater treatment systems. This conclusion is based on the small volume of nanosilver (i.e., < 4,500 kg/yr as estimated) expected to be introduced into commerce from AGS-20 treated textiles. However, if nanosilver is found to be released from AGS-20 treated textiles during leaching studies then EPA will require HeiQ to determine the impact to wastewater treatment processes.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty

factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 12: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0030](#))

I think approving this Nanosilver is not a good idea. The potential allergic reactions as well as general decline of hygiene and potential risks to others. It may also mislead some who have diseases. I remember there was a time when I had some sort of allergic reaction and the doctors asked me if I had used a new laundry detergent, type of underwear etc...I am now wondering if this may have been a cause. What do the track records in other countries read? We should not trust everything that is touted as good.

Response: HeiQ submitted short-term acute animal toxicity testing data for AGS-20 as detailed in the Decision Document. These data demonstrated that AGS-20 did not cause mortality or abnormalities in test animals after administration by oral, dermal, and inhalation routes, was moderately to non-irritating in skin and eye testing, and was not a skin sensitizer based on dermal testing. Thus, AGS-20 is not anticipated to cause allergic reactions in healthy humans. It should also be noted that nanosilver is being used in wound dressings for patients suffering from burns.

Comment 13: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0031](#))

Please do not allow this! We live in a world full of chemicals, pesticides, and additives. It is becoming harder and harder to control what we put in and on our bodies. Although we are thankfully able to make choices about foods and cosmetics, it worries me that manufactures will follow suit with this decision and that it will become the standard in clothing. Environmental toxins play a part in our health and the health and safety of our children. Let's go back to the basics! We've lived centuries without this, why start adding it to fabrics now?

Response: There is no evidence to indicate that registration of AGS-20 will lead to it becoming standard in clothing. EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 14: M. Pescatore (8/19/2010 [EPA-HQ-OPP-2009-1012-0032](#))

I am writing to voice my opposition to the use of nanosilver on fabrics. This is an unnecessary poison to be put on fabrics which will have direct contact with our skin. If nanosilver washes out in the laundry, it will be polluting our ground and water systems, and who is to say that sweating and open pores will not allow this substance to seep into our bodies. Why, when the public is so concerned with going green, would the EPA want to approve the use of this chemical. We need less chemicals, not more.

Response: EPA typically uses “leaching studies” to estimate the amount and form of silver that consumers wearing and chewing on AGS-20 treated textiles could potentially be exposed to. These studies typically involve immersing textiles in biological fluids such as simulated sweat and saliva solutions for extended periods of time at physiological temperatures (i.e., 98.6 °F or 37 °C) and measuring the amount and form of silver released to those fluids. HeiQ submitted two “leaching studies” one of which used a standard test for the color fastness of textiles during laundering to determine the effect of pH, surfactants, and bleaching agents on the rate of silver release. The leaching study performed by Geranio et al. (2009) did not use biological fluids and does not directly simulate the release of silver in saliva or perspiration. However, the ISO color fastness test involved the use of detergent, alkaline conditions, steel balls, and physiologic temperature (40 °C) to determine the persistence of color in textiles during laundering. EPA concludes that while this ISO color-fastness test does not exactly simulate wearing or chewing on textiles, because it involved aggressive conditions potentially resulting in greater release than might otherwise occur during chewing on or wearing textiles, it does provide a reasonable first estimate for the amount silver transferred to the mouth while chewing on and transferred to skin while wearing textiles treated with AGS-20.

The rate at which silver nanoparticles transform into ionic silver determines the length of time that these particles will reside in the environment. Although there are studies reporting that silver nanoparticles will completely transform into ionic silver within six days after being dispersed into deionized water (Liu and Hurt, 2010), these results are only for one form of nanosilver and under conditions which are not representative of the environment. In the environment, nanosilver is likely to complex with naturally occurring anions such as chloride and sulfide or natural organic matter such as humic acids, which will significantly delay the rate at which nanosilver transforms into ionic silver. For example, Choi et al., (2009) provided spectroscopic evidence showing that nanosilver reacts with sulfide to produce stable silver-sulfide complexes, which were shown by Liu et al. (2010) to have undetectable rates of nanosilver to ionic silver transformation. These stabilized nanosilver-sulfide complexes are likely to partition to sediments rather than remain suspended in water due to gravitational settling and coagulation processes. Likewise, nanosilver is anticipated to partition to biosolids during wastewater treatment but may also be released into the environment through the effluent. Thus, there is the potential for nanosilver to reside or persist in the environment for a significant period of time where these particles are most likely to be associated with sediments. Ionic silver typically has low concentrations in natural waters, in the nanogram per liter range, due to its reactivity with chloride, sulfides, and natural organic matter (Andren and Armstrong, 1999). As with nanosilver, ionic silver is found in sediments and associated with biosolids in wastewater treatment plants.

EPA has already registered a number of silver-based antimicrobial products for use as materials preservatives in textiles. Most antimicrobial silver-based pesticide products currently contain a silver salt, [e.g., AgCl or AgNO₃]. Compared to the amount of silver in HeiQ's product, most currently registered silver-based materials preservatives require larger amounts of silver to be added to textiles in order to provide a sufficient lifetime of activity for antimicrobial treatment. Therefore, the overall potential environmental loading of silver resulting from the lower-volume use of the HeiQ product should be smaller than from a comparable use of currently registered silver-based pesticides. For example, Geranio et al. (2009) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. As a result of this information, we believe AGS-20 is expected to displace the silver-salt based materials preservatives, which have significantly higher silver content, and if so, with this registration there exists the potential for a decrease in the net amount of silver entering the environment.

Comment 15: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0033](#))

This is not a very well-thought out idea. I'll just cite one example: the use of synthetic fertilizer and the use of pesticides. The fertilizer and pesticides have been linked to neuro-muscular deterioration such as Parkinson's Disease. These links, of course, were not detected for several generations. The testing on this nanosilver product is incomplete and definitely not longitudinal. Hint: wash your clothes frequently and there will be no problem with germs, odor, etc. What a complete waste of money for something that may have catastrophic side-effects.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

The Agency has determined that there is 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 reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity. Therefore, the Agency is using the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

Comment 16: Anonymous (8/19/2010, [EPA-HQ-OPP-2009-1012-0034](#))

I am against Nanosilver being given conditional approval. It allows a pesticide into the environment for four years which could present a danger for humans and the environment. This is not a product that saves lives. There is no need to rush and give it conditional approval while it is being tested.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand. HeiQ submitted results from testing of AGS-20 to determine the product identity and composition, physical and chemical properties, and acute health effects. EPA reviewed the 24 submitted test results and determined that 17 were acceptable. Furthermore, HeiQ also submitted five studies covering the amount of silver released from and the efficacy of AGS-20 treated textiles, the occupational exposures to AGS-20, and potential impacts to wastewater treatment. Thus, safety testing of AGS-20 was performed.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 17: T. Pruitt (8/19/2010, [EPA-HQ-OPP-2009-1012-0035](#))

No long drawn out speeches - just a NO for putting this nanosilver ingredient in our clothing. Being too lazy to take care of one's own clothing and hygiene is not reason enough to introduce more chemicals into our bodies and environments. Do we really think our pores don't allow such things into our system. Next thing we know we'll be trying to figure out why some new form of disease has been introduced....This is just not a necessary evil

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand. The potential for penetration of nanosilver through skin was included in EPA's evaluation of the risk from exposure to AGS-20 treated textiles. This was based on the available human *in vivo* study indicating absorption of nanosilver is below 0.1% and the *in vitro* data indicating absorption of nanosilver from intact and abraded human skin is substantially below 0.1% provide scientific support for setting a conservative dermal absorption factor (DAF) of 0.1% for the nanosilver that might break away from the AGS-20 composite. This DAF will be used by the Agency until Tier I dermal toxicity data are provided by HeiQ for AGS-20, which will provide a route-specific study for use in subsequent risk assessments.

where EPA assumed that 0.1% of the nanosilver would cross the skin.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 18: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0036](#))

I am opposed to the EPA's approval of the use of nanosilver on fabric. There are unknown health risks related to nanosilver. I ask that the EPA oppose the use of nanosilver for our own safety.

Response: EPA used the best available science to determine the risk posed by the nanosilver in AGS-20, which included evaluating the effects caused by feeding nanosilver to test animals for periods of up to 90 days. It is not possible to determine all possible health effects for all populations at this time. However, the Agency has determined that there is 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. Although the database is incomplete with respect to reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity, the Agency is using the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

Comment 19: R. Day (8/19/2010 [EPA-HQ-OPP-2009-1012-0037](#))

If the EPA's intent and purpose is to protect the environment and the population of the United States, then how does it make any sense to release a product that doesn't have complete health hazard testing into the market and have the test results completed while the product is already on the market. What happens if it's found out 3 years from now that nanosilver is highly toxic, and it's been washing off of clothes and into the water system for the past 3 years? The effects would be irreversible. Where is the logic in releasing this product without it being fully tested for the harm it could have on public health and the environment!? Any product, no matter what it is, should have complete testing before it's released to ensure it will not effect the environment or the public? If it were to be released untested, it only stands to put more money in the pocket of big business at the expense of the consumer and the population, that is, if it is harmful to them. It should either be test completely before it's marketed, or not marketed at all.

Response: There was sufficient health hazard testing to conclude that AGS-20 is not highly toxic. HeiQ submitted short-term acute animal toxicity testing data for AGS-20 as detailed in the Decision Document. These data demonstrated that AGS-20 did not cause abnormalities in test animals after administration by oral, dermal, and inhalation routes, was moderately to non-irritating in skin and eye testing, and was not a skin sensitizer based on dermal testing. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 20: L. Courtney (8/19/2010 [EPA-HQ-OPP-2009-1012-0038](#))

The purpose of the Environmental Protection Agency is to protect the environment of the United States, not the profits of clothing manufacturers. Please do not grant approval, now or ever, to this completely unnecessary use of the pesticide HeiQ AGS-20, antimicrobial nanosilver. Evidence is already mounting that this substance will have an adverse environmental impact, and the consequences for human health are as yet unknown.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand. EPA has already registered a number of silver-based antimicrobial products for use as materials preservatives in textiles. Most antimicrobial silver-based pesticide products currently contain a silver salt, [e.g., AgCl or AgNO₃]. Compared to the amount of silver in HeiQ's product, most currently registered silver-based materials preservatives require larger amounts of silver to be added to textiles in order to provide a sufficient lifetime of activity for antimicrobial treatment. Therefore, the overall potential environmental loading of silver resulting from the lower-volume use of the HeiQ product should be smaller than from a comparable use of currently registered silver-based pesticides. For example, Geranio et al. (2009) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. As a result of this information, with this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives.

Comment 21: P. Smith (8/19/2010 [EPA-HQ-OPP-2009-1012-0039](#))

As a consumer I do not support applying chemicals to any materials that would come into contact with the skin. If a product is labeled as no nanosilver, I would purchase it instead. If you do approve nanosilver to be applied to a product, please make sure you label these products so we have a choice in

not purchasing them. I'm shocked in this day and time that this agency would even consider looking at this concept considering our already chemical-laden society full of sick people living in a corrupted environment who just need to get back to basics. Can't you put yourselves in our shoes (without nanosilver)? If you can't think for all Americans, at least consider your own health and that of your own family.

Response: Consumers will be informed where there are marketing claims provided by product advertising. EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 22: Mother Raphaela (8/19/2010 [EPA-HQ-OPP-2009-1012-0040](#))

Our environment is already polluted by innumerable contaminants which we may or may not be able to neutralize. The members of our monastery are unanimous in their opposition to adding a known pesticide (read poison) to fabric that will be washed (traces added to ground water) and ultimately end up in land fills. While perhaps the immediate effects on humans may not be noticable, if already tests are indicating stunted growth in plants, the cumulative effect (especially given the number of toxins already present) to plants, animals and humans should not be risked. At some point we will tip over a balance point and our small planet will no longer be a hospitable place for life.

Response: Based on our review as detailed in the decision document, we believe that registration of AGS-20 has the potential to reduce environmental loading of silver. EPA has already registered a number of silver-based antimicrobial products for use as materials preservatives in textiles. Most antimicrobial silver-based pesticide products currently contain a silver salt, [e.g., AgCl or AgNO₃]. Compared to the amount of silver in HeiQ's product, most currently registered silver-based materials preservatives require larger amounts of silver to be added to textiles in order to provide a sufficient lifetime of activity for antimicrobial treatment. Therefore, the overall potential environmental loading of silver resulting from the lower-volume use of the HeiQ product should be smaller than from a comparable use of currently registered silver-based pesticides. For example, Geranio et al. (2009) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. As a result of this information, with this registration there exists the potential for a decrease in the net

amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives.

Comment 23: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0041](#))

I cannot believe that this agency that is charged with the enormously important task of protecting the citizens of this country would even consider allowing the use of pesticides in clothing-- especially without having done proper study of the material. We do not need more chemicals and pesticides in our environment. It is bad enough that harmful endocrine disruptors like BPA and phthalates are allowed to be put in products. This would be taking a step in the WRONG direction. We need to be moving toward products that are cleaner and contain LESS harmful chemicals. It would be a crime in my mind to allow this in the United States. If this happens, it will confirm to me and many others what we have suspected all along-- that the EPA can be persuaded by lobbyists and bought by big corporations. That your real concern is not for the citizens of this country, but padding your own wallets. Shame on you!

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand. In taking this action, EPA has the expectation of reducing the amount of silver entering the environment. EPA has already registered a number of silver-based antimicrobial products for use as materials preservatives in textiles. Most antimicrobial silver-based pesticide products currently contain a silver salt, [e.g., AgCl or AgNO₃]. Compared to the amount of silver in HeiQ's product, most currently registered silver-based materials preservatives require larger amounts of silver to be added to textiles in order to provide a sufficient lifetime of activity for antimicrobial treatment. Therefore, the overall potential environmental loading of silver resulting from the lower-volume use of the HeiQ product should be smaller than from a comparable use of currently registered silver-based pesticides. For example, Geranio et al. (2009) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. As a result of this information, with this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives.

Comment 25: Anonymous ([EPA-HQ-OPP-2009-1012-0043](#))

Please do not approve the use of nanosilver in clothing. We do not need another chemical on our skins and in our water systems. We are living in a stew of chemicals already and can simply wash our clothes to keep them fresh.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally

consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand. The potential for penetration of nanosilver through skin was included in EPA's evaluation of the risk from exposure to AGS-20 treated textiles. This was based on the available human *in vivo* study indicating absorption of nanosilver is below 0.1% and the *in vitro* data indicating absorption of nanosilver from intact and abraded human skin is substantially below 0.1% provide scientific support for setting a conservative dermal absorption factor (DAF) of 0.1% for the nanosilver that might break away from the AGS-20 composite. This DAF will be used by the Agency until Tier I dermal toxicity data are provided by HeiQ for AGS-20, which will provide a route-specific study for use in subsequent risk assessments.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 27: Anonymous (8/23/2010 [EPA-HQ-OPP-2009-1012-0045](#))

Please do not grant conditional approval for "HeiQ AGS-20." Nanoparticles have great potential to positively contribute to our lives; however, their unique properties also mean that we do not currently know enough about their effects on human health or the environment to authorize their use. We can not afford to simply "wait and see" if the effects are damaging, as we have with so many other technological advances. As a 22 year old, and part of the generation upon whom the "fate of the world" has begun to fall upon, I am deeply concerned about this conditional approval and hope you will not grant it. Thank you.

Response: The Agency is not taking a "wait and see" approach with nanosilver. EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 28: C. Landerg (8/23/2010 [EPA-HQ-OPP-2009-1012-0046](#))

I am a private citizen of the U.S. I am concerned about the use of nanotechnology, in this case, nanosilver being used in consumer goods. Actually, I am against it altogether. The ability of nano particles to move, freely and radically, within organisms, including our bodies, HAS to be studied further. We can look at TEFLON as good example of a technological product that was not studied extensively or properly. Now we know that using it on cookware is dangerous.

The same with margarine which we now know is harmful to people. The coating inside microwave popcorn bags is harmful. The "fake butter" served on popcorn in movie theaters is harmful. The list goes on.

I personally will not buy any piece of clothing/fabric that has been treated with nanosilver and I certainly hope that, if you allow nanosilver to be used., the product will be so labeled.....so that we can protect ourselves.

Response: Consumers will be informed where there are marketing claims provided by product advertising. EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 29: Brad Kahland (9/13/2010)

Dear Mr. Kiely,

By chance, I just learned of the possibility that the EPA may conditionally register a pesticide product containing nanosilver as a new active ingredient for a period of 4 years. The antimicrobial pesticide product, HeiQ AGS-20, is a silver-based product that is proposed for use as a preservative for textiles.

I am HIGHLY concerned about the research data I have seen showing the real danger of these nanosilver particles washing out into the environment and causing unknown and potentially devastating damage to other, potentially helpful, bacteria in our environment.

I am strongly opposed to any approval of nanosilver antimicrobial products.

December 1, 2011

Not knowing who at the EPA receives public comment on this topic, I must ask, please forward this email to anyone who receives public comment on this important topic.

Thank you for your stewardship of our public environment.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Silver is currently used as a broad spectrum antibiotic in wound dressings and thus will impact beneficial bacteria. However, the present concern is regarding the increase use of silver, such as silver nanoparticles for preserving textiles, which may result in more bacteria developing resistance to silver and limit its use as an antibiotic agent for wound care. In the wound care setting, a recent review by Chopra (2007) concluded that the threat of bacterial resistance to silver in the clinical setting is low.

In terms of environmental impact, a recent study involved releasing 1 mg/L of silver nanoparticles into microcosms containing estuary water overlying estuarine sediment cores (Bradford et al., 2009). The study found no impact to the microbial community over a 30 day monitoring period. Evidence for antibacterial resistance was also evaluated during this study and no increase in antibiotic resistance to the bacterial population in the sediment was found (Mühling et al. 2010). Wigginton et al. (2010) suggested that the lack of antimicrobial effect in the microcosm was expected given that bacterial proteins efficiently bind to silver nanoparticles.

The Agency concludes that while development of antibacterial resistance due to the use of silver nanoparticles in AGS-20 is possible, the likelihood is low that the levels used in AGS-20 treated textiles will lead to the development of widespread bacterial resistance to silver.

Uncategorized Citizen Comments

Comment 7: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0025](#))

I do not want nanosilver in my clothes. What is wrong with you people putting pesticides in clothing?

Comment 24: Anonymous (8/19/2010 [EPA-HQ-OPP-2009-1012-0042](#))

December 1, 2011

I am not in any govt office or organization but I do not want more chemicals in my clothing or water. Please do not approve this!!!!

Comment 29: M. Quinn (8/24/2010 [EPA-HQ-OPP-2009-1012-0047](#))

PLEASE KEEP NANOSILVER OUT OF CLOTHING!!

We have more than enough toxins in our environment.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

POTWs

Comment 35: Chris Hornback, National Association of Clean Water Agencies (NACWA) (9/13/2010 [EPA-HQ-OPP-2009-1012-0053](#))

1. NACWA Comment: Unfortunately, since this conditional registration was not released in the *Federal Register*, many stakeholders, including many wastewater treatment plants that could be impacted by this product, will not have an opportunity to provide comments.

Response: The HeiQ Decision Document was not posted to the Federal Register because there was no statutory requirement to do so. However, to provide transparency in Agency decision making, the document was posed to the Pesticides Public Regulatory Docket for public comment. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

2. NACWA Comment: “However, given that the proposed decision document also indicates that silver ionization is greater for nanoscale particles due to an increase in surface area, the supposition of a lower environmental silver exposure resulting from nanosilver products may be false. No studies have been provided comparing the environmental exposure resulting from conventional silver-based pesticides and nanosilver pesticides, so there are no data to support the hypothesis that the overall environmental exposure is lower with nanoscale silver products.”

Response: The decision document states that “As the size of silver particles decreases...the potential for releasing silver ions increases, due to the increasing unit of surface area...” However, the other factor to consider is that of release rate. The rate of silver ion release from conventional silver salts is greater than from a comparable amount of silver nanoparticles. This fact is inherent in the decision document statement that “...larger amounts of [conventional] silver [have] to be added to an article in order to provide sufficient lifetime of activity for antimicrobial treatment.” The slower rate of silver release from nanosilver particles means that a smaller amount of AGS-20 would be required to achieve the same level of antimicrobial activity over a comparable time period. Thus, it is the reduced amount of nanosilver, as compared to conventional silver salts, that would lead to a lower environmental silver exposure.

3. NACWA Comment: “NACWA believes EPA has insufficient information to declare that a particular nanosilver product has added value over other silver-based pesticides.”

Response: As a general matter, EPA does not consider the comparative value of antimicrobial pesticides. Rather, EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels.

Because EPA is granting a conditional registration, EPA identified public interests in the potential to reduce environmental loading of silver and the availability of a more durable antimicrobial treatment as compared to the currently registered silver-salt based material preservatives. With this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives. For example, Geranio et al. (2009, Environ. Sci. Technol., 43:8113) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. We have reviewed the registered silver containing pesticides and found for commercially available products (Simonic and Tomsic, 2010, Textile Research Journal, 80:1721) that the amount of silver allowed in textiles ranges from 0.03 to 40 mg/g. If the pending conditional registration for HeiQ were approved, it would restrict the amount AGS-20 to between 0.01 to 0.1 mg/g as silver, which is on the low end of the spectrum for registered silver containing products.

4. NACWA Comment: EPA's primary reason for the conditional approval appears to be its concerns over market fairness and the fact that other competing products are already on the market. NACWA believes that EPA should instead focus its efforts on existing products and make sure there are sufficient data to determine their potential impacts.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. Where EPA can make the requisite statutory findings, the result may be the creation of a level playing field between already

registered and new pesticides. The Agency plans to issue data call-ins for the existing nanosilver containing pesticides.

5. NACWA Comment: In terms of EPA's assessment of the potential for "unreasonable adverse effects", the environmental exposure for the conditional approval was calculated using the Down-the-Drain model and assumed a wastewater treatment removal efficiency of 88%. This removal rate was not based on the removal of nanosized materials and, therefore, such a high rate of removal cannot be assumed. The wastewater treatment process is typically far more effective at removing larger particles than smaller ones and so it is quite likely that there will be considerable pass through of small materials such as silver nanoparticles. The removal efficiency must be characterized based on nanosilver and not ionic silver.

Response: The down-the-drain assessment was revised to address the potential discharge of nanosilver in wash water. Instead of using a single value for wastewater treatment removal efficiency, EPA considered a range of removal efficiencies for nanosilver from 85 to 99%, which were based on the work by Blaser et al. (2008, Sci. Total Environ. 390:396).

6. NACWA Comment: Based on the model output, EPA made the determination that the level of environmental exposure was unlikely to cause environmental harm. However, EPA recognizes that neither model considers the additive effect of other silver nanoparticles or silver containing products on the market. In addition, the *Daphnia magna* toxicity values which were used to evaluate the potential for in-stream toxicity were based on ionic silver. This is problematic as the FIFRA Scientific Advisory Panel stated: "... nanomaterials can deliver ions directly to specific tissues, cell membranes and inside cells - places where other forms of silver cannot reach. Therefore, the hazard profile of silver nanomaterials may differ from other forms of silver." This, coupled with the EPA statement that "... existing data seem to indicate that [nanosilver's] effects are different and/or more severe than for silver", does not corroborate EPA's expectation of "no unreasonable adverse effects" associated with approval for this product.

Response: In response to this comment the down-the-drain assessment was revised to address the potential discharge of nanosilver in wash water. Nanosilver toxicity to aquatic organisms including freshwater algae, flea, and fish were used to calculate risk quotients (RQs) that were compared to the Agency's Level of Concern (LOC) values for listed and non-listed aquatic species. The effect level for nanosilver used to calculate the RQs (i.e., 1.0 µg/L) was chosen to represent the most sensitive aquatic organism *Daphnia magna* and to represent conditions of moderately hard reconstituted water (MHRW), which is a test medium representative of surface water in the United States. The RQs for *Daphnia magna* exposed to nanosilver ranged from 0.00005 to 0.016, which are not of concern for listed or non-listed organisms because they were less than the LOC of 0.5 and 0.05, respectively.

7. NACWA Comment: From a wastewater treatment perspective, the conditional approval of another nanosilver product is discouraging. Wastewater utilities have been working diligently to reduce the input of silver into their wastestream in order to limit its presence in biosolids and wastewater effluent. Though strict pretreatment programs can limit the amount of silver entering the wastestream,

treatment plants do not have the authority or capability to regulate residential waste which is likely to be a large contributor of nanosilver materials.

Response: To date, AGS-20 is the only nanosilver containing product for which EPA made a registration decision involving nanosilver. Other products which claim to contain nanosilver are in the marketplace; however, these products are registered as containing elemental silver. As to the total volume of nanosilver that will enter the market place as a result of registering AGS-20, this value is unknown at this time. However, based on Agency confidential records, the total mass of silver distributed as material preservative in the United States during 2009 was less than 6,800 kg. The Agency estimated that 4,500 kg/yr of HeiQ AGS-20 nanosilver could be expected to be used in the unlikely event that every person in America was to purchase one t-shirt treated with AGS-20 every year. While this volume is not insignificant, it is small relative to the approximately 500,000 kg of silver that was released into the environment from other industry sectors during 2008 according to the EPA's Toxic Release Inventory.

8. NACWA Comment: In addition to the other data requirements, EPA must require any nanosilver pesticide product to be evaluated to assess its potential for nitrification inhibition at the wastewater treatment plant. In addition, it is not clear if a measure of removal efficiency during the wastewater treatment process is a component of the Tier 2 study requirements. Information on treatability is vital to characterizing environmental exposure in the Down-the-Drain model and must be a requirement of any Tier 2 data collection efforts.

Response: There is the potential for silver nanoparticles released from AGS-20 treated textiles to reach publically owned wastewater treatment and privately owned septic systems where they will most likely complex with sulfide and partition to biosolids. Once entrained in the biosolids, the silver nanoparticles could serve as a long term source of ionic silver which may adversely affect microorganisms that are vital to the wastewater treatment process. To evaluate this potential, HeiQ submitted test results on the impact of AGS-20 to wastewater treatment bacteria (MRID 479344-01). This test involved introducing AGS-20 powder and an AGS-20 liquid formulation used to surface treat textiles (AGS-20 TF) into bottles containing biosolids obtained from a wastewater treatment plant. Based on the similarity between the biological oxygen demand (BOD) caused by introducing glucose into bottles with AGS-20 and those without, there was no impact to the microorganisms in these bottles for AGS-20 loadings from 3.8 to 188 mg/L (0.76 to 37.6 mg/L as silver) or the AGS-20 TF liquid at loadings from 1 to 50 g/L over the 26 day test period. Although this result suggests that the silver in AGS-20 would not be expected to negatively impact wastewater treatment systems, it is unclear if the 26 day test period was sufficient time to evaluate this impact given that the rate of ionic silver released from AGS-20 is unknown.

There are contradictory reports in the scientific literature regarding the impact of silver nanoparticles on wastewater treatment systems. For example, nanosilver was reported to inhibit nitrification in the range of 50% (Choi and Hu, 2009a) to 84% (Choi and Hu, 2009b) based on a reduction in oxygen uptake rate. However, Burkhardt et al. (2010) found no impact to nitrification at nanosilver dosages of 1 mg/L, the same dosage that Choi and Hu (2009a and 2009b) reported as inhibitory. These two research groups are reporting different findings with the Burkhardt group suggesting little impact of nanosilver to

nitrification and the Hu group suggesting that an impact to wastewater treatment systems from nanosilver is expected.

While there are reports suggesting the potential for silver nanoparticles to impact wastewater treatment operations, the Agency does not anticipate that registering AGS-20 will lead to negative impacts to wastewater treatment systems. This conclusion is based on the small volume of nanosilver (i.e., < 4,500 kg/yr as estimated) expected to be introduced into commerce from AGS-20 treated textiles. However, if nanosilver is found to be released from AGS-20 treated textiles during leaching studies then EPA will require HeiQ to determine the impact to wastewater treatment processes.

As a result of this information, with this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives.

9. NACWA Comment: In this case, there are no current data that can be used to support a conclusion of "no unreasonable adverse effects" for the unique properties of nanosilver. EPA should instead work, to the extent of its authority, to limit the use of the other nanosilver products that have been unknowingly registered until the necessary data are provided.

Response: The Agency respectfully disagrees. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

The Agency plans to issue data call-ins for the existing nanosilver containing pesticides.

Comment 36: Jamie Heisig-Mitchel, Hampton Roads Sanitation District (9/13/2010 [EPA-HQ-OPP-2009-1012-0054](#))

1. HRSD Comment: ...it is important to note that the manner in which this specific request for comment was disseminated greatly limited opportunity for public participation. This request for comment was not published in the federal register. At a minimum, EPA should have notified parties who had submitted comments on previous nanoparticle proposals of this comment request.

Response: The HeiQ Decision Document was not posted to the Federal Register because there was no statutory requirement to do so. However, to provide transparency in Agency decision making, the document was posed to the Pesticides Public Regulatory Docket to provide an opportunity for public comment. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfeed1/cb/csb_page/form/form.html.

2. HRSD Comment: EPA believes that the use of the HeiQ product should result in a lower potential environmental exposure to silver as compared to conventional silver-based pesticides. However, given that the document also indicates that silver ionization is greater for nanoscale particles due to an increase in surface area, the supposition of a lower environmental silver exposure resulting from nanosilver products may be false. No studies have been provided comparing the environmental exposure resulting from conventional silver-based pesticides and nanosilver pesticides. There is no data to support the hypothesis that the overall environmental exposure is lower with nanoscale silver products.

Response: The decision document states that “As the size of silver particles decreases...the potential for releasing silver ions increases, due to the increasing unit of surface area...” However, the other factor to consider is that of release rate. The rate of silver ion release from conventional silver salts is greater than from a comparable amount of silver nanoparticles. This fact is inherent in the decision document statement that “...larger amounts of [conventional] silver [have] to be added to an article in order to provide sufficient lifetime of activity for antimicrobial treatment.” The slower rate of silver release from nanosilver particles means that a smaller amount of AGS-20 would be required to achieve the same level of antimicrobial activity over a comparable time period. Thus, it is the reduced amount of nanosilver, as compared to conventional silver salts, that would lead to a lower environmental silver exposure.

3. HRSD Comment: The consumer benefit highlighted is the prolonged antimicrobial activity of silver nanoparticles relative to other silver-based pesticides. ...there is no data representative of HeiQ AGS-20 which supports a prolonged length of efficacy and no direct comparison with other conventional silver-based pesticides to indicate that this nanoparticle product has added value.

Response: HeiQ has recently submitted confidential testing results comparing AGS-20 treated fabric to fabric treated with other silver-based pesticides demonstrating AGS-20’s antimicrobial effectiveness at reduced silver loading.

4. HRSD Comment: ...the study provided by HeiQ which evaluated the leaching of AGS-20 in wash water was insufficient to assess the leachability of their product. Extrapolation of the results from leaching studies performed on other silver nanoparticle products is inappropriate as the size of the nanoparticle directly influences its properties. This was recognized in the FIFRA SAP report: “Particle size substantially impact particles properties, such as rate and concentration of silver ion release, reactivity...”

Response: The study performed by Geranio et al. (2009, Environ. Sci. Technol., 43:8113) used textiles NP-PES-SURF and NP-PES which contained the HeiQ AGS-20 product. Thus, there was no extrapolation in results.

5. HRSD Comment: Rather than granting conditional approval to this new product and allowing currently registered products to remain on the market, EPA must remove all nanosilver pesticide products from the marketplace until data is provided for each product which indicates its use will not result in an unreasonable adverse impact on the environment.

Response: The Agency will initiate cancellation action if it determines that dietary (food and drinking water) and/or non-dietary (occupational and ecological) risks of concern necessitate the cancellation of all currently registered uses of a pesticide, or such risks necessitate changes to the terms and conditions of registration that registrants have been unwilling to implement. The Agency plans to issue data call-ins for the existing nanosilver containing pesticides.

6. HRSD Comment: The environmental exposure was calculated using the Down-the-Drain model and assumed a wastewater treatment removal efficiency of 88%. This removal rate was not based on the removal of nanosized materials and, therefore, such a high rate of removal cannot be assumed.

Response: The down-the-drain assessment was revised to address the potential discharge of nanosilver in wash water. Instead of using a single value for wastewater treatment removal efficiency, EPA considered a range of nanosilver removal efficiencies from 85 to 99%, which were based on the work by Blaser et al. (2008, Sci. Total Environ. 390:396).

7. HRSD Comment: Based on the model output, EPA made the determination that the level of environmental exposure was unlikely to cause environmental harm. However, EPA recognizes that neither model considers the additive effect of other silver nanoparticles or silver containing products on the market.

Response: The maximum amount of ASG-20 that can be used in textiles is limited to 0.01%. See terms and conditions on the registration as explained in the decision document. As to the total volume of nanosilver that will enter the market place as a result of registering AGS-20, this value is unknown at this time. However, based on Agency confidential records, the total mass of silver distributed as material preservative in the United States during 2009 was less than 6,800 kg. The Agency estimated that 4,500 kg/yr of HeiQ AGS-20 nanosilver could be expected to be used in the unlikely event that every person in America was to purchase one t-shirt treated with AGS-20 every year. While this volume is not insignificant, it is small relative to the approximately 500,000 kg of silver that was released into the environment from other industry sectors during 2008 according to the EPA's Toxic Release Inventory.

8. HRSD Comment: ...the *Daphnia magna* toxicity values which were used to evaluate the potential for in-stream toxicity, were based on ionic silver.

Response: The down-the-drain assessment was revised to address the potential discharge of nanosilver in wash water. Nanosilver toxicity to aquatic organisms including freshwater algae, flea, and fish were used to calculate risk quotients (RQs) that were compared to the Agency's Level of Concern (LOC) values for listed and non-listed aquatic species. The effect level for nanosilver used to calculate the RQs (i.e., 1.0 µg/L) was chosen to represent the most sensitive aquatic organism *Daphnia magna* and to represent conditions of moderately hard reconstituted water (MHRW), which is a test medium representative of surface water in the United States. The RQs for *Daphnia magna* exposed to nanosilver ranged from 0.00005 to 0.016, which are not of concern for listed or non-listed organisms because they were less than the LOC of 0.5 and 0.05, respectively.

9. HRSD Comment: POTWs do not have the authority or capability to regulate residential waste which is likely to be a large contributor of nanosilver materials.

Response: With this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives. For example, Geranio et al. (2009, Environ. Sci. Technol., 43:8113) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. We have reviewed the registered silver containing pesticides and found for commercially available products (Simoncic and Tomsic, 2010, Textile Research Journal, 80:1721) that the amount of silver allowed in textiles ranges from 0.03 to 40 mg/g. If the pending conditional registration for HeiQ were approved, it would restrict the amount AGS-20 to between 0.01 to 0.1 mg/g as silver, which is on the low end of the spectrum for registered silver containing products.

10. HRSD Comment: In addition, the work by Choi and Hu (2008) and Choi et al. (2008), which indicates that silver nanoparticles can have an increased inhibitory effect on the bacterial community vital to the wastewater nutrient removal process, is deeply concerning. With strict nutrient limitations imposed by National Pollutant Discharge Elimination System (NPDES) permits, there is little tolerance for even minor upsets to the microbial community present within the wastewater treatment plants. In addition to the other data requirements, the EPA must require HeiQ to conduct a nitrification inhibition evaluation on its product to assess its potential for nitrification inhibition at wastewater treatment plants. In addition, it is not clear if a measure of removal efficacy during the wastewater treatment process is a component of the Tier 2 study requirements. Information on treatability is vital to characterizing environmental exposure in the Down-the-Drain model and must be a requirement of Tier 2 data collection efforts.

Response: There is the potential for silver nanoparticles released from AGS-20 treated textiles to reach publically owned wastewater treatment and privately owned septic systems where they will most likely complex with sulfide and partition to biosolids. Once entrained in the biosolids, the silver nanoparticles could serve as a long term source of ionic silver which may adversely affect microorganisms that are vital to the wastewater treatment process. To evaluate this potential, HeiQ submitted test results on the impact of AGS-20 to wastewater treatment bacteria (MRID 479344-01). This test involved introducing AGS-20 powder and an AGS-20 liquid formulation used to surface treat textiles (AGS-20 TF) into bottles containing biosolids obtained from a wastewater treatment plant. Based on the similarity between the biological oxygen demand (BOD) caused by introducing glucose into bottles with AGS-20 and those without, there was no impact to the microorganisms in these bottles for AGS-20 loadings from 3.8 to 188 mg/L (0.76 to 37.6 mg/L as silver) or the AGS-20 TF liquid at loadings from 1 to 50 g/L over the 26 day test period. Although this result suggests that the silver in AGS-20 would not be expected to negatively impact wastewater treatment systems, it is unclear if the 26 day test period was sufficient time to evaluate this impact given that the rate of ionic silver released from AGS-20 is unknown.

There are contradictory reports in the scientific literature regarding the impact of silver nanoparticles on wastewater treatment systems. For example, nanosilver was reported to inhibit nitrification in the range of 50% (Choi and Hu, 2009a) to 84% (Choi and Hu, 2009b) based on a reduction in oxygen uptake rate.

However, Burkhardt et al. (2010) found no impact to nitrification at nanosilver dosages of 1 mg/L, the same dosage that Choi and Hu (2009a and 2009b) reported as inhibitory. These two research groups are reporting different findings with the Burkhardt group suggesting little impact of nanosilver to nitrification and the Hu group suggesting that an impact to wastewater treatment systems from nanosilver is expected.

While there are reports suggesting the potential for silver nanoparticles to impact wastewater treatment operations, the Agency does not anticipate that registering AGS-20 will lead to negative impacts to wastewater treatment systems. This conclusion is based on the test results provided by HeiQ and the small volume of nanosilver (i.e., < 4,500 kg/yr) expected to be introduced into commerce from AGS-20 treated textiles. However, if nanosilver is found to be released from AGS-20 treated textiles during leaching studies then EPA will require HeiQ to determine the impact to wastewater treatment processes.

11. HRSD Comment: Of the 19 Tier 1 studies EPA has indicated it will require from HeiQ to complete its assessment of human and environmental risk, HeiQ has not completed a single one. This is not a scenario in which conditional approval is being granted pending the approval of a few additional studies. In this case, there is no data that can be used to support a conclusion of “no unreasonable adverse effects”. There is no data available that warrants conditional approval of this product.

Response: The Agency has determined that there is 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 reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity. Therefore, the Agency is using the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 39: Ben Horenstein, Tri-TAC (9/13/2010 [EPA-HQ-OPP-2009-1012-0057](#))

1. TriTAC Comment: If silver pesticide product use becomes common, wastewater silver discharges could reach levels not seen in the last two decades—and could have adverse impacts on our wastewater treatment process as well as on the quality of our effluent and biosolids.

Response: The use of AGS-20 could lead to reductions in the overall use of silver in textiles. For example, Geranio et al. (2009, Environ. Sci. Technol., 43:8113) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. We have reviewed the registered silver containing pesticides and found for commercially available products (Simoncic and Tomsic, 2010, Textile Research Journal, 80:1721) that the amount of silver allowed in textiles ranges from 0.03 to 40 mg/g. If the pending conditional registration for HeiQ were approved, it would restrict the amount AGS-20 to between 0.01 to 0.1 mg/g as silver, which is on the low end of the spectrum for registered silver containing products.

As to the volume of nanosilver that will enter the market place as a result of registering AGS-20, this value is unknown at this time. However, based on Agency confidential records, the total mass of silver distributed as material preservative in the United States during 2009 was less than 6,800 kg. The Agency estimated that 4,500 kg/yr of HeiQ AGS-20 nanosilver could expected to be used in the unlikely event that every person in America was to purchase one t-shirt treated with AGS-20 every year. While this volume is not insignificant, it is small relative to the approximately 500,000 kg of silver that was released into the environment during 2008 according to the EPA's Toxic Release Inventory.

2. TriTAC Comment: POTWs are subject to National Pollutant Discharge Elimination System (NPDES) permits under the Clean Water Act. These permits include toxicity limits and may also include quantitative effluent limitations for silver. Exceeding these limitations has serious consequences, including monetary fines and penalties and the risk of citizen lawsuits. Under California law, our members are liable for daily Mandatory Minimum Penalties should violations of their discharge permits occur.

Response: Based on Agency confidential records, the total mass of silver distributed as material preservative in the United States during 2009 was less than 6,800 kg. Assuming that HeiQ has a production volume of 4,500 kg/yr yields a total yearly volume of 11,300 kg/yr ($4,500 + 6,800 = 11,300$) or approximately 31 kg/day ($11,300 \text{ kg/yr} \div 365 \text{ days/yr} = 31 \text{ kg/day}$) for all silver preservatives. Given that the Benchmark for silver in discharge water is 0.0318 mg/L and the approximate treatment capacity of the Bay Area POTWs is 300 million gallons per day, this means that the silver Benchmark is 36 kg/day for Bay Area POTWs. Since not all silver preservatives are used in the Bay Area, the approximate usage is 0.72 kg/day after adjusting for the Bay Area population (e.g., 7 million people). This is 50 times less than the amount of silver that would potentially lead to an NPDES violation. This analysis assumes that 100% of the silver is released from these products and that 100% of this silver passes through the Bay Area POTWs. Thus, the mass of silver used as material preservatives is not anticipated to lead to violations of NPDES permits in the Bay Area.

Supporting Calculations

$$\begin{aligned} &6,800 \text{ kg silver (2009 Agency data)} + 4,500 \text{ kg silver (HeiQ AGS-20)} = 11,300 \text{ kg/yr silver (total)} \\ &11,300 \text{ kg/yr silver (total)} \times \text{yr}/365 \text{ day} = 31 \text{ kg silver/day (total)} \end{aligned}$$

7 million people (Bay Area Population) / 300 million people (U.S. Population) = 0.0233 (population adjustment factor for Bay area)

31 kg silver/day (total) × 0.0233 (population adjustment factor for Bay area) = 0.72 kg silver/day (Bay area)

0.0318 mg silver/L (current bench mark value) × 300,000,000 gal (estimated combined wastewater outflow for Bay area) × 3.7854 L/gal = 3.6×10^7 mg/day

3.6×10^7 mg/day = 36 kg/day (bench mark value for Bay Area POTWs)

36 kg silver/day (bench mark value for Bay Area POTWs) / 0.72 kg silver/day (Bay area) = 50 times

3. TriTAC Comment: ...Benn and Westerhoff (2008) found that for certain products, silver losses during washing were so large that most of the silver in these products would be washed into the municipal wastewater system during the products' lifetimes. Where small particles occur in products, the entire particle could be washed down the drain.

Response: Benn and Westerhoff (2008) tested products that are commercially available and are currently registered as material preservatives. The more recent work by Geranio et al. (2009, Environ. Sci. Technol., 43:8113) used textiles NP-PES-SURF and NP-PES containing the HeiQ AGS-20 product and showed significantly lower silver release rates during washing of the HeiQ AGS-20 treated product as compared to the currently registered silver materials preservatives.

4. TriTAC Comment: Nanosilver particle may have extraordinary effects on POTW treatment processes. In two related studies, Choi and Hu (2008) and Choi et al. (2008) found that silver particles less than 5 nanometers in diameter are uniquely toxic to nitrifying bacteria, which are critical to biological nutrient removal at POTWs.

Response: There is the potential for silver nanoparticles released from AGS-20 treated textiles to reach publically owned wastewater treatment and privately owned septic systems where they will most likely complex with sulfide and partition to biosolids. Once entrained in the biosolids, the silver nanoparticles could serve as a long term source of ionic silver which may adversely affect microorganisms that are vital to the wastewater treatment process. To evaluate this potential, HeiQ submitted test results on the impact of AGS-20 to wastewater treatment bacteria (MRID 479344-01). This test involved introducing AGS-20 powder and an AGS-20 liquid formulation used to surface treat textiles (AGS-20 TF) into bottles containing biosolids obtained from a wastewater treatment plant. Based on the similarity between the biological oxygen demand (BOD) caused by introducing glucose into bottles with AGS-20 and those without, there was no impact to the microorganisms in these bottles for AGS-20 loadings from 3.8 to 188 mg/L (0.76 to 37.6 mg/L as silver) or the AGS-20 TF liquid at loadings from 1 to 50 g/L over the 26 day test period. Although this result suggests that the silver in AGS-20 would not be expected to negatively impact wastewater treatment systems, it is unclear if the 26 day test period was sufficient time to evaluate this impact given that the rate of ionic silver released from AGS-20 is unknown.

There are contradictory reports in the scientific literature regarding the impact of silver nanoparticles on wastewater treatment systems. For example, nanosilver was reported to inhibit nitrification in the range of 50% (Choi and Hu, 2009a) to 84% (Choi and Hu, 2009b) based on a reduction in oxygen uptake rate.

However, Burkhardt et al. (2010) found no impact to nitrification at nanosilver dosages of 1 mg/L, the same dosage that Choi and Hu (2009a and 2009b) reported as inhibitory. These two research groups are reporting different findings with the Burkhardt group suggesting little impact of nanosilver to nitrification and the Hu group suggesting that an impact to wastewater treatment systems from nanosilver is expected.

While there are reports suggesting the potential for silver nanoparticles to impact wastewater treatment operations, the Agency does not anticipate that registering AGS-20 will lead to negative impacts to wastewater treatment systems. This conclusion is based on the small volume of nanosilver (i.e., < 4,500 kg/yr as estimated) expected to be introduced into commerce from AGS-20 treated textiles. However, if nanosilver is found to be released from AGS-20 treated textiles during leaching studies then EPA will require HeiQ to determine the impact to wastewater treatment processes.

5. TriTAC Comment: POTWs tend to be most efficient at removing larger particles from wastewater. Tiny particles and zeolites may have different potential to pass through POTWs than other forms of silver.

Response: While the Agency does not yet have removal efficiency rates for nanoscale materials, in the work by Kiser et al. (2009) they reported 70 to 85% removal efficiency for engineered TiO₂ nanoparticles at 8 US wastewater treatment plants with most of the TiO₂ mass detected in the settled biosolids. Similar removal efficiencies and associations to sludge were reported for CeO nanoparticles (Limbach et al., 2008). The down-the-drain assessment was revised to address the potential discharge of nanosilver in wash water. Instead of using a single value for wastewater treatment removal efficiency, EPA considered a range of removal efficiencies from 85 to 99%, which were based on the work by Blaser et al. (2008, Sci. Total Environ. 390:396). Recent work by Kaegi et al. (2011, Environ. Sci. Technol., 45:3902) reported removal efficiencies of 70% for nanosilver shock loadings of 2.4 g/L to a pilot scale wastewater treatment system and 97% for loadings of less than 0.13 g/L. Based on this work, the Agency anticipates that nanoscale materials will be readily removed during wastewater treatment.

6. TriTAC Comment: While POTWs have the authority to regulate industrial and commercial sources of silver and other toxic pollutants, we have little or no control over the discharge of pollutants from the thousands of households we serve. Silver is a toxic metal that cannot degrade in the environment and is registered for use as a pesticide in numerous products. To allow the unrestricted usage of products that intentionally release silver into the environment would be an irresponsible neglect of the principles of environmental sustainability that should strongly influence U.S. EPA's decisions.

Response: While silver cannot degrade, it can and is readily transformed into stable mineral forms that are not harmful. Recent work by Kim et al. (2010) reported finding nanosized silver-sulfide particulates in the sewage sludge samples collected as part of the Targeted National Sewage Sludge Survey (TNSSS). These silver nanoparticles, which may have originated from nanosilver or silver ions, were in the mineral form consisted of acanthite (Ag₂S). This hypothesis is supported in the recent work by Kaegi et al. (2011, Environ. Sci. Technol., 45:3902) who reported the near complete transformation of nanosilver into the silver-sulfide mineral after introducing nanosilver at concentrations between 2.4 and 0.13 g/L into a

pilot scale wastewater treatment system. Acanthite (Ag_2S) is a relatively insoluble mineral and was found to exhibit lower toxicity to organisms than silver ions or silver nanoparticles (Choi et al., 2009, Water Research, 43:1879).

Trade Association

Comment 37: Harold T. Michels, Copper Development Association (9/13/2010 [EPA-HQ-OPP-2009-1012-0055](#))

1. CDA Comment: Concerns of equity and fairness demand that instead of allowing silver-based antimicrobial products, including HeiQ AGS- 20, to be marketed with implied public health claims under the guise of the “treated article” exemption, that EPA insist that the efficacy of silver-based products be supported by meaningful, real world, GLP efficacy data.

Response: The EPA approved pesticide label for HeiQ AGS-20 does not contain public health claims.

2. CDA Comment: CDA remains concerned that this and similar silver-based “additives” are not marketed in a manner consistent with the clear requirements for “non-public health” “treated article” products.

Response: The Agency will take these comments into consideration during enforcement actions.

3. CDA Comment: [The label is] ambiguous and potentially misleading to consumers as it allows unqualified bacterial growth suppression claims without the requisite caveat that it only protects against bacteria that may cause odors, discoloration or deterioration.

Response: The EPA approved pesticide label for HeiQ AGS-20 does not contain unqualified bacterial growth suppression claims.

4. CDA Comment: CDA objects to the conclusion in the Proposed Decision Document that “consumers purchasing textile treated with nanosilver should receive a durable antimicrobial protection.” No such consumer benefit is demonstrated by the data provided for HeiQ AGS-20, as the testing does not demonstrate efficacy under real world conditions.

Response: HeiQ has submitted subsequent confidential test results demonstrating the durability of the AGS-20 treated textiles in comparison to other commercially available nanosilver treated textiles.

States

Comment 30: Lynda Knobeloch, Wisconsin DHS (9/1/2010 [EPA-HQ-OPP-2009-1012-0048](#))

We are writing to request that the deadline for submission of comments be extended by at least 30 days. This request is being made because of the number of documents that need to be reviewed and the amount of staff time needed to complete our review and prepare comments.

Response: The public comment period was from August 12, 2010 through September 13, 2010. There was no statutory requirement for public comment on the Decision Document. However, to provide transparency in Agency decision making, the document was posted to the Pesticides Public Regulatory Docket to provide an opportunity for public comment. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

Comment 40: Marylou Verder-Carlos, California Department of Pesticide Regulation (9/13/2010 [EPA-HQ-OPP-2009-1012-0058](#))

1. CalDPR Comment: Insufficient toxicology data are available with which to make a scientifically informed evaluation of potential toxicity issues associated with nanosilver. Nanosilver has a distinctly different hazard profile when compared to more traditional forms of silver. The Proposed Decision Document points out numerous ways in which the toxicity could be underestimated based on available data.

Response: The Agency presented results from two toxicity studies performed with nanoscale silver. One was a 28-day rat feeding study using 60 nm diameter nanosilver (Kim et al., *Inhal. Toxicol.*, 2008, 10:575), which reported liver toxicity as well as effects on blood and systemic distribution of silver in rat tissues. The second study was a 90-day rat inhalation study completed with 18 to 19 nm diameter nanosilver (Sung et al., *Toxicol. Sci.*, 2009, 108:452), which found toxic effects in the liver and lungs. There are two more recent studies which will be incorporated into the final Decision Document. One is a 90-day rat feeding study that used 56 nm diameter nanosilver (Kim et al., *Part. Fibre Toxicol.* 2010, 7:20) and the other is a 28-day mouse feeding study that used 42 nm diameter nanosilver (Park et al., *Environ. Tox. Pharm.*, 2010, 30:162).

The Agency has determined that there is 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 reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity. Therefore, the Agency is using the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

2. Cal DPR Comment: The proposed use of the product, HeiQ AGS-20, raises significant concerns for human exposure. The screening level assessment provides information and notes the potential problem with occupational inhalation of HeiQ AGS-20 during formulation and application processes. However, it does not address potential inhalation or dermal exposure to consumers who will be in direct contact with the nanosilver particles for prolonged periods of time through the daily wearing and use of treated textiles. Additionally, infant and toddler exposures may result from extended exposure to pillowcases,

bedding, and clothing. Washing may dislodge particles, making them available for inhalation and possibly dermal absorption.

Response: The Decision Document contains an evaluation of the risk to children from dermal and incidental oral exposures to textiles treated with HeiQ AGS-20. Results from these studies were used to calculate the dose that a 3 year old toddler might receive while wearing and chewing on textiles treated with AGS-20. One conclusion of this process was that a child wearing an AGS-20 treated t-shirt would be exposed to nanosilver at a level that was, at a minimum, 1,000 times lower than the no observed adverse effects dosage.

EPA recognizes the potential for inhalation exposure to nanosilver during laundry drying of AGS-20 treated textiles. However, EPA lacks information on the release rate of nanosilver from AGS-20 treated textiles during laundry drying and is therefore requiring HeiQ to perform an attrition study to determine this information. While exposure may occur during laundry drying, EPA believes that when compared to exposure through dermal and oral contact with AGS-20 treated textiles, exposure during laundry drying will likely be of lower significance. The final Decision Document contains an estimate of the dose of nanosilver that a consumer might receive when drying AGS-20 treated textiles. This estimate supports the expectation of lower exposure from laundry drying when compared to dermal and oral contact to AGS-20 treated textiles. EPA is requiring HeiQ to perform an attrition study to confirm the assessment of exposure to nanosilver during laundry drying of AGS-20 treated textiles.

EPA typically does not consider long-term consumer exposures for textiles treated with an antimicrobial preservative because 1) the portion of the antimicrobial that is not bound to the textile is available for transfer and is expected to be depleted or washed out of the textile in less than 6 months (the remaining antimicrobial is bound to the textile and not available for transfer) and 2) because there is a low probability that an individual will be exposed to the same antimicrobial on a continuous, daily basis for 6 months (the scenario classified as long-term). However, EPA has received comments from the public regarding long-term exposure to AGS-20 treated textiles. There are limited use scenarios where the potential for long-term exposure to AGS-20 treated textiles could be expected. For example, consumers could seek out textiles treated with AGS-20 because of its unique properties. Another example would be use of AGS-20 treated textiles by military personnel where there is a probability that they would be exposed to AGS-20 on a daily basis for more than 6 months. In the case of the surface applied treatment, given that 35% of the silver leached out after the color-fast test, EPA anticipates that the silver in this product will be depleted or washed out of the textile in less than 6 months (the remaining antimicrobial is bound to the textile and not available for transfer). In the case of AGS-20 incorporated into fibers, the fact that only 1.5% of the silver was removed during the color-fast test indicates that the silver in these textiles could be expected to remain in the textile for greater than 6 months. Regardless, the risk from long-term inhalation, incidental oral, and dermal exposure to AGS-20 treated textiles would not be of concern as the MOEs are greater than the target MOE of 3,000 for textiles treated with AGS-20.

3. CalDPR Comment: Very little is known about the environmental fate and ecotoxicology of nanosilver in the environment.

Response: The rate at which silver nanoparticles transform into ionic silver determines the length of time that these particles will reside in the environment. Although there are studies reporting that silver nanoparticles will completely transform into ionic silver within six days after being dispersed into deionized water (Liu and Hurt, 2010), these results are only for one form of nanosilver and under conditions which are not representative of the environment. In the environment, silver nanoparticles are likely to complex with naturally occurring anions such as chloride and sulfide or natural organic matter such as humic acids, which will significantly delay the rate at which nanosilver transforms into ionic silver. For example, Choi et al., (2009, *Wat. Res.* 43:1879) provided spectroscopic evidence showing that silver nanoparticles react with sulfide to produce stable silver-sulfide complexes, which were shown by Liu et al. (2010, *Environ. Sci. Technol.* 44:2169) and Levard et al. (2011, *Environ. Sci. Technol.* 45:5260) to have undetectable rates of nanosilver to ionic silver transformation. These stabilized silver nanoparticle complexes are likely to partition to sediments rather than remain suspended in water due to gravitational settling and coagulation processes (see Page 19 FIFRA SAP, 2009). Likewise, silver nanoparticles are anticipated to partition to biosolids during wastewater treatment but may also be released in the effluent. Thus, there is the potential for silver nanoparticles to reside or persist in the environment for a significant period of time where these particles are most likely to be associated with sediments.

The down-the-drain assessment was revised to address the potential discharge of nanosilver in wash water. Nanosilver toxicity to aquatic organisms including freshwater algae, flea, and fish were used to calculate risk quotients (RQs) that were compared to the Agency's Level of Concern (LOC) values for listed and non-listed aquatic species. The effect level for nanosilver used to calculate the RQs (i.e., 1.0 µg/L) was chosen to represent the most sensitive aquatic organism *Daphnia magna* and to represent conditions of moderately hard reconstituted water (MHRW), which is a test medium representative of surface water in the United States. The RQs for *Daphnia magna* exposed to nanosilver ranged from 0.00005 to 0.016, which are not of concern for listed or non-listed organisms because they were less than the LOC of 0.5 and 0.05, respectively.

4. CalDPR Comment: The pharmacokinetics or pharmacodynamics of nanosilver is unknown at this time.

Response: The Agency agrees that the pharmacokinetic and pharmacodynamic properties of nanosilver are largely uncharacterized at present, and that these properties can provide important information about toxicity. Guideline metabolism and pharmacokinetic studies are conditionally required in tiered testing strategies for pesticides and the Agency asks for them only if it is anticipated that they will provide additional information that is necessary for understanding the toxicity of the test material. The Agency is requiring toxicity studies that are relevant to both the routes and durations of exposure for the use patterns of nanosilver products. Thus, it is anticipated that these studies will be sufficient for identifying and characterizing hazard in the absence of absorption, distribution, metabolism, and excretion (ADME) data.

It is also important to note that ADME studies of nanosilver are likely to be technically complex since both the particle and ion content of tissues would have to be determined. This situation is exemplified by two recent studies that were used in the Agency's screening-level risk assessment. Rodent studies in

which silver nanoparticles were administered by the oral route (Kim et al., *Inhal. Toxicol.*, 2008, 10:575-583) or by inhalation (Sung et al., *Toxicol. Sci.*, 2009, 108:452-461) show dose-dependent increases in silver content in diverse tissues (testes, liver, kidney, lungs, brain, stomach) and differences between male and female silver content via the oral route, with up to 3-fold more silver in female kidney tissue (Kim et al 2008). The silver in these tissues was detected by flame analysis, meaning there was no distinction between nanoscale silver and silver ions. Thus, these studies suggest that silver can localize to diverse sites in the body following exposure to nanosilver by different routes, and that there may be gender differences in organ levels. Although these results share some commonalities with those of other nanomaterials (e.g. ultrafine particulate matter, quantum dots) which have shown uptake by the reticuloendothelial system and translocation to the brain following exposure by different routes (i.e. inhalation), there is still some uncertainty as to the form of silver in the tissues (nanoparticle or ion or both). One way of determining nanosilver content would involve counting silver nanoparticles in multiple tissue sections of diverse organs using electron microscopy, which is labor intensive and only assesses small subsamples of tissues. However, in spite of the uncertainty in ADME, both of these studies yielded toxicological effects that provided endpoints for quantitative risk assessment in the screening-level risk assessment conducted by the Agency.

5. CalDPR Comment: Nanosilver and nanometals may pose unique exposure profiles when compared to traditional silver/metals.

Response: HeiQ AGS-20 is intended for use on textiles which are also treated using conventional silver. So the exposure profiles for textiles preserved with conventional and nanoscale silver appear to be similar.

6. CalDPR Comment: The physico-chemical behavior among various size groups of nanoparticles is unknown, with the smallest particle size generally considered to be the most reactive. Additionally, nanoparticles have been shown to aggregate to form larger intermediate forms (e.g., colloids, agglomerates, composites) with potentially unique properties.

Response: HeiQ submitted test results for AGS-20 that included physical-chemical behavior such as water solubility, melting point, and density. While EPA does not have complete knowledge of all the behaviors of AGS-20, there is sufficient information available for making an informed scientific evaluation regarding the conditional registration of HeiQ AGS-20.

7. CalDPR Comment: Existing fate/transport models for metals (e.g., Down-the Drain Model, Biotic Ligand Model) were developed to address bulk, not nano-scale forms of metals.

Response: The down-the-drain model is a basic mass discharge calculation (i.e., production volume/river flow) and assumes complete solubility of nanosilver, similar to the modeling approach used by Mueller and Nowack (2008, *Environ. Sci. Technol.* 42:4447). In the revised Decision Document, the biotic ligand model (BLM) was replaced by route-specific nanosilver toxicity studies completed with aquatic species.

8. CalDPR Comment: It is not known whether the proposed enforcement analytical method will suitably quantify the amount of the nanosilver active ingredient in the product, particularly when the product is a “nano-silver-silica composite.”

Response: There remains a significant effort to develop protocols and analytical methods for the Tier 1 Required Data. EPA would welcome CalDPR assistance with reviewing the analytical approaches that will be prepared by HeiQ as part of the conditional registration we are granting.

9. CalDPR Comment: The proposed product label indicates that the active ingredient in the product is silver metal (AG)* (19.3%). The label does not clearly indicate that the silver in the product is nanosilver. Underneath the active ingredient statement the label reads, “*size range < 1 μm ” or 1,000 nanometers. Assuming an umbrella classification of 1-100 nanometers to be nanotechnology, the silver in the product would need to be less than 0.1 μm .

Response: The proposed label has been revised to read: includes particles in the size range between 1 to 100 nm.

Industry

Comment 1: Abigail Trueblood, The Dow Chemical Company (4-27-10, EPA-HQ-OPP-2009-1012-0002.1)

Silver is not a new active ingredient, and it is unclear why EPA has chosen to identify this submission as containing a new active. If the submission in question contains a different form of silver other than those currently recognized by the Agency as active ingredients, this should have been made clear in this Notice. At the very least, the Notice as written generates confusion among current registrants of the active ingredient silver.

Dow hopes to see the Agency address this issue publically with an explanation of why the silver contained in the submission identified in EPA-HQ-OPP-2009-1012 is regarded as a new active ingredient.

Response: Silver is not a new active ingredient; however, EPA could not conclude that the nanoscale material in AGS-20 was an active ingredient in any currently registered pesticide.

Historically, EPA has considered applications for pesticide products that claim to be identical or substantially similar in composition to a registered product as so-called “me-too registrations” under FIFRA registration authorities. Until recently, EPA generally has not focused on the size of an ingredient as an attribute relevant when determining if the product in an application is identical or substantially similar in composition to a registered pesticide product. However, a nanoscale ingredient may have properties that are different from those of conventionally-scaled ingredients and properties that differ from the atoms or molecules from which the nanoscale ingredient is constructed. Therefore, a nanoscale ingredient may also have different environmental health and safety properties. Accordingly, for a product containing an ingredient that is a nanoscale version of a conventionally-sized active or inert ingredient contained in an already-registered product or a different nanoscale version of a

nanoscale material that is an active or inert ingredient in an already registered pesticide product, EPA necessarily will need data on the nanoscale material to make the requisite statutory findings.

In September, 2008 HeiQ submitted an application for registration of AGS-20 as a “me-too” registration under FIFRA section 3(c)(7)(A). However, after consultation with the FIFRA Scientific Advisory Panel, which was held from November 3 through 5, 2009, EPA could not conclude that the nanoscale material in AGS-20 was an active ingredient in any currently registered pesticide. Consequently, EPA requested that HeiQ re-classify its application to register AGS-20 from “me-too” to a new active ingredient. HeiQ agreed to this request and on March 31, 2010 EPA announced that AGS-20 was re-classified as a product containing a new active ingredient (Federal Register, Vol. 75, No. 61, Page 16110).

Comment 2: Marie Paquette, BASF The Chemical Company (4-27-10, EPA-HQ-OPP-2009-1012-0003.1)

On March 31, 2010, EPA published a notice of receipt of applications for registration of pesticide products containing new active ingredients (75 FR 16109). In particular, the notice identified an application under File Number 85249-R, with silver identified as the new active ingredient, for uses as “antimicrobial and preservative additive used to treat fibers, plastics, polymers, latex products and ceramics.”

Silver is not a new active ingredient. Silver has been an active ingredient in pesticide products since the 1970’s. Silver was addressed during re-registration (RED issued 1992) and is being addressed through registration review. The former Ciba Corporation, which is now BASF Corporation, is a registrant of several pesticide products containing silver that are approved for the same uses.

Therefore, it is unclear as to why the Agency would list silver as a new active ingredient under this notice. If there is something that makes this a new active ingredient, the Agency must clearly identify what it is and why it is different, so that appropriate opportunity for public comment is provided in accordance with FIFRA § 3(c)(4) and 40 CFR § 152.102. Without providing that additional information and opportunity for comment, the Agency will have failed to meet its statutory obligations as well as its obligations under its regulations.

It is of concern to BASF Corporation that there is a change in the Agency’s determination of when silver is or is not a new active ingredient. We are requesting that the Agency extend the public comment period for this notice of receipt and provide a clear and specific explanation of why this silver is a new active ingredient so that there is appropriate opportunity for input on the basis for the Agency’s determination.

Response: Silver is not a new active ingredient; however, EPA could not conclude that the nanoscale material in AGS-20 was an active ingredient in any currently registered pesticide.

Historically, EPA has considered applications for pesticide products that claim to be identical or substantially similar in composition to a registered product as so-called “me-too registrations” under FIFRA registration authorities. Until recently, EPA generally has not focused on the size of an ingredient as an attribute relevant when determining if the product in an application is identical or substantially

similar in composition to a registered pesticide product. However, a nanoscale ingredient may have properties that are different from those of conventionally-scaled ingredients and properties that differ from the atoms or molecules from which the nanoscale ingredient is constructed. Therefore, a nanoscale ingredient may also have different environmental health and safety properties. Accordingly, for a product containing an ingredient that is a nanoscale version of a conventionally-sized active or inert ingredient contained in an already-registered product or a different nanoscale version of a nanoscale material that is an active or inert ingredient in an already registered pesticide product, EPA necessarily will need data on the nanoscale material to make the requisite statutory findings.

In September, 2008 HeiQ submitted an application for registration of AGS-20 as a “me-too” registration under FIFRA section 3(c)(7)(A). However, after consultation with the FIFRA Scientific Advisory Panel, which was held from November 3 through 5, 2009, EPA could not conclude that the nanoscale material in AGS-20 was an active ingredient in any currently registered pesticide. Consequently, EPA requested that HeiQ re-classify its application to register AGS-20 from “me-too” to a new active ingredient. HeiQ agreed to this request and on March 31, 2010 EPA announced that AGS-20 was re-classified as a product containing a new active ingredient (Federal Register, Vol. 75, No. 61, Page 16110).

Comment 41: James G. Votow WilmerHale for HeiQ Matierals AG (9/13/2010 [EPA-HQ-OPP-2009-1012-0059](#))

This comment was in support of the registration of AGS-20 and no EPA response was necessary.

NGOs

Comment 26: Jaydee Hanson, ICTA (8/23/2010 [EPA-HQ-OPP-2009-1012-0044](#))

The International Center for Technology Assessment (ICTA) would like to thank the agency for circulating its memorandum announcing the posting of documents to Docket Number EPA-HQ-OPP-2009-1012 and opening a public comment period regarding its proposed conditional registration of "HeiQ AGS-20". ICTA intends on fully participating in the comment process and welcomes this and any other opportunities to communicate with the agency on this topic.

We write at this time to respectfully request a 30-day extension of the September 11, 2010 deadline for public comment to October 10, 2010. As the agency and FIFRA Scientific Advisory Panel have both recognized, this is an important issue and as such the agency should gather as much information as possible about its next steps from all interested parties. We recognize that the agency chooses to act promptly on the matter, however between now and September 11th is a very problematic time for many interested parties due to legislative recess, seasonal transitions of staff, and vacation/holiday schedules. In light of these circumstances we are concerned that the current deadline will not be sufficient for some parties to provide comment. The proposed registration and broader nanosilver issue present many complicated legal and scientific issues and meaningful public input will require a

December 1, 2011

substantial amount of time and effort. The requested extension is necessary to provide interested parties an appropriate opportunity to develop meaningful comments on the agency's proposed action.

Response: The public comment period was from August 12, 2010 through September 13, 2010. There was no statutory requirement for public comment on the Decision Document. However, to provide transparency in Agency decision making, the document was posed to the Pesticides Public Regulatory Docket to provide an opportunity for public comment. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

Comment 31: Dr. Maria Powell, NanoCEO (9/7/2010 [EPA-HQ-OPP-2009-1012-0049](#))

Firstly, I would like to thank the agency for circulating a memorandum announcing the posting of documents to Docket Number EPA-HQ-OPP-2009-1012 and opening a public comment period regarding the proposed conditional registration of HeiQ AGS-20.

However, I (and my organization's members) find the extremely short period of time provided for public comment problematic. Moreover, this is a very difficult time for many people--many of whom take vacations in August or are busy with other summer-to-fall transitions. It is also a hard time for other interested parties such as university and government scientists and policymakers, due to legislative recess, seasonal transitions of staff, and vacation/holiday schedules.

The registration of a nanosilver product is an extremely important issue for public and environmental health, and as you know involves complex scientific, economic, political, and ethical issues. It is absolutely critical that enough time be provided for all the stakeholders--citizens, scientists, policymakers, etc--to read and review the information provided on the docket, discuss this information, and provide comments and questions to the docket that can be considered by the agency in deciding whether to grant conditional approval to this product.

Citizens and other stakeholders have relevant information to bring to this discussion, and will also bear any public health and environmental consequences of silver released from products treated with HeiQ nanosilver materials. Not allowing them adequate time to review the issues and comment, is not a truly democratic decision-making process.

We hope the agency will support democracy and citizen engagement in science and policymaking regarding nanosilver and other risk issues. Please extend the comment period for another 30 days, to October 10, 2010.

Response: The public comment period was from August 12, 2010 through September 13, 2010. There was no statutory requirement for public comment on the Decision Document. However, to provide transparency in Agency decision making, the document was posed to the Pesticides Public Regulatory Docket to provide an opportunity for public comment. Postings to the public docket are sent via an

December 1, 2011

automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

Comment 32: M. Griffin (9/7/2010 [EPA-HQ-OPP-2009-1012-0050](#))

We are very much interested in submitting comments. As this is a cross agency topic we respectfully request that an extension be granted to the deadline for these comments.

Thank you

Response: The public comment period was from August 12, 2010 through September 13, 2010. There was no statutory requirement for public comment on the Decision Document. However, to provide transparency in Agency decision making, the document was posed to the Pesticides Public Regulatory Docket to provide an opportunity for public comment. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

Comment 33: Wenonah Hauter, Food and Water Watch (9/8/2010 [EPA-HQ-OPP-2009-1012-0051](#))

Food & Water Watch would like to thank the agency for circulating its memorandum announcing the posting of documents to Docket Number EPA-HQ-OPP-2009-1012 and opening a public comment period regarding its proposed conditional registration of "HeiQ AGS-20."

Food & Water Watch intends on fully participating in the comment process. However, between now and September 11th is a very problematic time for many interested parties due to legislative recess vacation/holiday schedules, and demands created by pressing food safety issues like the massive recall of eggs due to salmonella contamination. In light of these circumstances we are concerned that the current deadline will not be sufficient for some parties to provide comment. Therefore, we write at this time to respectfully request a 30-day extension of the September 11, 2010 deadline for public comment.

Response: The public comment period was from August 12, 2010 through September 13, 2010. There was no statutory requirement for public comment on the Decision Document. However, to provide transparency in Agency decision making, the document was posed to the Pesticides Public Regulatory Docket to provide an opportunity for public comment. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

Comment 34: Caroline Cox, Center for Environmental Health (9/13/2010 [EPA-HQ-OPP-2009-1012-0052](#))

The following new research demonstrates an important public health hazard relevant to the use of nanosilver antimicrobials:

Laura K. Braydich-Stolle, et al. Silver Nanoparticles Disrupt GDNF/Fyn kinase Signaling in Spermatogonial Stem Cells TOXICOLOGICAL SCIENCES 116(2), 577–589 (2010).

In view of the significant health issues, registration of nanosilver products at this time is inconsistent with EPA's mandate to protect human and environmental health.

Response: The Agency has reviewed the cited study and concluded that it does show that nanosilvers of different sizes and coatings can get inside of virally transformed cells when added directly to the cells in vitro, resulting in reduced cell viability. This study suggests the potential for an effect of nanosilvers on male fertility, but did not address whether or not nanosilvers actually reach the testis when administered to test animals via different routes of exposure or if the ability of such males to reproduce is adversely affected.

The Agency has reviewed the literature and is aware of only two studies in which the ability of silver from nanosilver to reach the testis was measured. The Agency cited these in the screening-level risk assessment. These are a 90-day study via the inhalation route (Sung et. al., Toxicol. Sci., 2009, 108(2): 452) and a 28 day study via the oral route (Kim et al., Inhal. Toxicol., 2008, 20:575). Silver was found only in the testis of animals to which nanosilver was administered via the oral route. The only anticipated oral exposures to HeiQ's product are incidental oral exposures (from children sucking on treated fabric). Since these oral behaviors are generally restricted to very young children, the Agency does not consider the oral route to be a likely route of exposure for persons of reproductive age. However, the Agency is still requiring HeiQ to conduct an *in vivo* guideline 870.3650 combined repeated dose toxicity study via the oral route that includes reproductive and developmental endpoints. This study will include detailed histopathological examination of the male gonads to assess spermatogenesis, as well as assessment of reproductive function and effects in offspring.

Comment 38: Jo Anne Shatkin, CLF Ventures (9/13/2010 [EPA-HQ-OPP-2009-1012-0056](#))

1. CLF Comment: An additional occupational exposure scenario that OPP should evaluate includes professional laundering and dry cleaning of treated fabrics. Nanosilver particles may be released to water, solvents or air during commercial laundering, with potential occupational dermal and inhalation exposures to treated fabrics.

Response: EPA recognizes the potential for inhalation exposure to nanosilver during laundry drying of AGS-20 treated textiles. However, EPA lacks information on the release rate of nanosilver from AGS-20 treated textiles during laundry drying and is therefore requiring HeiQ to perform an attrition study to determine this information. While exposure may occur during laundry drying, EPA believes that when compared to exposure through dermal and oral contact with AGS-20 treated textiles, exposure during laundry drying will likely be of lower significance. The final Decision Document contains an estimate of the dose of nanosilver that a consumer might receive when drying AGS-20 treated textiles. This estimate supports the expectation of lower exposure from laundry drying when compared to dermal and oral contact to AGS-20 treated textiles. EPA is requiring HeiQ to perform an attrition study to confirm the assessment of exposure to nanosilver during laundry drying of AGS-20 treated textiles.

2. CLF Comment: ...recently published another study (Kim et al. 2010) with different nanosilver material, lasting 90 days instead of 28, and in a different species of rat. This additional study (which is not referenced by EPA) also determined a similar No Observable Adverse Effect Level of 30 mg/kg to the one used as the basis for the POD.

Response: The work by Kim et al. (Part. Fibre Toxicol. 2010, 7:20) and the repeated-dose toxicity and inflammatory responses in mice by oral administration of silver nanoparticles by Park et al. (Environ. Toxicol. Phar. 2010, 30:162) were made available after the Decision Document was prepared. The Agency incorporated the findings of these studies into the final version of the Decision Document.

3. CLF Comment: If, based on well designed and validated protocols that consider a breadth of water quality types and conditions, those additional exposure studies suggest low exposure and hence do not warrant detailed evaluation of toxicity for this product...

Response: The Agency agrees that unnecessary animal testing is to be avoided and have proposed that further testing only be conducted if textiles treated with HeiQ AGS-20 are found to release nanoscale silver particles.

4. CLF Comment: ...OPP should require labeling of fabrics containing nanosilver.

Response: Consumers will be informed where there are marketing claims provided by product advertising.

Comment 42: Olga V. Naidenko, Environmental Working Group (9/13/10 EPA-HQ-OPP-2009-1012-0060)

1. EWG Comment: EPA puts public health at unnecessary risk by approving nanomaterials for use in consumer products in the absence of the basic health and safety data the agency requires for antimicrobials (EPA 2010b).

Response: In September, 2008 HeiQ submitted an application for registration of AGS-20 as a “me-too” registration under FIFRA section 3(c)(7)(A). This application contained the required data regarding AGS-20 product identity and composition, physical and chemical properties, and health effects. HeiQ submitted short-term acute animal toxicity testing data for AGS-20 as detailed in the Decision Document. These data demonstrated that AGS-20 did not cause abnormalities or mortalities in test animals after administration by oral, dermal, and inhalation routes, was moderately to non-irritating in skin and eye testing, and was not a skin sensitizer based on dermal testing. Furthermore, HeiQ submitted five studies covering the amount of silver released from and the efficacy of AGS-20 treated textiles, the occupational exposures to AGS-20, and potential impacts to wastewater treatment. Thus, the base-line safety testing of AGS-20 was performed.

The Agency has determined that there is 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 reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity. Therefore, the Agency is using the maximum 10 fold

database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

2. EWG Comment: Risks to human health and the environment will be defined by cumulative exposures to HeiQ AGS-20 and other nanosilver-containing consumer products already on the market. Ignoring cumulative exposures, as EPA proposed with the AGS-20 conditional approval, could jeopardize human health.

Response: The Project on Emerging Nanotechnologies (PEN) has compiled an inventory of all consumer products reported by their manufacturers to contain nanomaterials. Based on the information PEN has compiled, nanosilver is the most common nanoscale material currently used in consumer products. Approximately a quarter of the identified consumer nanomaterial products are claimed to contain nanosilver. Nanosilver products are sold in the U.S. and in foreign markets such as Asia, Europe, Australia, and South America. As discussed in the Market Equity section, four registered antimicrobial products have recently been identified by the registrants as containing nanosilver. In addition, FDA has allowed the sale of bandages treated with nanosilver to control post-operative infections in surgical wounds and the sale of catheters and other devices, which may come in contact with human tissues, treated with nanosilver to control the growth of microorganisms. While EPA does not have data to quantify relative exposure to nanosilver from these products vs. HeiQ's product, given the number of other uses for silver in the market, EPA thinks it is reasonable to expect that nanosilver exposure resulting from the multiple consumer products and FDA uses is likely to be considerably higher than the consumer exposure that would result from wearing textile products treated with AGS-20.

3. EWG Comment: Nanosilver pesticide registrants, including the HeiQ Company and past registrants of similar approved products, should addresses outstanding data gaps on the potential toxicity of these materials. Until these gaps are filled, EPA cannot ensure that nanoparticles antimicrobials are safe for widespread use in consumer products.

Response: The Agency respectfully disagrees. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from

textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed. The Agency plans to issue data call-ins for the existing nanosilver containing pesticides.

Comment 43: Jennifer Sass, NRDC (9/13/10 EPA-HQ-OPP-2009-1012-0061)

1. NRDC Comment: The registrant has had sufficient time to generate and submit required data

Response: In September, 2008 HeiQ submitted an application for registration of AGS-20 as a “me-too” registration under FIFRA section 3(c)(7)(A). However, after consultation with the FIFRA Scientific Advisory Panel, which was held from November 3 through 5, 2009, EPA could not conclude that the nanoscale material in AGS-20 was an active ingredient in any currently registered pesticide. Consequently, EPA requested that HeiQ re-classify its application to register AGS-20 from “me-too” to a new active ingredient. HeiQ agreed to this request and on March 31, 2010 EPA announced that AGS-20 was re-classified as a product containing a new active ingredient (Federal Register, Vol. 75, No. 61, Page 16110). Because the Agency had not reached a final decision with regard to which types of data would be further required for nanoscale materials, HeiQ did not have the benefit in support of an application for a new active ingredient of a reasonable period of time within which to generate and submit this data to the Agency.

2. NRDC Comment: ...AGS-20 may cause “unreasonable adverse effects on the environment” The special considerations of the impact of these exposures on children and infants must be incorporated into EPA’s assessment of these unique materials. Because EPA has failed to consider or evaluate these exposures, the Agency may not make the required safety finding under FIFRA. When considering life-stage related sensitivities to nanoparticle toxicity, the elderly also represent a vulnerable subpopulation.

Response: EPA calculated conservative estimates for the risk to children and workers potentially exposed to AGS-20 based on toxicity data available for similar nanosilver compounds available in the scientific literature. One conclusion of this process was that a child wearing an AGS-20 treated t-shirt would be exposed to nanosilver at a level that was, at a minimum, 1,000 times lower than the no observed adverse effects dosage. Thus, the Agency did consider and evaluate exposures to children as part of its finding that AGS-20. Although these calculated for children, they are protective of adults wearing and working with clothing treated with AGS-20, since ratio of skin surface area to the body weight is greater for children than for adults.

3. NRDC Comment: Use of the pesticide is not in the public’s interest. ...EPA has not explained why consumers need antimicrobial textiles.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand.

With this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives. For example, Geranio et al. (2009, Environ. Sci. Technol., 43:8113) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. We have reviewed the registered silver containing pesticides and found for commercially available products (Simoncic and Tomsic, 2010, Textile Research Journal, 80:1721) that the amount of silver allowed in textiles ranges from 0.03 to 40 mg/g. If the pending conditional registration for HeiQ were approved, it would restrict the amount AGS-20 to between 0.01 to 0.1 mg/g as silver, which is on the low end of the spectrum for registered silver containing products. HeiQ has recently submitted confidential testing results comparing AGS-20 treated fabric to fabric treated with other silver-based pesticides demonstrating AGS-20's antimicrobial effectiveness at reduced silver loading.

4. NRDC Comment: Compared with silver, nanosilver releases more ions and is therefore more toxic, more biologically active, more deadly to microbes, and more persistent in the environment.

Response: The decision document states that "As the size of silver particles decreases...the potential for releasing silver ions increases, due to the increasing unit of surface area..." However, the other factor to consider is that of release rate. The rate of silver ion release from conventional silver salts is greater than from a comparable amount of silver nanoparticles. This fact is inherent in the decision document statement that "...larger amounts of [conventional] silver [have] to be added to an article in order to provide sufficient lifetime of activity for antimicrobial treatment." The slower rate of silver release from nanosilver particles means that a smaller amount of AGS-20 would be required to achieve the same level of antimicrobial activity over a comparable time period. Thus, it is the reduced amount of nanosilver, as compared to conventional silver salts, that would lead to a lower environmental silver exposure.

5. NRDC Comment: EPA bemoans the high costs of regulatory requirements, including new data generation, on the registrants and even frets that these regulatory costs may "discourage technology providers from pursuing the development of beneficial new applications of nanotechnology in the field of pesticides." (Decision Doc at 30). This argument is presented without any supporting data, or even "guesstimates" of the actual costs and benefits of this "innovative" technology.

Response: The Agency stated that "...meeting regulatory requirements can add costs and delay the marketing of new products" in the proposed Decision Document. This statement was removed from the final Decision Document. No economic analysis has been performed to quantify these costs and delays.

6. NRDC Comment: In addition, EPA does not appear to have a reliable tracking system to identify when required data for a conditional registration are still missing, identify and sort data that has been received, review the data and record the Agency staff conclusions, and incorporate the incoming data into the chemical assessment and product registrations in a timely and appropriate manner that reflects any hazards identified in the data.

Response: The pesticide program does not currently have an information technology system designed for tracking or managing conditional registration actions. In the absence of such a system, the program has utilized the Office of Pesticide Programs Information Network (OPPIN) to provide some minimal reporting capacity. OPPIN has some limited codes allowing identification of regulatory actions as conditional registrations. OPP is in the process of sunseting and replacing the OPPIN data system. As the new IT system is designed, the upgrades will include tools to improve the identification, tracking, reporting and program management of conditional registrations.

7. NRDC Comment: EPA has overused conditional registrations, as they now represent the majority of active registrations. The EPA Office of Pesticide Programs (OPP) has over 16,000 pesticide product active registrations (that is, currently registered). Of these, over 11,000 (68%) are conditionally registered.

Response: The OPP program has used the term 'conditional registration' to cover both actions intended by Section 3(c)(7) of FIFRA, and other activities outside that section of the statute. While the latter activities, such as requiring label changes, are legitimate program actions, OPP has been imprecise in its use of the term "conditional registration." It is likely that most of the of the registration decisions described in OPPIN as conditional registrations may not, in fact, have been registration actions taken under 3(c)(7). In the future, OPP needs to be more careful to eliminate potential confusion with the actions that meet the Section 3(c)(7) conditional registration criteria.

Over the past decades, OPPIN identifies approximately 1,400 registration actions which meet the FIFRA Section 3(c)(7)(B) and (C) criteria. This is less than 2% of the approximately 90,000 registration decisions in OPPIN. This indicates that, as statutorily intended, this authority for conditional registrations for registering new uses or new ingredients has been used in relatively narrow circumstances. Our analysis indicates that for the overwhelming majority of these conditional registrations the conditions of the registration have been satisfied in a timely fashion (See <http://www.epa.gov/pesticides/regulating/conditional-registration.html>). OPP's review of the data submitted for these conditional registrations has not justified a change in either the initial risk assessments or the risk management label conditions. Therefore, our use of conditional registrations has not resulted in greater risk to human health or the environment. This validates the quality of the safety finding that preceded the issuance of the conditional registrations.

Comment 44: Maria Powell, Nanotechnology Citizen Engagement Organization (9/13/10 EPA-HQ-OPP-2009-1012-0062)

1. NanoCEO Comment: We want to note that the public comment period on this docket was much too short for the members of our organization to review documents adequately and write comments, especially at this time of the year when many people are on vacation. Not providing adequate time for public to comment on critical environmental and public health decisions is not supportive of citizen engagement or democratic decision making.

Response: There was no statutory requirement to provide a public comment period for the HeiQ Decision Document. However, to provide transparency in Agency decision making, the document was

posed to the Pesticides Public Regulatory Docket to provide an opportunity for public comment. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

2. NanoCEO Comment: ...once emitted from all these products, it will continue to circulate in the environment, releasing silver ions over time under different conditions and environmental contexts, and bioaccumulate in organisms, including humans, over time.

Response: The rate at which silver nanoparticles transform into ionic silver determines the length of time that these particles will reside in the environment. Although there are studies reporting that silver nanoparticles will completely transform into ionic silver within six days after being dispersed into deionized water (Liu and Hurt, 2010), these results are only for one form of nanosilver and under conditions which are not representative of the environment. In the environment, silver nanoparticles are likely to complex with naturally occurring anions such as chloride and sulfide or natural organic matter such as humic acids, which will significantly delay the rate at which nanosilver transforms into ionic silver. For example, Choi et al., (2009) provided spectroscopic evidence showing that silver nanoparticles react with sulfide to produce stable silver-sulfide complexes, which were shown by Liu et al. (2010) and Levard et al. (2011) to have undetectable rates of nanosilver to ionic silver transformation. These stabilized silver nanoparticle complexes are likely to partition to sediments rather than remain suspended in water due to gravitational settling and coagulation processes (see Page 19 FIFRA SAP, 2009). Likewise, silver nanoparticles are anticipated to partition to biosolids during wastewater treatment but may also be released in the effluent. Thus, there is the potential for silver nanoparticles to reside or persist in the environment for a significant period of time where these particles are most likely to be associated with sediments.

To verify the expectation that the silver in AGS-20 will form stable complexes under environmental conditions, EPA is requiring HeiQ to conduct a dissolution kinetics study to measure the rate and form of silver released from AGS-20 in simulated natural water.

3. NanoCEO Comment: There is insufficient evidence supporting the widespread assumption that silver is “innocuous” to humans, and considerable evidence refuting it. Numerous experimental studies suggest that silver can affect mammalian cells in many of the same ways it affects non-mammalians at a range of doses—binding, interacting, and interfering with DNA, proteins and enzymes, altering membrane ion transport and membrane integrity, causing oxidative stress and cytotoxicity, significant immune responses, and more.

Response: The no observable adverse affects level (NOAEL) of 30 mg/kg/day used in the Proposed Decision Document, which was revised to 0.5 mg/kg/day in the Final Decision Document, was based on enzyme and liver abnormalities. In no way does the Agency support the notion that silver is “innocuous” to humans.

4. NanoCEO Comment: Most puzzlingly, regulatory standards to this day are primarily based on a small number of very old and limited studies—in particular, Gaul and Staud (1935) and Hill and Pillsbury (1939). We find it highly troubling that these two reports, one of which was an extremely limited study

on syphilis patients, continue to be the basis for health standards on silver currently, especially in light of the increasing uses of silver and nanosilver ubiquitously in commerce and the highly sophisticated methodologies and technologies that are currently available to scientists and risk assessors to study silver/nanosilver's risks to humans. NanoCEO Comment: Regardless, we know that nano-sized forms of silver are more potent than larger forms of silver in releasing silver ions because of their higher surface-to-volume ratio; indeed, this is why they are promoted and marketed as more potent antimicrobials. The proposed decision document for the registration of HeiQ AGS-20 states this clearly (p.3, p. 29).

Response: These studies were not used in evaluating the nanosilver found in AGS-20. Instead, recent work using contemporary toxicity techniques that evaluated a range of effects were used in determining the nanosilver dose that is thought not to cause any effects. The studies used to evaluate the toxicity of nanosilver involved dosing animals with nanosilver particles and evaluating a wide range of effects on the animals in the Proposed Decision Document. The Agency presented results from two toxicity studies performed with nanoscale silver. One was a 28-day rat feeding study using 60 nm diameter nanosilver (Kim et al., *Inhal. Toxicol.*, 2008, 10:575), which reported liver toxicity as well as effects on blood and systemic distribution of silver in rat tissues. The second study was a 90-day rat inhalation study completed with 18 to 19 nm diameter nanosilver particles (Sung et al., *Toxicol. Sci.*, 2009, 108:452), which found toxic effects in the liver and lungs. There are two more recent studies that were incorporated into the Final Decision Document. One involved 90-day rat feeding study using 60 nm diameter nanosilver (Kim et al., *Particle and Fibre Toxicology* 2010, 7:20) and the other is a 28-day mouse feeding study (Park et al., *Environ. Tox. and Pharm.*, 2010, 30:162).

The Agency has determined that there is 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 reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity. Therefore, the Agency is using the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

5. NanoCEO Comment: On a more practical level, the fact that nanosilver materials can be more readily incorporated into a wide variety of materials and products than larger forms of silver—and therefore are being incorporated into an incredibly wide range of consumer products and industrial materials—will undoubtedly result in increasing levels of silver being released from these materials and emitted into homes, workplaces, and air, water, soil, waste, etc. Many forms of silver (nano and not-nano) will end up in wastewater, sewage plant effluents, and sewage sludge, which is then often spread on agricultural land and food crops. This will clearly increase human and environmental exposures well beyond previous uses of silver.

Response: EPA has already registered a number of silver-based antimicrobial products for use as materials preservatives in textiles. Most antimicrobial silver-based pesticide products currently contain a silver salt, [e.g., AgCl or AgNO₃]. Compared to the amount of silver in HeiQ's product, most currently registered silver-based materials preservatives require larger amounts of silver to be added to textiles in order to provide a sufficient lifetime of activity for antimicrobial treatment. Therefore, the overall potential environmental loading of silver resulting from the lower-volume use of the HeiQ product should be smaller than from a comparable use of currently registered silver-based pesticides. For example, Geranio et al. (2009) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. As a result of this information, with this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives.

6. NanoCEO Comment: The EPA claims that one of the rationales for giving the HeiQ silver product conditional approval is its benefits to the public. What benefits is the EPA referring to? We have not seen any study showing that coating textiles with nanosilver reduces the rate of human illnesses. To the contrary, by disrupting healthy microbial balances on and in the human body, and by increasing microbial resistance, these widespread uses of nanosilver are more likely to *increase* than decrease human illnesses. Using silver/nanosilver ubiquitously and building microbial resistance to silver will make it impossible to use silver in serious burn and wound situations where it may be necessary to prevent and/or treat serious infections. We are very surprised that the EPA has apparently accepted the misleading marketing claims of companies promoting unnecessary uses of a potent antimicrobial for non-life threatening, primarily aesthetic uses.

Response: With this registration there exists the potential for a decrease in the net amount of silver entering the environment as compared to the currently registered silver-salt based material preservatives. For example, Geranio et al. (2009, Environ. Sci. Technol., 43:8113) reported that commercially available textiles treated with electrolytically deposited silver contained 21.6 mg/g silver as compared to textiles treated with AGS-20, which contained a maximum of 0.099 mg/g silver. We have reviewed the registered silver containing pesticides and found for commercially available products (Simoncic and Tomsic, 2010, Textile Research Journal, 80:1721) that the amount of silver allowed in textiles ranges from 0.03 to 40 mg/g. If the pending conditional registration for HeiQ were approved, it would restrict the amount AGS-20 to between 0.01 to 0.1 mg/g as silver, which is on the low end of the spectrum for registered silver containing products. HeiQ has recently submitted confidential testing results comparing AGS-20 treated fabric to fabric treated with other silver-based pesticides demonstrating AGS-20's antimicrobial effectiveness at reduced silver loading.

Silver is currently used as a broad spectrum antibiotic in wound dressings. There is a concern that increasing use of silver, such as silver nanoparticles for preserving textiles, may result in more bacteria developing resistance to silver and limit its use as an antibiotic agent for wound care (Gupta and Silver, 1998). In the wound care setting, a recent review by Chopra (2007) concluded that the threat of bacterial resistance to silver in the clinical setting is low. However, Chopra (2007) cautioned against use

of wound dressings that release sublethal levels of silver over a long period of time allowing bacterial to develop resistance.

In terms of environmental impact, a recent study involved releasing 1 mg/L of silver nanoparticles into microcosms containing estuary water overlying estuarine sediment cores (Bradford et al., 2009). The study found no impact to the microbial community over a 30 day monitoring period. Evidence for antibacterial resistance was also evaluated during this study and no increase in antibiotic resistance to the bacterial population in the sediment was found (Mühling et al. 2010). Wigginton et al. (2010) suggested that the lack of antimicrobial effect in the microcosm was expected given that bacterial proteins efficiently bind to silver nanoparticles.

The Agency concludes that while development of antibacterial resistance due to the use of silver nanoparticles in AGS-20 is possible, the likelihood is low that the levels used in AGS-20 treated textiles will lead to the development of widespread bacterial resistance to silver.

7. NanoCEO Comment: After outlining several key ways throughout the supporting and decision documents in which the HeiQ product could cause adverse effects to workers and to other vulnerable populations (children, elderly, etc), the EPA nevertheless goes on to conclude that the product will not cause unreasonable adverse effects. Is this to imply that that these vulnerable, more at-risk populations don't matter? Or that it is "reasonable" to take the chance of harming them?

Response: These more at-risk populations do matter, which is why the Agency evaluated the impact to children. The outcome of this evaluation is that it is unlikely that children will receive a dose of nanosilver by wearing or chewing on clothing treated with AGS-20 which would cause adverse effects.

Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from AGS-20 along with maximum values for risk uncertainty factors, EPA is able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles treated with AGS-20. Thus, the Agency concludes that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed. The Agency does have a risk concern for occupational exposure when handling AGS-20 powder during mixing and loading operations. As a result of this concern, HeiQ amended its application so that the pesticide label requires workers to wear personal protective equipment and use engineering controls when handling AGS-20 powder.

8. NanoCEO Comment: If there is no monitoring, how will the EPA actually know whether or not there are adverse effects in four years?

Response: The Agency is requesting that additional product specific testing be performed to verify the literature studies used in the screening-level risk assessment (see Appendix A of the Decision Document). If at any time during testing of AGS-20 the Agency receives information indicating there is a significant difference between the toxicity of AGS-20 and the literature studies, then the Agency will take action to remove AGS-20 from the marketplace.

9. NanoCEO Comment: As citizens we depend on our government agencies to protect us from harmful toxins in the environment and in commerce. Clearly, in this case, the EPA is more interested in protecting and benefiting the corporate interests involved with silver/nanosilver, not in protecting and/or benefiting the public and the environment. We are saddened and disheartened by this as citizens in a purported democracy.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

10. NanoCEO Comment: The HeiQ nanosilver product should be fully tested for human and environmental safety *before* it goes on the market.

Response: The Agency respectfully disagrees. Using conservative assumptions which overestimate the dose of nanosilver that could potentially be derived from the AGS-20 nanosilver-silica composite along with maximum values for risk uncertainty factors, EPA was able to determine that for the period of conditional registration, there is a low probability of adverse risk to children and the environment from textiles manufactured treated with AGS-20. Thus, the Agency concluded that use of AGS-20 will not cause unreasonable adverse effects on the environment during the period when newly required data are being developed.

Comment 45: Dr Gemma Buckland, Humane Society International (9/13/10 EPA-HQ-OPP-2009-1012-0063)

1. HSI Comment. The implication of such changes is not fully understood, so risk assessment cannot rely on existing toxicity data for the bulk material. The UK Royal Society and Royal Academy of Engineering have stated that nanomaterials should be treated as new chemicals from a risk point of view.

Response: The studies on bulk silver were not used in evaluating the nanosilver found in AGS-20. Instead, recent work using contemporary toxicity techniques that evaluated a range of effects were used in determining the nanosilver dose that is thought not to cause any effects. The studies used to evaluate the toxicity of nanosilver involved dosing animals with nanosilver particles and evaluating a wide range of effects on the animals in the Proposed Decision Document. The Agency presented results from two toxicity studies performed with nanoscale silver. One was a 28-day rat feeding study using 60 nm diameter nanosilver (Kim et al., *Inhal. Toxicol.*, 2008, 10:575), which reported liver toxicity as well as effects on blood and systemic distribution of silver in rat tissues. The second study was a 90-day rat inhalation study completed with 18 to 19 nm diameter nanosilver particles (Sung et al., *Toxicol. Sci.*, 2009, 108:452), which found toxic effects in the liver and lungs. There are two more recent studies that

were incorporated into the Final Decision Document. One involved 90-day rat feeding study using 60 nm diameter nanosilver (Kim et al., Particle and Fibre Toxicology 2010, 7:20) and the other is a 28-day mouse feeding study (Park et al., Environ. Tox. and Pharm., 2010, 30:162).

The Agency has determined that there is 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 reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity. Therefore, the Agency is using the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

2. HSI Comment. Existing *in vivo* toxicity test methods display inherent uncertainties surrounding their use¹. These include the difficulties of extrapolating test data between species, genders and breeds of animals including humans (due to anatomical, physiological, biochemical, metabolic and pharmacological differences). With a new field such as nanomaterials, the full range of potential toxicities is not known. Using standard animal toxicity tests, which are little more than “black box” methods, would risk overlooking novel unwanted effects. Human cell-based assays, in contrast, would allow the study and elucidation of a range of molecular and cellular mechanisms of toxicity. For example, human cell culture assays can be used to monitor the oxidative stress responses of cells exposed to nanoparticles.

Response: In addition to using standard whole animal toxicity tests, the Agency is requesting an *in vitro* micronucleus (MN) assay. Thus, the Agency is using cell-based assays to evaluate the toxicity of AGS-20.

3. HSI Comment. It is therefore not appropriate to release products that still require information regarding their safety. Indeed, the FIFRA SAP report itself (EPA, 2010) noted that the “*hazard profile of nanosilver may differ from other forms of silver*” and it is “*especially challenging to determine that there is no release of nanomaterials from a substrate under the current state of science and available measurement standards*”.

Response: While the Agency does not have sub-chronic toxicity testing for products that contain nanoscale silver, there are results in the scientific literature for the toxicology of nanosilver. The studies used to evaluate the toxicity of nanosilver involved dosing animals with nanosilver particles and evaluating a wide range of effects on the animals in the Proposed Decision Document. The Agency presented results from two toxicity studies performed with nanoscale silver. One was a 28-day rat feeding study using 60 nm diameter nanosilver (Kim et al., Inhal. Toxicol., 2008, 10:575), which reported liver toxicity as well as effects on blood and systemic distribution of silver in rat tissues. The second study was a 90-day rat inhalation study completed with 18 to 19 nm diameter nanosilver particles (Sung

¹ Langley G (2004). Chemical Safety and Animal Testing: A Regulatory Smokescreen? 35 pp. London: BUAV.

et al., *Toxicol. Sci.*, 2009, 108:452), which found toxic effects in the liver and lungs. There are two more recent studies that were incorporated into the Final Decision Document. One involved 90-day rat feeding study using 60 nm diameter nanosilver (Kim et al., *Particle and Fibre Toxicology* 2010, 7:20) and the other is a 28-day mouse feeding study (Park et al., *Environ. Tox. and Pharm.*, 2010, 30:162).

The Agency has determined that there is 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 reproductive and developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity. Therefore, the Agency is using the maximum 10 fold database uncertainty factor to extend the inhalation and oral toxicity data to cover the missing information on developmental toxicity, neurotoxicity, immunotoxicity, and mutagenicity (US EPA, 2002). The Agency is requiring studies investigating these effects in order to complete the toxicity database for AGS-20 and any material that leaches from treated textiles. A new risk assessment will be conducted when these data are available. In the interim, the Agency believes that the 10 fold database uncertainty factor is health protective.

4. HSI Comment. *EPA-HQ-OPP-2009-1012-0005.* ...we also noted a number of methodological variations in the protocols used for the standard toxicology tests, such as use of a carrier other than water without explanation, and a failure to monitor body weight changes of treated animals.

Response: As stated in the Acute Toxicity Review the use of PEG300, a polyethylene glycol often used in medical settings, instead of water was deemed acceptable since PEG300 has low toxicity. Also, body weights of test animals were recorded; however, body weight changes were not calculated. These studies were reviewed by EPA and deemed acceptable even though there were minor deviations in experimental protocol.

5. HSI Comment. *EPA-HQ-OPP-2009-1012-0010.* The studies performed do not confirm whether nanoparticles dissociate from the textiles due to the insufficient magnification used in the study.

Response: The work by Geranio et al. (2009, *Environ. Sci. Technol.*, 43:8113) was used to estimate the release of nanosilver from textiles. The Agency assumed that all silver released in the study was in the form nanosilver. For the risk assessment, the Agency evaluated the case where up to 35% of the nanosilver in the textile treated with AGS-20 would be transferred to the skin of child or to a child during chewing of the textile.

6. HSI Comment. *EPA-HQ-2009-1012-0008.* The researchers do not explore the release of embedded silver particles and omit exploration of the environmental fate of nanosilver particles.

Response: The work cited in this document was not used by the Agency in evaluating the proposed registration of HeiQ AGS-20.

7. HSI Comment. *EPA-HQ-2009-1012-0012.* There appears to be occupational inhalation exposure, yet the study is not clear on the routes of exposure or on the endpoints useful for assessment. Omitting

these data does not provide a full picture as to the life-cycle of the product and overlooks potential areas of risk.

Response: Based on this work, the Agency is requiring that engineering controls be used when mixing, loading, and applying AGS-20 powder along with requiring personnel to use personal protective equipment.

8. HSI Comment. *EPA-HQ-2009-1012-1015.* The efficiency of the nanosilver socks displays limitations considering that 50% of the nanosilver is reported to leach out as AgCl during the first wash. Not only does this raise issues on product description and efficacy but this also highlights environmental fate concerns. Regardless of the toxicity level of AgCl, releasing an increased amount into the environment may have consequences which have not been addressed in this study.

Response: The study by Impelliteri et al. (J. Environ. Qual., 2009, 38:1528) was not performed on AGS-20 treated textiles and was only presented as a study which informed the understanding that nanosilver, after exposure to oxidizing agents, could exist as insoluble silver chloride in the environment.

9. HSI Comment. EPA-HQ-2009-1012-0011 highlights that nanosilver is more toxic to nitrifying bacteria than regular silver ions; thus, if nanosilver particles are released at any stage from the product, the ensuing effects should be researched.

Response: There is the potential for silver nanoparticles released from AGS-20 treated textiles to reach publically owned wastewater treatment and privately owned septic systems where they will most likely complex with sulfide and partition to biosolids. Once entrained in the biosolids, the silver nanoparticles could serve as a long term source of ionic silver which may adversely affect microorganisms that are vital to the wastewater treatment process. To evaluate this potential, HeiQ submitted test results on the impact of AGS-20 to wastewater treatment bacteria (MRID 479344-01). This test involved introducing AGS-20 powder and an AGS-20 liquid formulation used to surface treat textiles (AGS-20 TF) into bottles containing biosolids obtained from a wastewater treatment plant. Based on the similarity between the biological oxygen demand (BOD) caused by introducing glucose into bottles with AGS-20 and those without, there was no impact to the microorganisms in these bottles for AGS-20 loadings from 3.8 to 188 mg/L (0.76 to 37.6 mg/L as silver) or the AGS-20 TF liquid at loadings from 1 to 50 g/L over the 26 day test period. Although this result suggests that the silver in AGS-20 would not be expected to negatively impact wastewater treatment systems, it is unclear if the 26 day test period was sufficient time to evaluate this impact given that the rate of ionic silver released from AGS-20 is unknown.

There are contradictory reports in the scientific literature regarding the impact of silver nanoparticles on wastewater treatment systems. For example, nanosilver was reported to inhibit nitrification in the range of 50% (Choi and Hu, 2009a) to 84% (Choi and Hu, 2009b) based on a reduction in oxygen uptake rate. However, Burkhardt et al. (2010) found no impact to nitrification at nanosilver dosages of 1 mg/L, the same dosage that Choi and Hu (2009a and 2009b) reported as inhibitory. These two research groups are reporting different findings with the Burkhardt group suggesting little impact of nanosilver to nitrification and the Hu group suggesting that an impact to wastewater treatment systems from nanosilver is expected.

While there are reports suggesting the potential for silver nanoparticles to impact wastewater treatment operations, the Agency does not anticipate that registering AGS-20 will lead to negative impacts to wastewater treatment systems. This conclusion is based on the small volume of nanosilver (i.e., < 4,500 kg/yr as estimated) expected to be introduced into commerce from AGS-20 treated textiles. However, if nanosilver is found to be released from AGS-20 treated textiles during leaching studies then EPA will require HeiQ to determine the impact to wastewater treatment processes.

10. HSI Comment. *EPA-HQ-2009-1012-0020.* Registration of HeiQ AGS-20 is apparently “*within the public interest*”; however, the urgency of the need for this product remains to be seen when there are clear safety ambiguities and data gaps. It is important to treat all nanosilver products equally; the fact that some nano-products are already on the market and have not submitted data to the same degree as the HeiQ AGS-20 suppliers identifies registration errors and not an automatic licence for HeiQ AGS-20 registration. A level playing field needs to be created for nano-products — one that ensures safety to consumers and the environment.

Response: EPA evaluates antimicrobial products to determine if they will perform their intended function without causing unreasonable adverse effects on the environment. EPA does not generally consider the need for nonpublic health pesticides unless the risks from use of such pesticide are of concern and such risks may not be mitigated to acceptable levels. Where the risks are not of concern, generally the need for the nonpublic health pesticide is determined by consumer demand. The Agency plans to issue data call-ins for the existing nanosilver containing pesticides.

11. HSI Comment. Nanomaterials in consumer products should also be viewed on a case-by-case basis due to the differences in properties that nanomaterials can display when differences in handling, preparation, use in mixtures etc exist for the same nanomaterial. Evidence already exists suggesting current regulatory testing approaches are not scientifically robust regarding the safety testing of nanomaterials and it is therefore germane that nano-specific approaches are in place before testing can be implemented. The overall production levels of nanomaterials and market volume should also be taken into consideration and not just the specific level of nanomaterial in a product.

Response: Historically, EPA has considered applications for pesticide products that claim to be identical or substantially similar in composition to a registered product as so-called “me-too registrations” under FIFRA registration authorities. Until recently, EPA generally has not focused on the size of an ingredient as an attribute relevant when determining if the product in an application is identical or substantially similar in composition to a registered pesticide product. However, a nanoscale ingredient may have properties that are different from those of conventionally-scaled ingredients and properties that differ from the atoms or molecules from which the nanoscale ingredient is constructed. Therefore, a nanoscale ingredient may also have different environmental health and safety properties. Accordingly, for a product containing an ingredient that is a nanoscale version of a conventionally-sized active or inert ingredient contained in an already-registered product or a different nanoscale version of a nanoscale material that is an active or inert ingredient in an already registered pesticide product, EPA necessarily will need data on the nanoscale material to make the requisite statutory findings.

12. HSI Comment. For such a new and potentially exciting field there are also concerns and dangers of the technology developing faster than the science. Therefore, the issues of transparency regarding information on testing methods and procedures have particular pertinence for public perception and understanding. It is essential for transparency to exist in order for full stakeholder understanding and ultimately consumer and environmental safety.

Response: The Agency is committed to transparency during the decision making and testing process to the extent that information is not claimed to be business confidential. An example of this commitment to transparency was posting the HeiQ Decision Document to the Pesticides Public Regulatory Docket for public comment for which there was no statutory requirement to do so. Postings to the public docket are sent via an automated email service, which can be accessed by going to http://www.epa.gov/oppfead1/cb/csb_page/form/form.html.

13. HSI Comment. Currently employed animal test methods are not suitable for nanomaterial testing and represent a scientifically inappropriate testing approach. HSI and its sister organizations would like to urge the EPA to ensure efforts are channeled into creating a toxicity testing strategy akin to the National Research Council's "Toxicity Testing in the 21st Century: A Vision and Strategy"², relying on high-throughput, advanced techniques with direct human and environmental relevance.

Response: The Agency is working to advance the 21st Century toxicity testing approaches as described in the NRC document. For example, in addition to using standard whole animal toxicity tests, the Agency is requesting an *in vitro* micronucleus (MN) assay. A larger scale effort is being undertaken through EPA's ToxCast™ program where *in vitro* methods are being developed and validated for the screening of nanoscale materials. Thus, the Agency is using cell-based assays, which are part of 21st Century toxicity testing, and developing new *in vitro* methods to evaluate the toxicity of nanoscale materials.

² National Research Council (2007). *Toxicity Testing in the 21st Century: A Vision and a Strategy*, 146pp. Washington, DC: National Academy Press.