Sept. 11, 2010

Comments from the
Nanotechnology Citizen Engagement Organization (NanoCEO)
On the proposed conditional registration of a pesticide product
HeiQ AGS-20, containing nanosilver

RE: Docket ID number EPA-HQ-OPP-2009-1012

We are writing regarding the EPA's proposed conditional approval of the HeiQ AGS-20 nanosilver-silica composite product.

Firstly, we thank you for the opportunity to comment on this important issue, as well as related decisions on nanosilver and other engineered nanomaterials. These decisions will have significant consequences for public and environmental health and it is critical that citizens have a say in them.[1]

Our organization, the Nanotechnology Citizen Engagement Organization (NanoCEO) is a non-profit, citizen-based organization with a mission to educate the community about emerging nanotechnologies and facilitate citizen engagement in discussions and decisions about these important technologies (see: http://www.nanoceo.net/about). NanoCEO became aware of the increasing uses of nanosilver in consumer products, medicine, and numerous other applications years ago shortly after the group formed in 2005. In 2006, one of our members purchased several nanosilver products at local stores. Following that, the group organized several Nano Cafes to discuss the applications and implications of these nanosilver products with scientific experts and other citizens (see http://www.nanoceo.net/past_events/03_22_07). The group continues to compile articles and reports about the implications of these products on our website: http://www.nanoceo.net/nanoproducts_antibacterial.

We have also been gathering scientific research related to the potential environmental and public health implications of silver and nanosilver materials, and compiling this literature on our website. Hundreds of research papers and reports about nanosilver have been published in recent years, and this number continues to grow. See our website for a listing of many of these papers: http://www.nanoceo.net/nanorisks/silver-particles.

Based on our understanding of the growing body of scientific literature on silver and nanosilver, and the increasing use of silver/nanosilver materials in commerce, we are strongly opposed to the proposed "conditional approval" of HeiQs nanosilver-silica compound, for a number of reasons, which we outline next.

[1] 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 decisionmaking.

1. Silver is a toxic heavy metal—nano or not

Environmentally, ionic silver is considered the second most toxic metal after mercury because it can cause harm to prokaryotic and non-mammalian organisms at very low levels when it is bioavailable to them (Eisler 1996; Ratte 1999; Luoma 2008). Silver ions have a strong tendency to bind to sulfhydryl, amino, carboxyl, phosphate and imidazole groups that are found in enzymes, proteins, DNA, RNA. They can induce oxidation reactions and mimic ions that play essential roles in many organisms, such as sodium, calcium, and copper ions, thereby affecting the transport of these ions (Fung and Bowen 1996; Hollinger 1996; Luoma 2008). Consequently, silver ions interfere with numerous functions critical to organisms—e.g., disrupting enzymes on cell membranes or cell walls that are responsible for critical cell functions such as cell respiration and electron transport across membranes. Silver ions are also highly toxic to fish because they perturb ion regulation in the gills by disrupting membrane transport of sodium (Luoma 2008). These effects are in part what makes silver such an effective antibacterial—the ions induce oxidative stress at bacteria's cell wall, reducing the bacterial cells' ability to respire and maintain ion balance—thereby killing the cells.[2]

Silver is a trace element, and normally silver levels in the ambient environment are extremely low. Most of the increasing amounts of silver used in commerce—nano or not—will end up in the environment one way or another. Once all this silver/nanosilver from consumer products enters the environment, it cannot be removed. Even if it is bound to natural molecules and materials, perhaps rendering it less biologically available in some cases, silver is non-biodegradable element; 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.

There is insufficient evidence supporting the widespread assumption that silver is "innocuous" to humans, and considerable evidence refuting it. While it is well-known that silver is very toxic environmentally, it is often stated that silver is "harmless" to mammalian cells and humans even though it is not a normal or essential element in humans. However, this assumption has never been supported by comprehensive evidence, and there is ample evidence questioning 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. These effects are usually attributed to silver ions—either directly or via release of ions from other silver compounds (Hollinger, 1996).

In recent years several scientists have suggested that silver's risk to humans be re-evaluated, especially in light of its increasing uses (Hollinger 1996; Poon and Burd 2004; Luoma 2008). **See attached draft document outlining and describing some of the studies we have gathered on "conventional" silver that support this call for re-evaluation.**

---

[2] For a thorough review of the environmental effects of silver and new risks posed by nanosilver, see Luoma (2008): http://www.nanotechproject.org/process/assets/files/7036/nano_pen_15_final.pdf

It is repeatedly stated in silver risk assessment literature that in humans, argyria "detoxifies" silver, protecting the body from the detrimental effects documented in experimental studies. Many hundreds of argyria cases related to silver exposures have been documented in the last couple hundred years. But the health effects documented related to silver exposures go well beyond argyria. Numerous workplace and case studies on human silver exposures suggest that a variety of forms of conventional silver can cause harm in humans other than argyria—e.g., kidney and liver damage, cardiovascular problems, neurological problems, and a variety of other problems in exposed people, at a range of levels.

While we realize that many of these case studies involved relatively large doses (or, more often than not, unclear or unknown doses), they nevertheless indicate that silver is not completely "detoxified" by argyria, and can have significant negative effects in humans that parallel what might be expected given experimental studies on mammalian cells and organisms. Further, some of the studies outlined in the attached document suggest that silver can cause harm in mammals at relatively low levels.

Substantial data gaps in the body of studies on silver also make it very problematic to conclude that silver is harmless to humans. To date, oddly, there have been no epidemiological or long-term studies on humans chronically exposed to silver (e.g., people who chronically use silver compounds) that explore the range of subclinical effects that could potentially be associated with silver exposures that experimental findings suggest they could have (liver, kidney, cardiovascular, neurological, immune system problems, etc). **Without these kinds of studies, it is inappropriate to conclude that chronic exposures to silver do not have human health effects.** Given that environmentally, silver is considered 2^{nd} most toxic after mercury—and its effects in cells are very similar to those of mercury—it seems critical that further studies be done, particularly given the widespread use and availability of silver and nanosilver products on the market.

Oddly, in their risk assessments and standards for silver, the EPA and other regulatory agencies have ignored the experimental research studies and clinical case studies suggesting that silver can cause many effects besides argyria, and also ignored significant data gaps, developing health standards based on argyria outcomes only.

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.

The weak basis on which these standards on silver were developed are important to this discussion because these standards are stated in many documents in this docket as justification for the safety of conventional silver—and now by extension, nanosilver. We strongly disagree with these arguments, for reasons explained below.

2. Engineered nanosilver materials pose new, unique, and heightened risks

Debates about whether nano forms of silver pose new risks are closely related to risk assessments and standards already developed for "conventional" silver—and the problematic assumptions related to these assessments, outlined above. Colloidal silver forms that have been on the market for well over a hundred years contain some proportion of nano-sized particles. Yet contrary to statements of the silver industry and other silver proponents—made repeatedly in documents submitted to this docket in arguing that nanosilver is safe—these "conventional" forms of silver have *not* been proven to be safe (per discussion above), and their detrimental effects may be in part due to their nano-sized components.[3] This can't be easily assessed, unfortunately, because past studies on colloidal silver and other silver compounds did not characterize the sizes of the materials used in studies or the silver compounds people were exposed to.

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).

Of course, the higher potency of nanosilver materials in releasing silver ions is also a key reason why they are more potent toxicologically. *Hundreds of toxicological and ecotoxicological studies have already been done on nanosilver in recent years—and the majority of them have found that nanosilver causes detrimental toxicological effects at relatively low levels in both non-mammalian and mammalian cells and organisms.* Again, see our website for a listing of many of these studies: http://www.nanoceo.net/nanorisks/silver-particles

Moreover, perhaps not surprisingly, the effects of nanosilver on non-mammalian and mammalian cells are documented in a rapidly growing number of recent studies listed on our website largely parallel those of conventional silver, and they include: (1) binding with sulfydryl groups, disrupting proteins, RNA, DNA, glutathione, and other molecules that play critical roles in cells; (2) disrupting membrane transport processes and causing other membrane damage; (3) generating reactive oxygen species in the cell and causing apoptosis and cytotoxicity; and several more. These effects of nanosilver are likely due to the release of silver ions, just as with other forms of silver, but likely at higher rates and/or levels over time because of the higher surface-to-volume ratios of nanoparticles. A number of studies have indicated that nanosilver can be more toxic *in vitro* and *in vivo* than larger forms (Wijnhoven, Peijnenburg et al. 2009).

Further, nanoparticulate forms of silver may pose new and unique mechanisms of toxicity that go beyond the release of silver ions. Via endocytotic mechanisms in which cells can "engulf" nano-sized particles, nanosilver particles may be more able to enter eukaryotic cells than larger silver forms, where they could deliver silver ions to the interior of cells, in the proximity of cell machinery (Luoma 2008; Park, Jongheop et al. 2010). Indeed, nanoparticles have been found to be transported more easily into the cytoplasm of cells (Sondi and Salopek-Sondi 2004; Morones,

[3] This can't be easily assessed, unfortunately, because past studies on colloidal silver and other silver compounds did not characterize the sizes of the materials used in studies or the silver compounds people were exposed to.

Elechiguerra et al. 2005; Pal, Tak et al. 2007; Shrivastava, Bera et al. 2007; Skebo 2007; Raffi, Hussain et al. 2008), the cell nucleus (Asharani, Wu et al. 2008), and the brain (Takenaka, Karg et al. 2001; Ji, Jung et al. 2007; Kim, Kim et al. 2008; Sung, Ji et al. 2009). Silver nanoparticles could carry heavy metals and other toxins into cells in a "Trojan horse-type mechanism" (Lubick 2008; Luoma 2008; Park, Jongheop et al. 2010). Once inside cells, they could continue to release silver ions for long periods of time. The proposed decision document, in fact, clearly touts the "prolonged efficacy" of nanosilver materials as antimicrobials (EPA Proposed Decision Document, p. 3, p. 29). This "prolonged efficacy" is likely to be "prolonged toxicity" within cells and organisms.

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.**

3. EPA reasoning that the product will not cause unreasonable adverse effects lacks consistency and defies common sense.

The rationales given by the EPA for the conditional approval of HeiQ AGS-20 are illogical, unsupported, and/or contradicted by scientific evidence. In some cases they are directly at odds with questions and statements of EPA staff elsewhere in the supporting documents.

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.

The EPA decision document also argues that uses of nanosilver will result in less silver being used because of its higher potency, along with its prolonged release properties. These arguments make no sense. Firstly, this is based on the assumption that these nanosilver products are necessary at all. **Why do people need antimicrobials all over their clothing and other goods (why is basic hygiene and laundering clothing regularly insufficient)?** Secondly, this argument avoids the fact that by nano-sizing silver, it can now be incorporated into all sorts of materials in ways it couldn't be before in other forms. Consequently, there is likely to be ***more*** **silver/nanosilver—in super-potent nano sizes—in workplaces, homes, and the environment** from the ubiquitous use of many products that didn't include silver at all in the past but now cab incorporate nanosilver. More importantly, of course, if the nanosilver is more potent in killing microbes, with prolonged release and efficacy, then it is more potent toxicologically as well (as discussed above). Saying that it is beneficial to the public or the environment to approve the use of a more potent toxin clearly defies common sense. Moreover, it is irresponsible and unethical.

4. EPA's conditional authorization is likely to harm vulnerable groups, who are in effect being used as test subjects in an experiment. This is unjust and unethical.

The EPA's rationales are unjust and unethical in that they treat the most vulnerable groups in society as guinea pigs. 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?**

Similarly, the decision document and other supporting documents describe numerous significant data gaps throughout that make it impossible to say that this product will not cause unreasonable adverse effects. Given these data gaps, how can the EPA conclude now that the product will not cause unreasonable adverse effects? These circular arguments make no sense.

Following from this, giving the company four years to gather data to prove that their product does not cause unreasonable adverse effects implicitly negates the claim that enough is known to say it doesn't cause unreasonable adverse effects. Most troublingly, this rationale also **treats the most vulnerable groups—workers at the front lines of nanosilver production, children exposed to nanosilver products in the home, and other at-risk groups—as guinea pigs in a four-year, and likely much longer, experiment. Again, we find this highly unethical and it violates core principles of environmental and health justice.**

After four years, if it is shown that the products treated with AGS-20 have been releasing silver/nanosilver into workplaces, homes, and the environment and are causing harm, the workers will have already been exposed for four years (probably at the highest levels of any group), as will consumers who used these products in their homes and on their bodies. Nanosilver released from the products will be in workplaces, homes, and the environment and there will be no way to get it out. At that point, **these exposures cannot be reversed,** nor can the silver be removed from the environment, even if the EPA does decide that the product causes unreasonable effects after all the data is submitted.

Moreover, risk assessments that only consider exposure to AGS-20 nanosilver are also not realistic. As stated in the proposed decision document, **there are numerous silver/nanosilver antimicrobial products already on the market.** Workers and consumers will be exposed to the combined silver/nanosilver from all of these products, not just levels from one product at a time. Many consumers who buy one of these products, having been convinced by misleading marketing claims that they will prevent illness, are likely to buy others as well. The combined levels of silver from all these products will be in their households and will be emitted into waste streams to landfills, sewage treatment plants, and again, eventually into the environment. **To**

assess one silver product at time is therefore clearly far underestimating the potential human health and environment risks from the hundreds of silver and nanosilver products on the market.

Finally, EPA decisions such as this one and other approvals of silver/nanosilver products will have serious and costly repercussions for state and local agencies. Who will monitor where silver and nanosilver materials are going in workplaces, the environment, and organisms, and what levels build up in various environments and organisms? These tasks will primarily be the responsibilities of under-funded, under-staffed, and inadequately equipped state and local agencies. **Who will fund this monitoring? If there is no monitoring, how will the EPA actually know whether or not there are adverse effects in four years? If silver levels do rise in the environment, and adverse effects are shown, who will fund remediation and control?** We ask that you consider these issues when making this decision and other decisions about engineered nanomaterials and other potential environmental pollutants.[4]

5. The EPA's mission should be to protect environmental and public health, not to protect industry

Last but not least, and most disturbingly, the EPA makes the argument that not granting conditional approval to HeiQ would unfairly disadvantage this company since other companies already have nanosilver products on the market (due to the EPA's own lack of oversight).

We find these rationales, like the others outlined above, highly irresponsible and unethical. **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.**

<u>**In conclusion, we ask that the EPA reconsider this proposed decision and *not* grant HeiQ conditional approval. We support the NRDC's call for the EPA to issue fines against this company and others that have marketed nanosilver pesticidal products without having undergone the full registration process.**</u>

The HeiQ nanosilver product should be fully tested for human and environmental safety *before* it goes on the market. We would like to see full and transparent analyses of the proposed benefits of this product, as well as a comprehensive risk assessment that fills all the gaps identified by the EPA documents and the 2009 SAP document as being necessary to understand the effects of this product and other nanosilver products. If it is shown to cause harm to consumer, public, and/or environmental health, it should not be approved at all nor should other nanosilver products.

Further, whether or not this and other nanosilver products are approved, **state and local agencies should be provided federal funding for monitoring all the silver/nanosilver that will be**

---

[4] See Powell, M., Griffin, M. P. A., Tai, S. Bottom-up risk regulation? How nanotechnology risk knowledge gaps challenge federal and state agencies. *Environmental Management*, 42: 426-443.

emitted into the environment, workplaces, and homes from all these nanosilver products on the market, so these agencies can do their jobs to protect public and environmental health. Moreover, these products should be labeled and citizens should be given access to as much information as possible about their known and potential effects.

Most importantly, **citizens should be provided with frequent, ongoing and meaningful opportunities to engage in discussions and decisions with government and other decisionmakers about the development and use of these silver/nanosilver products, as well as other emerging nanotechnologies and nanomaterials. In a purported democracy, our knowledge and perspectives should be more important than the interests and profits of corporations.**

Thank you for considering our comments.

Sincerely,

Maria Powell, PhD
Community-based Participatory Scholar
Research Director, Nanotechnology Citizen Engagement Organization
Madison, Wisconsin
mariapowell@nanoceo.net, www.nanoceo.net

Mathilde Colin, MS
Education, Outreach, and Community Organizing Staff,
Nanotechnology Citizen Engagement Organization

Along with the *NanoCEO Board of Directors* and *NanoCEO Members*

References

For a full list of research studies on nanosilver, see also:
http://www.nanoceo.net/nanorisks/silver-particles.

Asharani, P. V., Y. L. Wu, et al. (2008). "Toxicity of silver nanoparticles in zebrafish models." Nanotechnology **19**(25): 255102-255110.

Eisler, R. (1996). Silver hazards to fish, wildlife, and invertebrates: A synoptic review. Contaminant Hazard Reviews, Pautuxent Wildlife Research Center, US Geological Survey. **Reston VA** 63 pp.

Fung, M. C. and D. L. Bowen (1996). "Silver products for medical indications: risk-benefit assessment." Clinical Toxicology **34**(1): 119-126.

Gaul, L. E. and A. H. Staud (1935). "Clinical spectroscopy: Seventy cases of generalized argyrosis following organic and colloidal silver medication, including a biospectrometric analysis of ten cases." Journal of the American Medical Association **104**(16): 1387-1390.

Hill, W. R. and D. M. Pillsubry (1939). Argyria: The Pharnacology of Silver. Baltimore, The Williams & Wilkins Company.

Hollinger, M. A. (1996). "Toxicological aspects of topical silver pharmaceuticals." CRC Critical Reviews in Toxicology **26**(3): 255-260.

Ji, J. H., J. H. Jung, et al. (2007). "Long-term stability characteristics of metal nanoparticle generator using small ceramic heater for inhalation toxicity studies." Inhalation Toxicology **19**(9): 745-751.

Kim, Y. S., J. S. Kim, et al. (2008). "Twenty-Eight-Day Oral Toxicity, Genotoxicity, and Gender-Related Tissue Distribution of Silver Nanoparticles in Sprague-Dawley Rats." Inhalation Toxicology **20**(6): 575-583.

Lubick, N. (2008). "Nanosilver toxicity: Ions, nanoparticles--or both? ." Environmental Science & Technology **42**(23): 8617.

Luoma, S. N. (2008). Silver Nanotechnologies and the Environment: Old problems or new challenges? Washington, DC, The Project on Emerging Nanotechnologies, Woodrow Wilson International Center for Scholars**:** 66.

Morones, J. R., J. L. Elechiguerra, et al. (2005). "The bactericidal effect of silver nanoparticles." Nanotechnology **16**(10): 2346-2353.

Pal, S., Y. K. Tak, et al. (2007). "Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium Escherichia coli." Applied and Environmental Microbiology **73**(6): 1712-1720.

Park, E.-J., Y. Jongheop, et al. (2010). "Silver nanoparticles induce cytotoxicity by a Trojan-horse type mechanism." Toxicology in Vitro **24**: 872-878.

Poon, V. K. M. and A. Burd (2004). "In vitro cytotoxity of silver: implication for clinical wound care." Burns: Journal of the International Society for Burn Injuries **30**(2): 140-147.

Raffi, M., F. Hussain, et al. (2008). "Antibacterial Characterization of Silver Nanoparticles against E. Coli ATCC-15224." J. Mater. Sci. Technol **24**(2): 192-196.

Ratte, H. T. (1999). "Bioaccumulation and Toxicity of Silver Compounds: a Review." Environmental Toxicology and Chemistry **18**(1): 89-108.

Shrivastava, S., T. Bera, et al. (2007). "Characterization of enhanced antibacterial effects of novel silver nanoparticles." Nanotechnology **18**(22): 225103.

Skebo, J. E. (2007). "Assessment of Metal Nanoparticle Agglomeration, Uptake, and Interaction Using High-Illuminating System." International Journal of Toxicology **26**(2): 135-141.

Sondi, I. and B. Salopek-Sondi (2004). "Silver nanoparticles as antimicrobial agent: a case study on E. coli as a model for Gram-negative bacteria." Journal of Colloid And Interface Science **275**(1): 177-182.

Sung, J. H., J. H. Ji, et al. (2009). "Subchronic inhalation toxicity of silver nanoparticles." Toxicological Sciences **108**(2): 452-461.

Takenaka, S., E. Karg, et al. (2001). "Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats." Environmental Health Perspectives **109**(Suppl 4): 547-551.

Wijnhoven, S. W. P., W. J. G. M. Peijnenburg, et al. (2009). "Nano-silver – a review of available data and knowledge gaps in human and environmental risk assessment." Nanotoxicology **3**(2): 109-138.