THE SILVER INSTITUTE

A WORLDWIDE ASSOCIATION OF MINERS, REFINERS, FABRICATORS AND MANUFACTURERS

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May 10, 2007

Dr. Scott A. Masten
Director
Office of Chemical Nomination and Selection (NIEHS/NTP)
111 T.W. Alexander Drive
P.O. Box 12233
Research Triangle Park, North Carolina 27709

RE: Comments on the Nomination of Nanosilver and Nanogold for Toxicological Study to the National Toxicology Program

Dear Dr. Masten:

The Silver Institute is pleased to have this opportunity to provide comments to the Federal Register notice published earlier this year announcing the Toxicological Study Nominations of the Nanoforms of Silver and Gold to the National Toxicology Program ("NTP"). See 72 Fed. Reg. 14,816 (March 29, 2007). While the Silver Institute supports any program of study that helps to further the understanding of the risks and benefits of precious metals in any form, we also wish to caution the NTP not to overlook existing studies, data and information about these metals – especially silver, which has been used safely in various forms for centuries, including at the sub-nano-scale. The Silver Institute believes that any meaningful and scientifically sound review must take into account this large volume of existing knowledge. Our comments are provided in greater detail below.

I. Who is the Silver Institute?

Established in 1971, the Silver Institute is the international trade organization that represents silver interests, including miners, refiners, fabricators, and wholesalers of silver and silver products. The Institute serves as the industry's voice in increasing public understanding of the many uses and values of silver, including the science and technology of silver. The Silver Institute also continues to be involved with the preparation of sound scientific information relating to the nature and impacts of silver on human health and the environment. For example, a focus on the chemistry of silver was one of the leading drivers for the Silver Institute's founding sponsorship of the Silver Research Consortium ("SRC") in 2002,

(continued)

conducted under the auspices of the International Lead Zinc Research Organization, Inc. ("ILZRO").[1] The SRC and its sponsors are committed to the sound scientific assessment of any risks posed to the environment or human health from the production and use of silver. In order to achieve this goal, a current research program underway at the SRC is designed to increase understanding of the behavior of silver in the environment. Ultimately, the work seeks to enable quantitative prediction of bioavailability of silver in soils, water and sediment through the development of specific models based on simple parameters such as metal concentration and classic abiotic factors such as pH, organic carbon content, water hardness etc. This work expressly extends to all forms of silver from silver ions dissolved in solutions at ng/L levels all the way to bulk metals. Accordingly, nanosized versions of silver would also be captured as part of that research. We would, of course, be happy to share the results of those efforts with the NTP as part of your review of nanosilver and nanogold.

In addition to the SRC, the Silver Institute also has a long history of working cooperatively with the U.S. Environmental Protection Agency ("EPA") on furthering the understanding of the risks and benefits of various uses of silver. For example, the Silver Institute has worked with the EPA on the silver Re-registration Eligibility Document (RED) in years past and is currently working with them on the latest update. As it has with EPA, the Silver Institute would also welcome the opportunity to work with the NTP as it moves forward with its review of nanosilver and nanogold.

The Silver Institute also urges the NTP to take into consideration the historic uses of silver and its long-known bactericidal effectiveness. We provide this information because we are concerned about the mischaracterizations of the properties of silver and their effects on human health and the environment that have been put forth by a number of special interest groups. For example, last year, in response to the pending market introduction of a washing machine capable of injecting silver ions into wash water for antimicrobial purposes, the Natural Resources Defense Council ("NRDC") submitted a letter to EPA complaining about this device. NRDC specifically attempted to justify "a prohibition or stringent restrictions" on the use of silver in nanoform through the use of questionable science. NRDC's use of the studies was misplaced, however, in that the organization attempted to bridge animal toxicity data typically used to examine human health risks as the basis for claiming an ecological risk. Bridging animal toxicity studies to environmental effects, however, is not scientifically sound practice. Indeed, as was conceded by NRDC in its letter to EPA, the animal studies cited by NRDC were of

[1] See the ILZRO web site for additional detail at http://www.ilzro.org/src/

limited value even for human health risks because such risks from silver are already well understood as outlined below.[2]

II. The Therapeutic Impact of Silver on the Human Environment

Silver has been recognized and used for centuries in a variety of applications such as coinage, tableware and jewelry. Modern day uses include those historic applications as well as photographic processing, mirror production, dental alloys, solder, electroplating, the manufacture of inks and dyes, the processing of food and beverages, and various antimicrobial uses. Silver salts and silver nitrate also are currently used as therapeutic agents in treating warts, burns and eye infections. Through the course of these various uses, the body of knowledge built up about silver and its effects on human health and the human environment has been considerable. All of these various studies have universally concluded that silver and silver ions pose little threat of harm to human health.

Because of its inherent antimicrobial properties, silver has been long recognized as an effective biocide. As such, silver has been registered for use as a pesticide in the United States since December 1954.[3] Pesticides, as you know, are highly regulated by EPA. Any product sold in the United States as a pesticide must be registered with EPA prior to sale or distribution. Since the registration process involves substantial data review, a considerable amount of data has been generated about the toxic profile of silver on human health and the environment. Based on the EPA's own findings as part of reregistration review, for example, the toxicity to humans of silver is primarily limited to skin discoloration.[4]

> Silver is not known to have human carcinogen potential, and does not appear to be a mutagen. Although long-term ingestion of silver may cause argyria [blue to gray discoloration of the skin] in humans and animals, this effect is cosmetic only and is not harmful to health. (emphasis added).[5]

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[2] See attached letter to J.Jones, Director, Office of Pesticide Programs, U.S. EPA from J.Sass and M.Wu, Natural Resources Defense Council (November 22, 2006).

[3] See EPA Re-registration Eligibility Document for Silver, Case 4082, published 1993 (available at http://www.epa.gov/oppsrrd1/REDs/old_reds/silver.pdf).

[4] EPA RED for Silver at 6.

[5] EPA Fact Sheet for Silver at 3.

Perhaps the only significant concern regarding silver use is its acute toxicity to fish, aquatic invertebrates and estuarine organisms.[6] This toxicity arises almost exclusively from exposure to ionic silver. However, even this exposure is quite limited since concentrations of silver ions in aquatic environments are extremely low. The low concentrations are due to ionic silver's tendency to almost immediately bind with naturally occurring substances such as sulfide, chloride or organic carbon. When combined with these naturally occurring substances, the bioavailability and toxicity of ionic silver are significantly reduced. In fact, the presence of environmentally relevant levels of naturally occurring sulfide alone reduces acute silver toxicity by a factor of approximately 5.5.[7] Additional information about the fate of and effects of silver in aquatic environments has been published and this work should be considered as the NTP assesses nanosilver's toxicological profile.[8]

Of course, EPA is not the only federal agency that has had occasion to review the toxicity profile of silver. For example, your colleagues at the Department of Health and Human Services' Center for Disease Control ("CDC") have also reviewed silver in-depth.[9] While that study recognized the potential hazards from silver, those hazards were generally limited to argyria and some limited reports of breathing difficulty and gastrointestinal distress in workers exposed to high levels of silver through inhalation exposure. Overall, however, the study clearly noted that the limited number of observed adverse effects from silver, including argyria, allergic reaction, respiratory and gastrointestinal distress, were the result of ingestion or exposure to large quantities of silver – i.e., in the grams range versus parts per million or lower. Importantly, the study sets forth several conclusions regarding the health effects of silver, including:

> A single exposure to a silver compound may also cause silver to be deposited in the skin and in other parts of the body; however, this is not known to be harmful. It is likely that many exposures to silver are necessary to develop argyria. Once you have argyria it is permanent. However,

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[6] Id. at 4.

[7] J. W. Gorsuch et al., *Silver, Environmental Transport, Fate, Effects and Models* (Setac Press, 2003), pp.147-154.

[8] J. R. Ellis and K. Jayachandran, *Future Needs for Environmental Research on Silver and Resources Available,* Presented at 2006 Annual Conference of the American Wood Preservers Association.

[9] Agency for Toxic Substances and Disease Registry U.S. Public Health Service, "Toxicological Profile for Silver" (December 1990), available at: http://www.atsdr.cdc.gov/toxprofiles/tp146.pdf.

> the condition is thought to be only a "cosmetic" problem. Most doctors and scientists believe that the discoloration of the skin seen in argyria is the most serious health effect of silver.[10]
>
> Tests in animals show that silver compounds are likely to be life threatening for humans only when large amounts (that is, grams) are swallower (sic) and that skin contact with silver compounds is very unlikely to be life threatening.[11]

III. Conclusion

Based on the well-understood nature of silver and the numerous studies conducted on this element, the Silver Institute urges the NTP to take into consideration this proven past information as it moves forward with consideration of its toxicology review. Consideration of these prior studies and data is not simply appropriate; it is demanded by principles of sound science. In conducting its review, the NTP should also strive to ensure that the agency is not caught up in the political agendas that would otherwise quash innovation of different forms and applications for silver. The Silver Institute is committed to working with the NTP (and all regulatory bodies) to better help understanding of the uses of silver and their potential impacts to human health and the environment. We welcome any further dialogue on this issue and are committed to sharing information available to the Institute. On behalf of the Silver Institute and its many members, I thank you for your time and consideration in this matter.

If you have any questions or comments regarding this issue, or if we can be of any assistance, please do not hesitate to contact me at 202.835.0185.

Sincerely,

[Redacted]

Michael DiRienzo
Executive Director
The Silver Institute

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[10] See Id. at 3.

[11] See Id. at 4.

NRDC
THE EARTH'S BEST DEFENSE

22 November 2006

Jim Jones, Director
Office of Pesticide Programs
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

Re: Registration of Nanosilver as a Pesticide under FIFRA

Dear Mr. Jones:

The Natural Resources Defense Council (NRDC) commends the EPA Office of Pesticide Programs' recent decision to regulate the use of nanosilver as a pesticide under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA") as reported in the Daily Environment Report on November 21.[i] This action is an important step in the right direction; however, there are currently more than 40 consumer products in the marketplace that contain nanosilver, some of which either expressly make pesticidal claims or imply pesticidal effectiveness and none of which are currently registered with EPA. EPA is obligated to examine these products and require registration for any product that uses nanosilver as a biocide. Furthermore, we are confident that once EPA has specifically examined nanosilver pursuant to the appropriate FIFRA risk assessment provisions, EPA will recognize the significant harm that this substance inflicts on the environment (particularly on aquatic organisms) and will be compelled either to prohibit or significantly restrict its use.

With the expanding commercial penetration of nanotechnologies into various industries, the world has seen an explosion in the use of nanoparticles in common consumer products. One manifestation of this phenomenon is the extensive use of nanosilver as an antimicrobial pesticide with the potential for widespread population exposure and run-off into waterways. In the U.S., among other examples, Samsung and The Sharper Image are marketing various products that use nanosilver as an antimicrobial agent. In particular, Samsung has developed a washing machine that uses SilverCare™ Technology to clean clothes and kill biological organisms by releasing nanosilver ions into the washwater, and The Sharper Image has developed socks, slippers, and food containers impregnated with

nanosilver. In addition to these examples, however, there are numerous other consumer products that contain nanosilver and that also pose serious risks to the environment.

In connection with its reported decision to regulate the use of nanosilver in washing machines, presumably EPA has recognized that nanosilver is a pesticide under the applicable provisions of FIFRA. Consequently, as discussed below, EPA is obligated to examine and require the registration of any product that uses nanosilver for its biocidal qualities.

Nanosilver is a pesticide that must be regulated under 7 U.S.C. §136a

FIFRA requires that pesticides and pesticide products be registered before they can be legally sold in the United States. 7 U.S.C. §136a. To comply with FIFRA, a pesticide must be evaluated through an extensive process to assess any potential risks it may pose to human health or the environment. If EPA makes a finding that a pesticide will cause unreasonable adverse effects on the environment, EPA must deny its registration. 7 U.S.C. §136a(c)(5)(C).

A pesticide is, among others, "any substance... intended for... destroying...any pest," and "fungus, bacterium, virus, or other microorganisms" are considered pests. 40 C.F.R. 152.3. Additionally, a pesticide product is "a pesticide in the particular form (including composition, packaging, and labeling) in which the pesticide is, or is intended to be, distributed or sold." 40 C.F.R. § 152.3. While generally deodorizers, bleaches and cleaners are not pesticides subject to FIFRA regulation, a "pesticidal claim" on the label or in connection with the sale or distribution of the product will trigger the registration requirement for pesticides. 40 C.F.R. §152.10(a).

The following discussion of two products that use nanosilver as a pesticide provides a compelling illustration of why immediate EPA action is both legally required and essential to address more broadly the use of this potentially harmful substance in consumer products.

The Sharper Image's FresherLonger™ Miracle Food Storage Containers

The Sharper Image has been marketing nanosilver-treated slippers, socks, and food containers. Recently, the company removed public statements of pesticidal claims without removing nanosilver from the products; this action denies the public's right to know the active ingredient of these products. This is a direct violation of FIFRA, which requires that pesticides must be registered to be sold in the United States. 7 U.S.C. §136a(a).

The Sharper Image currently claims on its website that its "exclusive FresherLonger™ Miracle Food Storage Containers are made of specially treated air- and odor-impermeable polypropylene and they feature a patent-pending, airtight silicone-gasket locking system that helps to retard spoilage" but, no longer makes specific references to either nanosilver or to biocide activity.[ii] However, by searching archived webpages, an

April 2006 version of the same advertisement includes the following additional description:

> FresherLonger containers are infused with silver nanoparticles because silver (yes, the metal found in silverware) is safe and naturally anti-germ, anti-mold and anti-fungus. In tests comparing FresherLonger to conventional containers, the 24-hour growth of bacteria inside FresherLonger containers was reduced by over 98 percent because of the silver nanoparticles![iii]

Moreover, the archived Sharper Image website makes the following specific pesticidal claim:

> FresherLonger™ Miracle Food Storage Containers Are Naturally Anti-Germ, Anti-Mold & Anti-Fungus…Silver in microscopic particle form is a safe, medically proven antibacterial agent. That is why silver nanoparticles are infused into the polypropylene containers of the FresherLonger system. Compared to your regular food storage containers, tests showed the 24-hour growth of bacteria inside FresherLonger containers — with antibacterial silver nanoparticles — was reduced by over 98 percent. [iv]

The archived website even includes a specific description of the nanosilver ingredient:

> Created by advanced nanotechnology ("nano" indicating one billionth), these silver nanoparticles average only about 25nm (nanometers) in diameter — 25 billionths of a meter; one 200 thousandth of a human hair. Their natural color gives FresherLonger Miracle Food Storage containers their distinctive golden hue.[v]

EPA regulations impose certain labeling requirements for pesticide products. A statement identifying the name and percentage by weight of all active ingredients and all inert ingredients must be placed on any pesticide product. 40 C.F.R. §156.10(g)(1). Removal of pesticidal claims from its products does not shield the products from FIFRA regulation. Pesticidal claims will bring deodorizers and cleaning agents, which are normally not classified as pesticides, within the purview of FIFRA regulation. However, these Sharper Image products go beyond deodorizing and cleaning, and they fall clearly within the definition of a pesticide. The claims of the "Anti-Germ, Anti-Mold & Anti-Fungus" qualities of the FresherLonger™ containers underscore the nanosilver's ability to "destroy" "any fungus [or] bacterium." Accordingly, failure to identify nano-scale pesticide ingredients should not be an excuse to circumvent the FIFRA registration requirements.

The Samsung washing machine with SilverCare™ Technology is a pesticide product under 40 CFR §152.3

Samsung has produced a line of washing machines incorporating its SilverCare™ Technology, which releases nanosilver ions into the water during the laundering process. The manufacturer touts the SilverCare™ Technology's "superb microbe killing capabilities..." in its marketing campaign.[vi]

As noted in the report of EPA's decision to regulate nanosilver, the Agency's earlier determination that the Samsung washing machine with SilverCare™ Technology is a "device" and not subject to the same rigorous evaluations as pesticides was inappropriate.[vii]

Under FIFRA, a device is "any instrument or contrivance...which is intended for trapping, destroying, repelling, or mitigating any pest...; but not including equipment used for the application of pesticides when sold separately there from." 7 U.S.C. §136(h). Furthermore, the regulations note that pesticide product "includes any physical apparatus used to deliver or apply the pesticide if used to deliver or apply the pesticide if distributed or sold with the pesticide." 40 C.F.R. §152.3.

Without doubt, nanosilver is a pesticide active ingredient. The Samsung washing machine with SilverCare™ Technology works by releasing "100 quadrillion silver ions" into the water during the wash and rinse cycles to kill microbes on the clothes. [viii] As such, the Samsung washing machine is an apparatus that delivers the pesticide active ingredient (nanosilver) and qualifies as a pesticide product subject to regulation by EPA.

Nanosilver is harmful to the natural environment

Although the literature is inconclusive with regard to silver nanoparticles' impact on human health, several studies have indicated that silver nanoparticles are highly cytotoxic *in vitro*. First, Braydich-Stolle et al., found that silver nanoparticles (15 and 100 nm) were more toxic than both molybdenum (30 nm) and aluminum nanoparticles (30 nm) to a mouse-derived spermatogonial stem cell line, inducing apoptotic cell death, impaired mitochondrial function, and increased plasma membrane leakage.[ix]

Second, a comparison of the cytotoxicity of silver (15, 100 nm), molybdenum (30, 150 nm), aluminum (30, 103 nm), iron oxide (30, 47 nm), manganese oxide (1-2 μm) and tungsten (27 μm) particles in an immortalized rat liver cell line *in vitro* showed that silver nanoparticles are the most toxic, causing membrane leakage and reduced mitochondrial functioning at lower doses. [x] Hussain et al. also showed that silver nanoparticles may cause cytotoxicity through generation of radical oxygen species leading to oxidative stress within cells.

Finally, in a study assessing neurological aspects of nanoparticle toxicity, Hussain et al. reported that silver nanoparticles (15 nm) were less acutely toxic than manganese oxide (40 nm) in a rat neuroendocrine cell line, but that the nanosilver still impaired

mitochondrial function and caused depletion of the neurotransmitter dopamine at high enough doses.[xi] Taken together, these studies indicate that the potential for harm to wildlife and ecosystems may be significant. Caution should be taken to prevent environmental releases until the toxicity of these particles is better understood, and they can be used safely.

In light of these concerns, EPA must evaluate the use of nanosilver in consumer products, and particularly the SilverCare™ Technology and The Sharper Image antimicrobial products using nanosilver, and appropriately regulate such products in accordance with FIFRA.

Conclusion

As we begin to learn about the devastating effects of nanosilver on aquatic species, we must be vigilant in ensuring that these particles are not released into the environment. Products that are laundered or washed (e.g. socks and food containers) or washing machines that inject the particles directly into the water facilitate the release of nanosilver into the wastewater and eventually into the environment. While we applaud EPA's decision to subject Samsung's use of this pesticide to full toxicity testing requirements under FIFRA, because of the significant potential for serious environmental harm, EPA must conduct a comprehensive assessment of all products that use nanosilver as a pesticide. EPA's implementation of FIFRA is a nondiscretionary duty, and the Agency may not abdicate its responsibility in this regard. We believe that EPA will conclude, after full review and assessment, that the weight of the scientific evidence justifies either a prohibition or stringent restrictions on the use of nanosilver as a pesticide.

Respectfully,

Jennifer Sass, Ph.D.
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Natural Resources Defense Council
Washington, DC

Mae C Wu
Program Attorney
Natural Resources Defense Council
Washington, DC

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[i] Kinney, J. EPA to regulate nanoscale silver used in washing machines to kill bacteria. Daily Environmental Reporter, No. 224, November 21, 2006. Page A-3.

[ii] http://www.sharperimage.com/us/en/catalog/productdetails/sku__ZN020

[iii] Feb 8, 2006 and April 28, 2006. http://web.archive.org/web/20060208021530/http://www.sharperimage.com/us/en/catalog/productdetails/sku__ZN020

[iv] "FresherLonger™ Miracle Food Storage Containers Are Naturally Anti-Germ, Anti-Mold & Anti-Fungus". http://web.archive.org/web/20060208021530/http://www.sharperimage.com/us/en/catalog/productdetails/sku__ZN020

[v] "FresherLonger™ Miracle Food Storage Containers Are Naturally Anti-Germ, Anti-Mold & Anti-Fungus". http://web.archive.org/web/20060208021530/http://www.sharperimage.com/us/en/catalog/productdetails/sku__ZN020

[vi] "SAMSUNG Laundry Featuring SilverCare™ Technology: Silver Ions Sanitize Clothing, All In An Energy-Saving Cold Water Wash" Samsung Press Release, 13 February 2006 http://www.samsung.com/PressCenter/PressRelease/PressRelease.asp?seq=20060213_0000233684 (20 November 2006).

[vii] Letter from California Department of Pesticide Regulation to TriTAC, dated February 22, 2006, available at http://www.tritac.org/letters.htm.

[viii] "SAMSUNG Laundry Featuring SilverCare™ Technology: Silver Ions Sanitize Clothing, All In An Energy-Saving Cold Water Wash" Samsung Press Release, 13 February 2006 http://www.samsung.com/PressCenter/PressRelease/PressRelease.asp?seq=20060213_0000233684 (20 November 2006).

[ix] Braydich-Stolle L, Hussain S, Schlager JJ, Hoffman MC. In vitro cytoxicity of nanoparticles in mammalian germline stem cells. Toxicol Sci. 2005 Dec; 88(2): 412-9. Epub 2005 Jul 13.

[x] Hussain, S.M., K.L. Hess, J.M. Gearhart, K.T. Geiss, and J.J. Schlager. 2005. In vitro toxicity of nanoparticles in BRL 3A rat liver cells. Toxicology in Vitro. 19:975–983.

[xi] Hussain, S.M., A.K. Javorina, A.M. Schrand, H.M. Duhart, S.F. Ali, and J.J. Schlager. 2006. The interaction of manganese nanoparticles with PC-12 cells induces dopamine depletion. Toxicological Sciences. 92(2):456–463