

Washington Watch

Nanosilver: EPA's Pesticide Office Considers How Best to Proceed

A forthcoming report from the FIFRA Scientific Advisory Panel may have long-range implications

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In the super-hyped world of nano, nanosilver is the proverbial poster child for all things good and evil, depending upon your perspective. Silver enjoys many commercial applications, and its well recognized antimicrobial properties have been utilized since the beginnings of recorded history. Perhaps because of this success and high visibility, some are taking aim at silver and questioning whether there is too much silver used in industrial applications -- and in particular whether there is too much silver used in consumer product applications in the form of nanoscale silver.

Nanoscale silver or "nanosilver" has become one of the most commonly used nanomaterials in consumer products. Some believe there is evidence suggesting that nanosilver may be detrimental to the environment. Others vigorously disagree, and point to a long safety record of products including nanosilver, unblemished by any known adverse impact on human health or the environment.

This column provides some background on silver and nanosilver and their applications and discusses the U.S. Environmental Protection Agency's (EPA's) recent Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) review of nanosilver. The discussion also notes the significance of the controversy surrounding nanosilver -- and EPA's eventual resolution of it -- for nanotechnology stakeholders.

Background: Silver and Its Applications

Silver is a metallic chemical element with many commercially appealing properties. It has the highest electrical and thermal conductivity of all metals, is very malleable, and is found in relatively abundant supply. Silver is well known for its precious-metal properties, reflected in its use as currency, in jewelry, and in other valuable items. Because of its catalytic properties, silver is also used as a catalyst in oxidation reactions in many industrial applications.

In the context of this discussion, silver's most relevant property is its antimicrobial potency. It is said that Hippocrates, the father of medicine, claimed around 400 B.C. that silver had healing properties. Silver's biocidal properties have been acknowledged by EPA for decades.

Silver was first registered as a pesticide in the United States in 1954 for use in disinfectants, sanitizers, and fungicides.¹ Currently, there are approximately 110 pesticide registrations for silver, involving several active ingredients.² Silver-containing antimicrobial products are used in medical premises and on medical equipment, in human drinking water systems, as materials preservatives (in plastic film, paint, paper coatings, adhesives, and synthetic fibers), and in swimming pools.

Nanotechnology and Nanomaterials

Products that contain nanoscale silver are being caught up in the general debate surrounding nanotechnology -- including issues about how the relevant terms should be defined and used.

Although there is no legal or practical requirement for any one definition of nanotechnology, a rough consensus on at least one aspect of the definition has nevertheless emerged. Both EPA and the National Nanotechnology Initiative (a U.S. government project to coordinate nanotechnology research and development launched by Congress in 2001) define nanotechnology as involving a length scale of approximately one to one hundred nanometers in any dimension.³

Small size alone is not sufficient to define nanomaterials, however, as very small things have always existed in nature. For example, volcanic ash can involve particles in the specified size range. To constitute nanotechnology as EPA generally uses the term, small structures must have been intentionally engineered through use of specific chemical, physical, or biological processes. These can include "bottom up" processes that create structures from atoms and molecules, as well as "top down" processes (such as milling or machining) that turn larger particles into smaller particles.⁴

Despite some consensus on the meaning of nanotechnology, there is as yet no established, clear regulatory definition of "nanomaterials" for purposes of pesticides or industrial chemical applications. This definitional gap creates problems and invites confusion.

In this context, it is important to note that some very small things involve conventional chemical processes that have long been in commercial use. These processes do not involve the more advanced engineering and fabrication techniques that are typically associated with nanotechnology.

One familiar example of very small particles that have long been in commercial use is ions in solution. This example is particularly relevant to the current discussion because EPA has determined that washing machines that generate silver ions for antimicrobial purposes (as well as other devices that generate free ions for a pesticidal purpose) are pesticides that must be registered.⁵

The Nanopesticide Issue

For years, EPA has struggled with the question of how best to address "nanopesticides." One of the challenges for the Agency in developing a regulatory framework is that there is no universally accepted definition of what constitutes a nanopesticide.⁶

To assist EPA in working through these challenging issues, EPA's Office of Pesticide Programs (OPP) established an internal OPP Nanotechnology Workgroup in late 2006.⁷ Co-chaired by senior managers in OPP's Antimicrobials Division and Health Effects Division, the workgroup includes legal, science, and policy experts from across OPP and EPA's Office of General Counsel.⁸

The workgroup has dual purposes: First, it seeks to help OPP develop a regulatory and technical framework (including data needs) for reviewing nanopesticides submitted for registration under FIFRA.⁹ Second, it advises OPP decision makers on the technical and

policy issues that arise on a case-by-case basis with specific applications.¹⁰

OPP has yet to issue or propose any specific details on a national regulatory framework for FIFRA nanopesticide applications. As such, it remains to be seen what long-term impact the workgroup will have on OPP's general or product-specific nanotechnology policy.

The Nanosilver Debate

At the heart of the nanosilver debate is the core question of whether, as some assert, nanosilver is significantly more toxic than its bulk counterpart. Others assert that silver nanoparticles do not contribute to the toxicity of silver ions, which are the source of silver's overall toxicity.

One of the most vocal critics of nanosilver is the International Center for Technology Assessment (ICTA), which filed a petition for rulemaking on May 1, 2008, urging EPA to regulate nanosilver products as pesticides.¹¹ According to ICTA, even in its bulk form, "silver is extremely toxic to fish and other aquatic species" and at the nanoscale, can be "many times more toxic."¹² Because nanoparticles of silver have a greater surface area than larger silver particles, nanosilver is, according to ICTA, "more chemically reactive and more readily ionized than silver in larger particle form."¹³

Nanosilver, according to ICTA, has greater antibacterial and toxic effects compared to larger silver particles in part "because it is more readily converted to silver ions." ICTA points to "preliminary evidence" that nanosilver "can exert effective antibacterial action at a considerably lower concentration than that of silver ions, suggesting that the antibacterial properties and toxicity of nano-silver are not explained by its chemical composition and by the production of silver ions alone."¹⁴

This position is vigorously challenged by, among others, the Silver Nanotechnology Working Group (SNWG), an industry consortium that seeks to foster beneficial uses of silver nanoparticles. The SNWG asserts that "nanoscale silver is less toxic per unit mass than silver nitrate," an existing EPA registered pesticide.¹⁵ The consortium claims that silver ions released by silver nanoparticles are "the sole source of toxicity." The SNWG argues that this concept of "indirect toxicity" (also referred to as the O-hypothesis) is well supported by the scientific literature.¹⁶

FIFRA SAP Consideration of Nanosilver

It is precisely this debate that compelled EPA to convene a meeting of the FIFRA Scientific Advisory Panel to consider nanosilver. Specifically, the SAP is expected to provide the Agency with answers to questions posed by OPP arising in connection with four pending applications that seek pesticide registrations for products containing nanosilver-based active ingredients. Reportedly, the particular applications at issue relate to products intended for the same uses as currently registered silver products.

The FIFRA SAP "serves as the primary scientific peer review mechanism of EPA's Office of Prevention, Pesticides and Toxic Substances (OPPTS) and is structured to provide scientific advice, information and recommendations to the EPA Administrator on pesticides and pesticide-related issues as to the impact of regulatory actions on health and the environment."¹⁷

Issues and Uncertainties

In the background paper on nanosilver prepared for the SAP, EPA states that “the current state of the science does not contain sufficient information to determine definitively whether (and, if so, to what extent) various forms of nanosilver particles may cause toxic effects beyond those attributable to the release of silver ions.”¹⁸ In light of this uncertainty, the threshold question placed before the SAP is whether, with respect to the four pending applications, the Agency can make a safety finding under FIFRA that these pesticide products will not cause unreasonable adverse effects on the environment.

According to EPA, the registration applicants claim that the mode of action for nanosilver is the same as that for conventionally sized silver -- i.e., that the release of silver ions is the source of antimicrobial activity. Because the pesticidal mode of action of nanosilver is asserted to be the same as for conventionally sized silver, it follows that the potential hazards to human health and the environment resulting from the use of nanosilver as a pesticide would be the same as from the use of silver ions.

The registration applicants reportedly also claim that because nanosilver particles will not leach from their finished products, there will be little or no human exposure to nanoparticles. As a result, any toxic effect to humans associated with their products would arise solely from exposure to silver ions. Since the effects of exposure to silver ions are already well understood, the argument goes, no new toxicity testing should be necessary.

EPA expresses several concerns about this reasoning. First, the Agency notes that the acute toxicity studies routinely submitted with pesticide registration applications do not evaluate the effects of repeated low levels of exposure, and that the only endpoints measured are mortality and clinical signs.

Second, the acute toxicity studies that have been done on nanosilver and nanosilver composites were conducted according to guideline standards intended for conventionally sized antimicrobial pesticides, and “there is no characterization of the test material provided in the study reports.”¹⁹ Thus, the results may be biased or confounded.

Third, EPA has expressed concern about exposure to nanosilver among people who handle or apply the nanosilver pesticide products, as well as concern about consumers' exposure to nanoparticles when using the final products as intended.²⁰

Specific SAP Charge Questions

To address these uncertainties, the Agency asked the FIFRA SAP to consider responding to several questions. These include, among others:

- whether pesticide products containing nanosilver as the active ingredient pose potential hazards different from those associated with products containing conventionally sized silver;
- what types of data EPA would need to consider to address any potential risks associated with the use of nanosilver particles;
- how information concerning the percentages of particles in a product that fall within the nanoscale range could affect the risks associated with the product; and
- what types of new information on individual products would be most useful to EPA in

assessing the potential risks posed by antimicrobial pesticides containing nanosilver or nanosilver composites.

Panel Members' Concerns

During a FIFRA SAP public consultation meeting held in November 2009, panel members acknowledged the significant amount of data available on conventional silver, particularly on elemental silver and monovalent silver ions. They also noted the toxicological relevance of the type of studies conducted on various forms of silver (*in vitro* studies versus other types of studies) in terms of influencing the hazard profile of silver. The panel cautioned, however, that there are significant data deficits pertinent to the effects of exposure to nanosilver particles over the lifecycle of a product.

The panel members expressed uncertainty about how to bridge toxicity data between and among various kinds of nanosilver or nanometal oxide products with different physicochemical properties. They also noted concerns about other crucially important scientific issues that panel members believe remain unresolved.

The FIFRA SAP Report: What Is at Stake

The FIFRA SAP report is expected to be issued in early 2010. Although the document was not available as of this writing in late 2009, it has already become clear that the report will have significant impacts for the nano-community. How the SAP addresses outstanding issues, and the recommendations it makes to EPA, will likely influence the Agency's approach under FIFRA to both nanosilver-based active ingredients and nanopesticides in general.

To the listening public at the November 2009 consultation meeting, the SAP appeared to conclude that significant data deficits exist with regard to nanosilver, thus precluding EPA from making the safety finding that it is required to make under FIFRA in order to register a pesticide product. Until the SAP report is released, however, it is unclear exactly how the panel will respond to EPA's charge questions.

Once the report is released, the Agency will have to decide whether to rely upon any recommendations the SAP may make -- and, if so, how to translate them into regulatory action. As an immediate and preliminary step, EPA may wish to consider obtaining more information from existing silver pesticide registrants regarding particle size distribution, surface area, and related physicochemical characteristics pertinent to the silver component of registered products. Such additional information could enable EPA to characterize more precisely the nano-potential of existing silver pesticide registrations.

Is Nanosilver Really New?

This step would appear essential in light of a claim made by the SNWG. According to the consortium, "all EPA registered silver products through to 1994 were nanoscale silver."²¹ The SNWG states, "it is undeniable that products containing nanoscale metallic silver particles (often colloquially referred to as 'nanosilver') have been commercially available for over 100 years and pesticidal products containing nanosilver have been registered under FIFRA for more than 50 years."²²

The implicit assertion here is that changes in nomenclature and terminology over the few past years have simply confused scientists and policymakers, obscuring the fact that nanoscale silver has actually been used in pesticides for many years. If this claim is true, it

is essential for EPA to better understand whether existing silver pesticide registrations are in fact materially different from the four pending nanosilver-based pesticide applications. It could be that there really is nothing new here except a change in nomenclature.

Keeping the Commercial Playing Field Level

Ultimately, EPA may conclude that it lacks sufficient data to make a FIFRA safety finding with respect to the pending applications for nanosilver pesticide products. If this is the case, an important issue that remains unclear is how the Agency will ensure that the commercial playing field for silver-containing products remains competitive.

EPA itself acknowledges that out of the 110 silver-based products already registered as antimicrobial pesticides, many actually contain nanosilver. The Agency will therefore need to consider the thorny question of how to provide fair treatment for both nanosilver pesticide products that are already being marketed and pending nanosilver pesticide registration applications that EPA may disallow for marketing on the grounds that a FIFRA safety finding cannot be made.

How exactly EPA will decide to undertake this process is anything but clear. One regulatory response might be to register pending products conditionally (assuming all other aspects of the registration application are in order), and then subject each product to any forthcoming new data requirements that ultimately may be inspired by the SAP review. EPA also has other options under FIFRA, including use limitations, product suspension authority, and use and/or product cancellation. The appropriate remedy may well be product-specific and could require a resource-intensive review of all 110 currently registered silver-based products.

Conclusion

As the Obama Administration enters its second year, nano stakeholders are understandably eager to know how nanotechnology -- and the many, many science policy issues it inspires -- will fare. EPA's response to the FIFRA SAP recommendations will be carefully watched, parsed, and dissected by the nano-community as a harbinger of things to come.

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Notes

¹ See Comments of the Silver Nanotechnology Working Group for Review by the FIFRA Scientific Advisory Panel (October 30, 2009) at 3. Available online at http://www.silverinstitute.org/images/stories/silver/PDF/epa_hq_opp2009.pdf

² OPP FIFRA Scientific Advisory Panel Background Paper: Evaluation of Hazard and Exposure Associated with Nanosilver and Other Nanometals, (November 3-6, 2009) at 11. Silver-based antimicrobial pesticide active ingredients include metallic silver, silver salts (such as silver nitrate and silver chloride), zeolite-based silver compounds (such as silver-copper zeolite and silver-zinc zeolite), powdered glass materials, and silver mixtures.

³ U.S. Environmental Protection Agency (2007, February). Nanotechnology white paper at 5. Available online at <http://www.epa.gov/osa/pdfs/nanotech/epa-nanotechnology-whitepaper-0207.pdf>.

⁴ *Ibid.* at 7.

⁵ Environmental Protection Agency (2007, September 21). Pesticide registration; clarification for ion-generating equipment, 72 Fed. Reg. 54039.

⁶ See, e.g., Davies, J.C. (2007, May). EPA and nanotechnology: Oversight for the 21st century. Washington, DC: Woodrow Wilson International Center for Scholars (“EPA needs to craft a category of nanopesticides and decide how to regulate them.”). Available online at http://www.nanotechproject.org/file_download/files/Nano&EPA_PEN9.pdf.

⁷ See OPP presentation on Nanotechnology to the Pesticide Program Dialogue Committee (2006, November 9). Available online at <http://www.epa.gov/pesticides/ppdc/2006/november06/session7-nanotec.pdf>.

⁸ *Ibid.* at slide 26 (listing members of the OPP Nanotech Workgroup).

⁹ *Ibid.* at slide 25

¹⁰ *Ibid.*

¹¹ See International Center for Technology Assessment (2008, May 1). Citizen Petition for Rulemaking to the U.S. Environmental Protection Agency. Available online at http://www.icta.org/nanoaction/doc/CTA_nano-silver%20petition_final_5_1_08.pdf

¹² *Ibid.* at 16.

¹³ *Ibid.*

¹⁴ *Ibid.*

¹⁵ See Comments of the Silver Nanotechnology Working Group for Review by the FIFRA Scientific Advisory Panel, note 1, at 7.

¹⁶ See Wijnhoven, S.W.P., Peijnenburg, W.J.G.M., Herberts, C.A., Hagens, W.I., Oomen,

A.G., Heugens, E.H.W., Roszek, B., Bisschops, J., Gosens, I., Van De Meent, D., Dekkers, S., De Jong, W.H, van Zijverden, M., Sips, A.J.A.M., & Geertsma, R.E. (2009, June). Nano-silver -- a review of available data and knowledge gaps in human and environmental risk assessment. *Nanotoxicology*, 3(2), 109-138.

¹⁷ Environmental Protection Agency (2009, September 16). FIFRA Scientific Advisory Panel; notice of public meeting, 74 Fed. Reg. 47575, 47577.

¹⁸ OPP FIFRA Scientific Advisory Panel Background Paper, note 2 above, at 12.

¹⁹ *Ibid.* at 18.

²⁰ *Ibid.* at 13.

²¹ Comments of the Silver Nanotechnology Working Group, note 1 above, at 7.

²² *Ibid.* at 2.