BEFORE THE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF PESTICIDE PROGRAMS

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Re: FIFRA Scientific Advisory Panel; Notice of Public Meeting
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COMMENTS OF THE SILVER NANOTECHNOLOGY WORKING GROUP

FOR REVIEW BY THE

FIFRA SCIENTIFIC ADVISORY PANEL

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PART 1. Comment on the History of Nanoscale Silver.

The Silver Nanotechnology Working Group (SNWG)[†] appreciates the opportunity to provide written comment to the FIFRA Scientific Advisory Panel regarding the evaluation of hazard and exposure associated with nanosilver and other nanometal oxide pesticide products.

While changes in nomenclature over the decades have created confusion amongst scientists and policy makers, 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.[1]

An extraordinary amount of research into the chemistry of nanoscale silver has been conducted over the past 120 years as nanosilver particles photoreduced from silver halides are the basis for traditional photography. Nanoscale metallic silver particles ranging from 20 to 40 nm were prepared and isolated as early as 1889.[2] The intervening hundred years of commercial photographic silver research has provided a clear understanding of how environmental exposure to nanoscale metallic silver and silver ions is mitigated via the conversion of these species to insoluble sulfides, halides and thiol complexes.[3]

In the early part of the 20th century, the commercial sale of medicinal nanoscale silver colloids such as Collargol, Argyrol and Protargol began and over a 50 year period their use became widespread.[4] While the medicinal claims associated with these products were often dubious, it is clear that toxic effects were remarkably few given their ubiquity as a topical, oral, ophthalmic and intranasal antiseptic.[5] In the absence of a toxic endpoint, numerous cases studies[6] on the non-toxic, cosmetic condition argyria were documented during this period. To this day, EPA cites these case studies on nanosilver

[†] The Silver Nanotechnology Working Group (SNWG) is an industry effort intended to foster the collection of data on silver and nanotechnology in order to advance the science and public understanding of the beneficial uses of silver nanoparticles in a wide-range of consumer and industrial products.

colloids and medicinal soluble silver compounds as the dataset upon which every significant exposure limit[7,8,9] of silver is based. It is noteworthy that studies on micron-sized metallic silver particles are absent from the seminal literature and, contrary to popular assumptions, have not informed our current understanding of silver toxicity in any appreciable way.

The first silver product registered under FIFRA in 1954 was a nanosilver product. The algaecide product, Algaedyn®, was invented by Z. Moudry of the Movidyn Corporation and is thoroughly documented in the patent literature.[10] Moudry prepared non-agglomerated metallic silver particles of particles sizes ranging from 7.5 to 70 nm via the photoreduction of silver salts in the presence of a gelatin stabilizer. Even at that time it was recognized that small particle size and uniform dispersion were required for maximum antimicrobial activity. In support of this fact, particle size was characterized using electron micrographs. Recent, dynamic light scattering studies of Algaedyn, which has been commercially available in identical form continually since 1954, confirm the particle size reports from the patent literature.[11]

Similarly, a review of the 1960s patent literature reveals that FIFRA-registered silver impregnated carbon water filters, the most common type of registered silver product, contain nanosilver. In fact, the authors understood that the viability of the technology required nanoscale silver: "for proper efficiency, the silver must be dispersed as particles of colloidal size (less than 250 Å [25 nm] in crystallite size)".[12]

EPA is not the only agency to review and approve uses of nanoscale silver products. Over the last 15 years, Food and Drug Administration (FDA) granted 510(k) approval to dozens of products containing nanosilver to prevent colonization on various surfaces, including wound dressings, catheters and topical gels. Clinical evidence of reduced infection rates, anti-inflammatory effects and improved wound healing is abundant.[13] Since then, numerous nanoscale silver products have been registered by EPA, including spray disinfectants, dental line cleaners, and additives. Our analysis[14] of particle sizes of

EPA registered silver products reveals that approximately 82% of all silver products currently registered with EPA are estimated to be nanoscale or smaller, picoscale ions.

Part 2. Comment on the FIFRA Silver (Including Nanoscale Silver) Registration and Re-registration Processes.

Changes in terminology over time, culminating in the recent use of the yet-to-be-defined term ‘nano’, and the subsequent use of ‘nano’ in product marketing have created the impression that, in spite of an extensive and well documented history, nanoscale silver products are new and carry significant knowledge gaps. If we set aside arbitrary labels it becomes readily apparent that the commonplace use of nanoscale silver in a wide variety of real-life use patterns over the last 100+ years provides ample data from which to draw for risk assessment purposes. Given the long history, diversity of use patterns and enormous collection of datasets available, it is highly possible that more is known about nanoscale silver than any other pesticide product.

If knowledge gaps are identified, EPA has a well defined process for addressing them in the mandated periodic Silver Registration Review process. For example, while the scientific underpinning is not provided, the recently published Silver and Compounds Registration Review Document (EPA-HQ-OPP-2009- 033) states that there is concern about extremely small particles in registered products and that the re-registration process will require particle size information and information if nanotechnology has been used to manufacture the products. We strongly support the EPAs decision to collect particle size information on all registered pesticides, as it will undoubtedly reveal the commonplace nature of nanoscale active and inert components and confirm that EPA has provided exemplary regulatory oversight of nanoscale silver for many decades with no incidents of significance.

We hope that the FIFRA Scientific Advisory Panel will appreciate that the successful regulation and risk management of silver as a FIFRA-registered pesticide over the past 50 years is inseparable from the successful regulation and risk management of what we now call ‘nanosilver’ over that same period. As such, new nanoscale silver registration applications should continue to be managed within the existing silver registration framework. To do otherwise unfairly holds new applicants to a different standard than the dozens of current registrants of nanoscale silver products; all in the absence of an accepted 'nano' definition and any significant reported incidents. Worse yet, the creation of a new registration standard for nanoscale silver products would hold these applicants to a higher standard than applicants of micron-size silver products which are less sustainable and, in comparison to the significant regulatory history of nanoscale silver, about which very little is known.

If the periodic review of the 100+ year history of nanosilver does reveal relevant knowledge gaps, the agency has a robust mechanism to fill these data gaps through the Silver Registration Review process. To the extent that extra-procedural activities such as this SAP review of 'nanosilver' are necessary, these activities should be coordinated through the periodic Registration Review process to avoid the confusion associated with redundant and seemingly contradictory regulatory activity.

Part 3. Comments on FIFRA Scientific Advisory Panel Background Paper

The EPA Background Paper[15] provides an overview of several key issues related to nanoscale silver. It is important for the Panel to note that the background paper contains several oversights in the analysis of scientific data as it relates to risk assessment. Specifically, the background paper cites several *in vitro* studies yet makes no effort to analyze the relevance to ‘real world’ situations. For example, the background paper does not mention if the exposure levels used in the experimentation can reasonably be expected under any ‘real world’ conditions or whether the exposures are even relevant due to well documented mitigating factors such as well established silver sequestering background species such as environmentally ubiquitous chloride and sulfide ions.

In selecting information to include as background, the EPA paper fails to acknowledge that the majority of existing registered silver products are nanosilver, including the algaecides and water filters that have been in use for decades. In fact all EPA registered silver products through to 1994 were nanoscale silver. The fact that these nanosilver products have been used commercially for decades with no incidents of significance reported in the EPA OPP IDS incident database should be taken into consideration by the Panel.

The Background Paper also fails to acknowledge that the EPA Office of Water SMCL, IRIS Oral RfD and the OSHA PEL values cited in the background paper are in fact based on case studies of non-toxic exposure endpoints of nanosilver and soluble silver compounds. Contrary to present assumptions of the agency, very little of what we know about silver toxicity has been derived from studies of micron size (also referred to as macro, bulk and conventional) metallic silver.

The background paper also fails to mention that ample evidence is available to conclude that nanoscale silver is less toxic per unit mass than silver nitrate.[1] This fact is important, as it shows that the toxicity of nanoscale silver per unit mass lies in the middle of a continuum of silver and silver compounds – with silver nitrate comprising the most potent 'bookend'. According to the background paper, EPA allows data bridging for this group: "For purposes of human health assessment, EPA previously determined that silver and several of its salts (chloride, sulfate, nitrate and acetate) would be reviewed as a group. EPA concluded that the data generated on one member of the group could be used to assess the risks of the other materials in the group since exposure from all was to the silver ion, as discussed previously." Recognizing that silver nitrate is more toxic than silver nanoparticles, we can logically conclude that the risks associated with silver nanoparticles are not unreasonable, given that the risks associated with silver nitrate have been accurately assessed and successfully managed for decades.

The mechanism whereby silver ion exposure to wastewater treatment plants (WWTPs) and downstream aquatic species is mitigated is well understood. Citing the 1993 EPA Silver RED document[16]: "Silver from products used for swimming pool and human drinking water systems is discharged into the municipal wastewater effluent and treated in municipal water treatment plants. In these sewage treatment plants, microorganisms convert silver (I) in insoluble silver sulfides…. The Agency does not expect unreasonable adverse effects to the environment from these uses." The Panel should note that this assessment was made on the basis of silver products in safe use for decades at that time that were in fact all based on nanoscale silver (even though the term 'nano' was not used at that time.)

Furthermore, a recent research article authored by scientists from the U.S. EPA National Risk Management Research Lab (Impellitteri, et al. "The Speciation of Silver Nanoparticles in Antimicrobial Fabric Before and After Exposure to a Hypochlorite /Detergent Solution", J. Environ. Qual. 38:1528–1530 (2009)[17] is unequivocal: "**recent research suggests that the environmental risk from nanoscale Ag particles is low**."[17] This paper goes on to confirm that "[any] silver that does manage to make its way to a WWTP from Ag-containing materials will most likely be in the form of AgCl.... This is important because AgCl is one of the most insoluble chloride salts known and much less reactive than elemental Ag." The EPA's own research supports the historical real-world experience of legacy EPA registered materials that nanoscale silver poses minimal environmental risk.

The reaction of silver ions and silver nanoparticles with the high concentration of scavenging species in WWPTs and the environment, primarily sulfides and chlorides, limits the relevance of toxicity mechanisms in real world conditions. Simply put, nanosilver is converted to insoluble silver compounds before exposure is possible. For example, a 2009 study on silver nanoparticles (Choi et al. "Nitrification inhibition by silver nanoparticles" *Water Sci & Tech.* 59, p. 9, 2009)[18] discharged to sewer systems confirms the accuracy of the 1993 Silver RED assessement: "Silver nanoparticles may continuously changes their forms/sizes in the sewer pipes and the WWTPs through oxidation, dissolution and complexation…Nanosilver may complex with sulfide in the pipe to reduce its toxicity."[16]

While the relative toxicity of silver nanoparticles to silver nitrate is not particularly relevant for risk assessment purposes, the following references confirm the low toxicity of silver nanoparticles relative to silver nitrate and/or confirm that silver ions released by silver nanoparticles are the sole source of toxicity. This concept of indirect toxicity – also referred to as the '0-hypothesis' by Wijnhoven[19] – is supported by the following references:

Navarro et al. "Toxicity of Silver Nanoparticles to Chlamydomonas reinhardtii." Environmental Science and Technology 42 (23): 8959-8964, (2008)[20]:

The EPA background paper correctly states that that the toxicity was 18 times higher for silver nitrate compared to nanosilver based on total silver concentration. However the background paper incorrectly interprets the finding with regard to silver nanoparticle toxicity. Navarro and coauthors are clear that "the results present indirect evidence that toxicity of AgNP [silver nanoparticles] is mediated by Ag+ [silver ions]" and there is no suggestion that nanoparticles themselves contribute to the toxicity beyond their role as the source of Ag+. The main point of this article is that algae promotes the rate of dissolution of nanoparticles into Ag+ when compared to the steady state concentrations of Ag+ found at the beginning of the experiment. The background paper also omits the important fact that the addition of cysteine completely abolishes the toxicity of both silver nitrate and silver nanoparticles, confirming that the silver ion scavenging mechanisms by which risks to aquatic species from silver ion are mitigated are applicable to silver nanoparticles and that silver nanoparticles themselves do not produce a toxic response in algae. Both facts, conspicuously absent from the EPA analysis, are in direct support of the Wijnhoven '0-hypothesis'[19] that the action of silver nanoparticles derives from the action of silver ions.

A.-J. Miao et al. "The algal toxicity of silver engineered nanoparticles and detoxification by exopolymeric substances" Environmental Pollution 157, 3034–3041 (2009)[21].

This article, which is not referenced by the background paper, found that silver nanoparticles "were found to only have indirect toxic effects on marine phytoplankton as a result of their rapid Ag+ release….When the free Ag+ concentration was greatly reduced by diafiltration or thiol complexation, no toxicity was observed"[21]. Going further, Miao et al. state "unlike other frequently examined ENs [engineered nanoparticles] (e.g., TiO_2, C_{60}), whose toxicity is mainly due to their direct interaction with target organisms or the production and release of reactive oxygen species from ENs our findings imply that the toxicity of Ag-ENs is mainly brought about by the release of Ag+"[21]. Again, this reference is in direct support of the Wijnhoven '0-hypothesis'[19] that the action of silver nanoparticles derives from the action of silver ions.

Griffitt et al. "Comparison of molecular and histological changes in zebrafish gills exposed to metallic nanoparticles." Toxicol Sci. Feb;107(2):404-15 (2009)[22]. The authors studied the gill histopathology of zebrafish in response to exposure to silver nanoparticles and silver nitrate. Zebrafish exposed to soluble silver (as silver nitrate) exhibited significant thickening of the gill filament, while no change in filament width was observed in zebrafish exposed to nanoparticulate silver.

The heightened relative toxicity of silver nitrate compared to silver nanoparticles in colloidal form has also been established for decades, demonstrating that data from the era of colloidal science is fully applicable today. For example, Dequipt et al. found in 1974 that "silver nitrate is 20 times more toxic than colloidal silver when given intraperitoneally."[23]

In summary, nanoscale silver has been used in patterns that discharge to municipal sewer systems for decades with no reported incidents. The reason is well understood: reactive species entrained in the sewer system convert silver nanoparticles to insoluble species that are not toxic in any appreciable way. This exposure mitigation process is established for silver nitrate. Recognizing that the hazard associated with silver nanoparticles is less than that of silver nitrate – it is readily apparent that silver nanoparticles do not pose an unreasonable risk in any of the use patterns under discussion.

Comments on Selected Cited Submissions from the Background Paper.

Several research articles submitted to the SAP require comment as they either misrepresent results, lack proper controls or state their findings using unconventional units of measure in a way that creates confusion. It is important that the Panel be made aware of these oversights.

<u>Luoma, Samuel N., 2008. Silver Nanotechnologies and the Environment: Old Problems or New Challenges? Project of Emerging Nanotechnologies 15 Suppl, (September 2008)[24].</u>

This non-peer reviewed article is well written, however the basis for the 'near term' maximum silver discharge calculation in Table 6 is misrepresented. The calculation shows 279 Tons of silver will be discharged if 30% of the US population buys 100 nanosilver-containing products. The rational for the scenario is described in Text Box 11: "The maximum scenario uses the highest mass of silver lost from socks in a single wash, as observed experimentally: 0.031 g (Benn and Westerhoff, 2008)."[24] In fact, the highest mass of silver lost from socks in a single wash is actually 0.00065 g (650 micrograms). If the value used in the published model (31,000 micrograms discharged) is compared to the experimentally determined maximum value from the original article (650 micrograms) it becomes clear that the Luoma model <u>exaggerates the maximum discharge scenario from textiles by at least 50x</u>.

Asharani P.V. et al.,. Toxicity of Silver Nanoparticles in Zebrafish Models. Nanotechnology 19(255102): 8pp.(2008)[25].

Zebrafish embryos were incubated with different concentrations (5, 10, 25, 50 or 100 μg/ml) of silver nanoparticles. The subsequent toxic response of silver nanoparticles was then compared to the toxic response of 20 nM silver nitrate. A close look at the units associated with the dose metrics reveals that, while the silver nitrate exposure may resemble a relevant control experiment, the maximum dose of silver nitrate investigated (in *nanomolar* units) is in fact merely 0.0021 μg/ml Ag+. It is unclear why the authors chose to use 2500-50000x more silver for the silver nanoparticle exposure, but it is undeniable that this artifact of different units creates the impression that silver nanoparticles are more toxic when in fact multiple aforementioned references demonstrate the contrary. Unfortunately the EPA background paper fails to consider the vast difference in exposure concentrations that this artifact represents and misinterprets the stated results as an indication of heightened toxicity of nanoscale silver over silver nitrate.

Lok et al. Proteomic analysis of the mode of antibacterial action of silver nanoparticles. J Proteome Res 5:916, 924. (2006)[26].

While not referenced in the background paper, this article is referenced repeatedly in the ICTA petition[27] submitted to EPA in 2008. While the Lok et al. paper does conclude that the mode of action of nano-Ag is similar to that of Ag+ ions, the authors use an unconventional choice of units and therein create the incorrect impression that silver nanoparticles are more toxic than silver ions. Specifically, the authors express both silver nanoparticle and silver nitrate exposure in terms of *nanomolar* concentrations; however, the concentrations of nano-Ag indicated in this paper are quoted as the number of moles of particles per unit volume. Therefore, a 1 nanomolar (nM) concentration of silver nanoparticles contains thousands of times more silver atoms than 1 nM of silver nitrate. This difference in units readily explains the claim that the effective concentrations of nano-Ag and Ag+ ions were at nanomolar and micromolar levels, respectively.

Comments on Appendix C: Subchronic and Chronic Toxicity Data on Silver.

The collection of references provided in Appendix C: Subchronic and Chronic Toxicity Data of the EPA background paper provides an excellent example of how our understanding of 'silver toxicity' is primarily based on experiments with soluble silver compounds and nanosilver. Predictably, one reference (Rungy, 1983a)[28] in Appendix C tested 2 nm metallic silver nanoparticles in the form of Protargol (a well established colloidal (nano) silver product). The ubiquity of nanosilver toxicity data among EPA's datasets on 'silver' is again confirmed - as we have established for the IRIS Oral RfD, the Office of Water's SMCL and OSHA's PEL. For particle size measurements that confirm the nanoscale size range of Protargol see, "Activity of colloidal silver preparations towards smallpox virus, Pharmaceutical Chemistry Journal," N. E. Bogdanchikova, A. V. Kurbatov, V. V. Tretyakov, P. P. Rodionov. 26, 9-10, 778 (1992)[29].

Part 4. Comments on Charge Questions posed in the Draft Agenda

The Silver Nanotechnology Working Group appreciates the opportunity to provide comments to the SAP charge questions below. Comments are provided in bold italic font directly below each charge question provided to the Panel.

Charge Question 1. Potential Risks from Nanosilver Materials Issue: Whether pesticide products containing nanosilver as the active ingredient pose potential hazards and exposures to humans and the environment that are different from those associated with products containing conventional silver.

The question is posed in the absence of a definition of 'conventional silver'. Assuming that silver nitrate is categorized as conventional silver, it is well established that silver nanoparticles pose less hazard per unit mass.

A. Available scientific literature indicates that nanosilver products may exert an antimicrobial effect by releasing silver ions, and that these ions may pose potential hazards to humans and the environment. The Agency is unaware on any information that would suggest exposures to silver ions released from nanosilver products differ from the hazards of silver ions released by non-nanosilver (hereafter referred to as silver) based products and, therefore, might present a different hazard profile. Is the Panel aware of any information inconsistent with this determination?

Silver ions demonstrate the same behavior, regardless of their source. This is a fundamental fact of sound chemical principles.

B. Available scientific literature also indicates that, in addition to any hazards resulting from the release of silver ions, nanosilver particles themselves may present hazards that differ from those of silver particles. What, if anything, does the existing scientific literature indicate about the potential for nanosilver materials with specific particle sizes in the range of 1 to 20 nm, 21 to 50 nm, and 51 to 100 nm to pose different hazards than those of larger-sized particles of the same material, particularly nanosilver vs. silver?

As stated previously, there is substantial evidence that silver nanoparticles exert no appreciable toxic effect beyond their role as a source of silver ions (unlike TiO_2 or C_{60} nanoparticles)[21] therefore the hazard is very low. However, the question of direct vs. indirect (ion mediated) toxicity is of little relevance, as decades of use in a variety of use patterns indicates that silver nanoparticles are not appreciably toxic to humans and that reactive species in sewer systems reduce exposure via the conversion of silver nanoparticles and silver ions to non-toxic, insoluble silver compounds. Contrary to the implicit assumption underlying the EPA charge question, there is scant evidence that the hazards associated with larger size particles have been directly assessed, which is clearly in contrast to the case of nanoscale silver.

What does the existing scientific literature indicate about the potential for particular physicochemical properties of nanosilver materials (e.g., shape, surface characteristics, composition, etc.) to pose hazards that are different from larger-sized particles of the same material? Does existing literature support "bridging" data? In other words, can hazard or exposure data developed on 1 to 20 nm silver particles or silver composites be used to assess the risks for 51 to 100 nm silver particles or silver composites?

It is well established that the hazards associated with metallic silver, insoluble silver compounds and soluble silver compounds are not the same, yet the agency commonly bridges data across these compounds on the basis that any action derives from silver ions. The hazard profile of silver nanoparticles resides in the middle of the continuum bracketed by silver nitrate and silver sulfide. Therefore, logic dictates that data <u>from all sizes of silver particles</u> can be bridged based on the common action of silver ions. Earlier analysis in this document makes clear that the action of nanoscale silver derives directly from silver ions (Wijnhoven '0-hypothesis'[19]). It is clear that the nanoscale nature of silver nanoparticles does not confer any unique toxicity; composition (silver as a source of silver ions) is the determinant factor.

C. What, if anything, does the existing scientific literature indicate about the potential for nanosilver particles in the range of 100 nm – 1000 nm (or "agglomerated" nanosilver or nanometals/nanometal oxides) to pose hazards that are different from larger-sized particles of the same material?

While few studies have been performed on silver particles in the 100nm to 1000nm size range, these particles again fall in the middle of the broader silver compound continuum and are unlikely to pose a greater hazard than silver nitrate.

D. If nanosilver particles present different hazards than either silver or agglomerated nanosilver, the potential risks to human health and the environment will depend on the extent of exposure. Several types of nanosilver pesticide products are described in the attached Background Paper, and other types seem possible in the near future (e.g., sanitizers and disinfectants; and chemicals used in or on industrial, commercial or residential systems, such as slimicides, preservatives, antifoulants, metal working fluids, etc.). What do available data on the release, fate, transport and transformation of nanosilver particles suggest regarding potential human or ecological systems exposure to nanosilver particles (individual or agglomerated) under realistic use scenarios?

The 100+ year history of human exposure through medicinal nanosilver colloids, the 50+ year history of FIFRA-registered swimming pool and spa algaecides, the 40+ year history of FIFRA-registered nanosilver impregnated water filtration, the 10+ year history of nanosilver impregnated FDA-approved medical devices – all with no reports of significant incidents - is ample proof that no unreasonable exposures and/or risks are posed by nanosilver.

E. The Agency would like the Panel's advice as to whether the models currently used by the Agency would be appropriate to predict potential environmental exposures to nanosilver and if not, what, if any, modifications would be necessary.

Based on the long history of safe use of nanosilver, including a plethora of FIFRA registered nanoscale silver products over 6 decades, it is clear that the EPA has adequately assessed and managed the low level of risk from nanoscale silver using existing models.

Charge Question 2. Data Requirements Issue: If the panel believes that nanosilver is different in terms of hazard/exposure what type of data (studies) would EPA need to adequately assess the potential risks associated with the use of an antimicrobial pesticide containing nanosilver particles, when the product is intended for use as an additive to various substrates (e.g., textiles, plastics, ceramics) to impart antimicrobial properties to the treated substrate? In liquid, spray form?

The extent of exposure from nanosilver applications of textile, plastics and ceramics will clearly be less than that of the current FIFRA-registered nanosilver swimming pool algaecides, and the hazard/exposure potential will be <u>significantly less</u> than that of FIFRA-registered silver nitrate swimming pool algaecides. These products were recently reviewed as part of the 2009 Silver Registration Review process and only minor additional data requirements were proposed. As stated previously, the agency should avoid redundant date requirement review processes, as they create confusing and contradictory regulatory outcomes.

A. What types of data on the nanoscale material would be sufficient to adequately evaluate whether the hazard and exposure properties of the nanoscale material were comparable to that of a macroscale/bulk form of the same material? Could EPA rely on toxicity data for the bulk material to assess the risk of the nanoscale material?

As has been demonstrated several times in this document, datasets used by the agency contain <u>little or no information on macroscale/bulk silver</u>. Contrary to agency assumptions, virtually all data used to assess risks from silver has been derived from studies of nanosilver or soluble silver compounds. As such, considering that the datasets have already been based on nanoscale silvers no additional information is necessary to assess the risks associated with nanoscale silver.

B. What types of data would be sufficient to:

1) Evaluate whether the nanoscale material, once it has been applied to or incorporated within a substrate, remains associated with the substrate through the whole-life cycle of that substrate to such an extent that there would be essentially no human or environmental exposure to the nanoscale material or nanosized composite, and

2) Measure and characterize exposures to nanomaterials that may leach from treated materials?

It is unclear why the agency assumes that the leaching characteristics are a determinant of risk, as FIFRA-registered nanosilver algaecides are designed for whole body exposure and can be disposed of exclusively via discharge to the municipal sewer. These fully non-bound particles (associated with no substrate to leach from) have been used for decades <u>without incident to humans or the environment</u>. As such, fully bound or partially bound nanosilver additives used in much lower concentrations and commercial volumes can pose no greater risk.

C. Assuming appropriate studies could adequately show that nanosilver, which is applied to a substrate, would bind with that substrate to such an extent that there is essentially no exposure to the nanosilver, does the Panel think that other types of data (such as toxicity studies on the nanosilver particles or composite) would be needed? Similarly, if only silver ions are released from substrate containing nanosilver, would consideration of the potential risks associated with the silver ions be sufficient or would additional data be needed to assess hazards and exposure to human health and the environment from nanosilver?

As above, no additional data is required. According to any reasonable basis of risk assessment, no exposure is synonymous with no risk. Furthermore, as discussed previously and demonstrated by sound chemical principles – a silver ion behaves the same way regardless of the form of the source material.

Charge Question 3. Other Risk Assessment Issues.

A. Products developed using nanotechnology may contain a distribution of particle sizes. Please comment on how information concerning the percentage of the particles in a product falling within the nanoscale range (e.g., 1 - ~100 nm) could affect the risks of a product. Are particles at the lower end of the range (e.g., 1 nm) likely to behave like particles at the upper end of the range (e.g., 100 nm)?

Scale does not per se confer any uniform risk or specific physical property. While minor differences in in vitro toxicity may be observed under some conditions, they are not necessarily relevant or correlated with particle size. For example, Hussain et al.[30] found that 100 nm silver particles elicited a greater toxic response than 15 nm particles under certain conditions, while no statistically significant difference in toxicity was observed under a different set of conditions.

B. Please comment on the extent to which the scientific literature indicates that data on one form of a nanosilver particle or other nanometal/nanometal oxide particle can be used to assess the potential hazards and exposures of another form of nanosilver that has different physicochemical properties (e.g., is a different size or shape or has different surface properties). For example, if nanosilver is reacted with a non-metal material to form a nanosilver complex or composite, to what extent could data developed for the nanosilver be used to predict the toxicity of the complex or composite?

There is no evidence to suggest that any one particular size of nanoscale silver is characterized by markedly different behavior than another and certainly no evidence that any form of metallic silver creates an unreasonable risk under the current and proposed use patterns. Furthermore, the agency has indicated that FIFRA-registered silver salts (that are frequently in the nanoscale size range) can be directly assessed on the basis of silver ions.

C. Please comment on the extent to which the scientific literature indicates that nanosilver physicochemical properties change under different environmental or physiological conditions, what those conditions are, and how this variation could be best addressed.

The conversion of silver nanoparticle and silver ions to insoluble, non-toxic sulfides or halides is well established. This passivating speciation under real-world conditions is fundamental to the low level of environmental risk, a fact that is repeatedly recognized by the agency's own documents[16,17].

Charge Question 4. Research Needs.

A. In the next year, what types of new information on individual products would be most useful to EPA for assessing potential risks of antimicrobial pesticides containing nanosilver or nanosilver composites, such as toxicity studies, exposure studies, etc.

Given that 80%+ of FIFRA registered products are nanoscale or ionic in nature, and no incidents of significance have been reported in 6 decades of regulatory oversight, it is clear that the available data is adequate.

B. What types of long term research would be most helpful for improving the assessment of the potential risks of antimicrobial pesticide products containing nanosilver or nanosilver composites?

More research is always welcome. However, identification of appropriate research needed to guide cost-effective regulatory decision making should proceed on considered reflection of historical precedent in terms of scientific literature and real-world usage. The fact is that risk assessment of nanoscale silver can already draw from a profound body of both historical data and regulatory experience despite a sense of 'newness' that appears to be based solely on a general change in terminology to 'nano'. In this respect nanoscale silver is **not representative of the broader debate relating to nanomaterials** ***and should be considered independently from generic generalizations of knowledge uncertainty of nanomaterials.***

In terms of a formal framework for generating and reviewing data for regulatory risk assessment of silver antimicrobials there is little evidence to suggest that long term research is necessary for facilitating informed current day risk assessment of nanoscale silver beyond the periodic review of data that already occurs during the Silver Registration Review process – a well established and successfully applied regulatory mechanism that accommodates crucial considerations of equitable market access, cost-effective data generation by all concerned stakeholders and mechanisms to minimize animal testing.

REFERENCES

1. Algaedyn, a nanosilver algaecide, was first registered under FIFRA in 1954 (pre-dating establishment of EPA in 1971). FIFRA registration dates are available on-line at the NPIRS website. (http://ppis.ceris.purdue.edu);

2. Argyrol silver colloid (particle size ~35 nm) was commercialized in 1902 by A.C. Barnes. http://www.barnesfoundation.org/h_main.html

3. See for example: J. W. Gorsuch et al., Silver: Environmental Transport, Fate, Effects, & Models: Papers from ET&C, 1983 to 2002.

4. Collargol was determined to be 20 millimicron (nanometer) metallic silver particles by Bechhold in 1908. Bechhold, H., Z. Chem. u. Ind. Kolloide, 1907-08, ii, The particle size of Protargol was reported to be 2 nm by Bogdanchikova and the nanoscale particle size of Collargol was validated in 1992 in the article "Activity of colloidal silver preparations towards smallpox virus," Pharmaceutical Chemistry Journal, N. E. Bogdanchikova, A. V. Kurbatov, V. V. Tretyakov, P. P. Rodionov. 26, 9-10, 778 (**1992**). An estimated 5 million prescriptions of these colloidal silver products and soluble silver compounds were written in 1929 alone. http://resultsrna.com/products/a_novel_approach.php

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