Nanosilver Final Work Plan (FWP)

Registration Review: Initial Docket Case Number 5042

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Approved by: _____

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Table of Contents

List of Tables

1 Introduction

This document is the United States Environmental Protection Agency's (USEPA, EPA or "the Agency") Final Work Plan (FWP) for nanosilver. The FWP document explains what the Agency's Office of Pesticide Programs (OPP) knows about nanosilver generally, highlighting anticipated data and assessment needs for each unique nanosilver chemistry, identifying the types of information that would be especially useful to the Agency in conducting the review, and providing an anticipated timeline for completing review of the nanosilver case.

The registration review process was designed to include a public participation component to solicit input from interested stakeholders. By sharing this information in the docket, the Agency intends to inform the public of what it knows about nanosilver and what types of new data or other information would be helpful for the Agency to receive as it moves toward a registration review decision on nanosilver.

1.1 Statutory and Regulatory Authority

The Food Quality Protection Act (FQPA) of 1996 mandated a registration review program. All pesticides distributed or sold in the United States generally must be registered by the USEPA based on scientific data showing that they will not cause unreasonable risks to human health or the environment when used as directed on product labeling. The registration review program is intended to make sure that, as the ability to assess risk evolves and as policies and practices change, all registered pesticides continue to meet the statutory standard of no unreasonable adverse effects to human health or the environment. Changes in science, public policy, and pesticide use practices will occur over time. Through the registration review program, the Agency periodically reevaluates pesticides to make sure that as change occurs, products in the marketplace can be used safely. Information on this program is provided at https://www2.epa.gov/pesticide-reevaluation.

The Agency is implementing the registration review program pursuant to Section 3(g) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and will review each registered pesticide every 15 years to determine whether it continues to meet the FIFRA standard for registration. The regulations governing registration review begin at 40 CFR 155.40. The Agency will consider benefits information and data as required by FIFRA. The public phase of registration review begins when the initial docket is opened for each case. The docket is the Agency's opportunity to state what it knows about the pesticide and what additional risk analyses and data or information it believes are needed to make a registration review decision.

1.2 Updates to the Work Plan

Since the publication of the Nanosilver Preliminary Work Plan (PWP), the Agency has made the following updates:

- Revised the introduction section, created subsections to give an overview of the FWP, described statutory and regulatory authority, and added the case overview.

- Added Table 1 – Summary of Anticipated Risk Assessments and Data Needs for Registration Review: Nanosilver, Table 3 – Chemical Identification of Nanosilver, Table 4 – Physical-Chemical and Environmental Fate Properties for Nanosilver, Table 6 – Summary of Nanosilver Registered Uses, Table 7 – Studies Anticipated as Needed for Registration Review of Nanosilver, Table 8 – Residential Handler Exposure Scenarios for Nanosilver, Table 9 – Residential Post-Application Exposures, and Table 10 – Occupational Handler Exposures in Nanosilver.
- Updated Table 2 with the anticipated registration review schedule.
- Updated Section 1.5.1 on registrations with the current number of active nanosilver registrations including those registered under the silver and compounds case under PC code 072501. Five products registered under the silver and compounds case, EPA Reg. Nos. 10324-18, 68161-1, 69681-35, 7124-101, and 83587-3 are being reclassified and included in the nanosilver case.
- Updated Section 1.6 on the regulatory history to show that certain products are now cancelled or no longer considered nanosilver products.
- Updated Table 5 – Summary of Nanosilver Registered Uses to include the latest list of products believed to contain a nanosilver active ingredient.
- Added Section 4.3 on Endangered Species.
- Deleted "Guidance for Commenters" section.
- Updated Section 7 which summarizes the next steps for this registration review case.
- Added Section 8 to list references.
- Added Appendix A.
- Added Appendix B, the Agency's Response to Public Comments received concerning the PWP.
- Corrected formatting and typographical errors.

The Agency received 12 submissions to the docket during the public comment period on the PWP. The Agency's responses to these comments are given in Appendix B. Although the comments received do not result in a modification to the anticipated data needs identified in the nanosilver PWP, the data needs have been revised based on the finalization of Part 158W in 2013 and in some cases from review of nanosilver chemistries. This document is the Final Work Plan (FWP) for the nanosilver registration review process.

1.3 Case Overview

The PWP for nanosilver (case 5042) was published on July 6, 2012 and the 60-day public comment period ended on September 6, 2012. The Agency received 12 submissions on materials included in the docket during the public comment period. The FWP was put on hold while products in the silver and compounds (cases 4082 and 5015; docket number EPA-HQ-OPP-2009-0334) were undergoing evaluation for possible active ingredient reclassification, including

the possibility for products to be classified as having nano-sized silver active ingredients that are manufactured to retain the particle's unique size-related properties.[1]

Documents associated with the nanosilver registration review case can be viewed at http://www.regulations.gov in docket EPA-HQ-OPP-2011-0370.

The use patterns that have been identified to date include swimming pool/spa treatments and material preservative products for coatings, textiles, and plastics. People may be exposed to nanosilver through inhalation and dermal exposures while applying the products to swimming pools and from incidental oral exposures during swimming. Further exposures may come from material preservative uses either while applying or from nanosilver which leaches out when textiles and plastics are washed. Nontarget organisms can be exposed when swimming pool water is released or when nanosilver used as a material preservative leaches. Table 1 summarizes the risk assessments and data needs anticipated for registration review of nanosilver, taking into account the use patterns for the products covered. Table 2 summarizes the anticipated registration review schedule. Data needs are anticipated for each unique nanosilver active ingredient in this registration review.

Table 1 – Anticipated Risk Assessments and Data Needs for Nanosilver Registration Review

Risk Assessment	Assessment Necessary to Support Registration Review	Type of Assessment Required (None/New)	Data Anticipated as Needed (See Table 7 for details)*
Dietary (food)	No	None	None
Dietary (drinking water)	Yes	New	Neurotoxicity, Immunotoxicity 90 Day Oral Toxicity Mutagenicity Prenatal Developmental Toxicity (two species) Reproductive Toxicity Chronic Oral Toxicity Carcinogenicity – two rodent species
Occupational Handler	Yes	New	90 Day Dermal Toxicity 90 Day Inhalation Toxicity Dermal and Inhalation Exposure – Indoor Carcinogenicity – two rodent species
Occupational Post-application	Yes	New	Textile Attrition Data 90 Day Inhalation Toxicity

[1] When the Agency performs a nanomaterial risk assessment, a crucial consideration is whether exposure would be to the nanoparticles or to a degradate (e.g., component ions). For example, if the nanoparticle rapidly dissolves into component ions, then the Agency may limit some exposure evaluations to just the ions. In such cases, exposure would be considered based on the appropriate non-nano-sized active ingredient(s).

Risk Assessment	Assessment Necessary to Support Registration Review	Type of Assessment Required (None/New)	Data Anticipated as Needed (See Table 7 for details)*
Residential Handler	Yes	New	90 Day Dermal Toxicity 90 Day Inhalation Toxicity Dermal and Inhalation Exposure – Indoor Carcinogenicity – two rodent species
Residential Post-application (Dermal)	Yes	New	90 Day Dermal Toxicity Indoor Surface Residue Chronic Oral Toxicity Carcinogenicity – two rodent species
Residential Post-application (Incidental Oral)	Yes	New	Neurotoxicity, Immunotoxicity 90 Day Oral Toxicity Prenatal Developmental Toxicity (two species) Reproductive Toxicity Indoor Surface Residue Pool Water Residues
Residential Post-application (Inhalation)	Yes	New	90 Day Inhalation Toxicity Textile Attrition Carcinogenicity – two rodent species
Aggregate	Yes	New	Same data requirements as dietary drinking water and incidental oral.
Cumulative	No	None	None
Tolerance Review	No	None	None
Ecological	Yes	New	Avian Toxicity Fish Toxicity Acute and Chronic Aquatic Invertebrate Toxicity Acute and Chronic Algal Toxicity Fish Bioconcentration Wastewater Treatment Plant studies Leaching data

*Table 7 provides a comprehensive listing of the studies anticipated as needed for the registration review of nanosilver.

Table 2 - Anticipated Registration Review Schedule

Anticipated Activity	Target Date*	Completion Date
Phase 1: Opening the Docket		
Open Docket and 60-Day Comment Period for Preliminary Work Plan	2012-06	2012-06-07
Close Public Comment Period	2012-08	2012-06-09
Phase 2: Case Development		

Anticipated Activity	Target Date*	Completion Date
Issue Final Work Plan	2018-09	2018-10
Issue Data Call-In (DCI)	2018-10	
Receive Data to be Considered in Risk Assessment	2020-10	
Open 60-Day Public Comment Period for Preliminary Risk Assessment(s)	2021-06	
Close Public Comment Period	2021-08	
Phase 3: Registration Review Decision and Implementation		
Open 60-Day Public Comment Period for Proposed Decision	2022-01	
Close Public Comment Period	2022-03	
Issue Final Decision	2022-05	
Begin Post-Decision Follow-up	2022	
Total (years)	10	

*The anticipated schedule will be revised as necessary (*e.g.*, need arising under the Endocrine Disruptor Screening Program with respect to the active ingredients in this case).

In most workplans, the date of the most recent risk assessment is usually provided to identify those assessments that the Agency will rely upon to inform the registration review risk assessment. For the nanosilver case, there are no nanosilver-specific assessments for products registered as conventional (non-nano) silver products. The assessments conducted for products registered as containing nanosilver, EPA. Reg. Nos. 85249-1 (HeiQ AGS-20) and 85294-2 (HeiQ AGS-20 U) and the vacated registration for EPA Reg. No. 84610-2 (NSPW-L30SS), can be found in dockets EPA-HQ-OPP-2009-1012 and EPA-HQ-OPP-2012-0595 at www.regulations.gov. While these assessments may be informative as to the risks from these particular products, the assessments do not necessarily cover the potential risks from other unique nanoparticle chemistries.

In November 2009, the Agency convened a meeting of the FIFRA Scientific Advisory Panel (SAP) to address a number of questions associated with assessing the hazard of and exposure to nanosilver and other nanoscale metal-based pesticides. The materials for this meeting can be found on www.regulations.gov at docket number EPA-HQ-OPP-2009-0683. In general, the SAP advised that the toxicity of nanosilver could differ from and might be higher than other forms of silver (e.g. silver ions).

The SAP was generally unsupportive of bridging among silver-based materials with different properties. However, the SAP indicated that bridging might be appropriate for materials of similar size and essentially identical physical properties and that bridging between silver ions released from nanosilver and the existing database for silver ions is feasible.[2] The SAP cautioned about extrapolating from one nanosilver formulation to another when assessing hazards, because

[2] Bailey, J. (January 26, 2010). *Transmittal of meeting minutes of the FIFRA Scientific Advisory Panel meeting held November 3-5, 2009 on the evaluation of hazard and exposure associated with nanosilver and other nanometal pesticide product* [Memorandum]. Arlington, VA: Environmental Protection Agency. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0683-0177

differences in particle formulation (e.g. coating and inert ingredients) are likely to affect biological activity, among other things.

The SAP commented that insufficient literature is available to draw any firm conclusions regarding human (occupational or consumer) and environmental exposures to nanosilver under typical use scenarios. Three major routes are considered for human exposure to nanoparticles: oral, inhalation, and dermal. Only a few studies in rodents are available that investigate the toxicity of nanosilver from exposure by these routes. Similarly, information on the level of human exposure to nanosilver products by these routes for workers or consumers is generally limited. In addition, environmental fate and transport data for nanosilver are limited. The ability to measure concentrations of nanosilver in the environment along with the environmental exposure pathways, bioavailability, toxicity, and potential impact of nanosilver on ecological systems is not well developed. Furthermore, little or no information on the fate of nanosilver in soils and sediments is available.

As a result, the SAP recommended a case-by-case approach to hazard and exposure assessment (i.e. product-by-product) where each new nanosilver could be treated as a new active ingredient. The SAP also advised that existing data requirements may have to be adjusted to obtain data appropriate to assess the fate, degradation, metabolism, mobility, dissipation, and accumulation of nanomaterials. In addition, protocol submissions from registrants to the Agency were highly encouraged by the SAP.

The SAP report further suggested that existing information on conventional silver could be useful, but not necessarily sufficient in assessing potential nanosilver risks. The SAP recommended that the Agency treat nanosilver differently from its conventional silver counterpart in evaluating proposed nanosilver product applications (in terms of both data requirements and the conduct of risk assessments). Moreover, the SAP recommended that EPA require additional data on the physical chemistry, exposure potential, and the potential hazard of nanosilver to human health and the environment.

The Agency generally agrees with the SAP about the inadequacy of data on nanosilvers and that the hazards of unique nanosilver chemistries cannot be fully characterized using data for the silver ion alone or by using data on other nanosilver chemistries. As a consequence, the Agency is requiring data consistent with Part 158 data requirements. A DCI will be issued for new registrations containing a unique nanosilver chemistry and for existing registrations with a unique nanosilver chemistry. The Agency will consider citations by applicants and registrants to relevant data on a similar unique nanosilver chemistry covered by the data requirement, with explanations of the similarities (i.e., bridging rationales). However, citing to data on a nanosilver chemistry that is not similar may not be sufficient to satisfy the outstanding data requirement. Data being generated in accordance with Table 7 should be done in a phased approach, with product characterization data being generated prior to developing protocols, which is highly encouraged, for subsequent effects testing.

1.4 Chemical Identification and Properties

Table 3 – Identification Information for the Nanosilver Registration Review Case

Registration Review Case Name	Nanosilver
PC Code*	072599
Registration Review Case No.	5042

*Additional PC codes may be created based on case-by-case determination of each unique formulation.

A general summary of the physical-chemical and environmental fate properties of nanosilver relevant to risk assessment is included in Table 4.

Table 4 – General Physical-Chemical and Environmental Fate Properties for Nanosilver

Guideline No.	Parameter	Value	Reference (MRID)/Comments
830.7050	UV/Visible Absorption	414 nm	MRID 49536605. Value may range from ~410-450 nm, depending on particle size.
830.7370	Dissociation constant (pKa)	Not applicable	No acid or base functionality
830.7550	Octanol-water partition coefficient (Log K_{ow})	Not applicable	Inorganic and nonpolar
830.7840	Solubility in water	Insoluble*	None
830.7950	Vapor pressure	Not applicable	None
None (calculated)	Henry's law constant	Not applicable	None

*Silver nanoparticles are insoluble but may exist in a colloid or suspension, and this dispersion may increase with the addition of a water-soluble polymer or other stabilizing agents.

1.5 Use/Usage Description

1.5.1 Registrations

Particle size data using a non-guideline method to measure in the nanoscale were required via data call-in of products in the silver case to determine if any of these products should be classified as a unique active ingredient because they have a unique nanosilver chemistry. As shown in Table 5, there are seven registered end-use products with five distinct types of nanosilver chemistries. EPA is considering treating each unique nanosilver chemistry as a separate active ingredient (a.i.), and thus this registration review case may address at least five separate nanosilver active ingredients. The products are formulated as liquid suspensions, powders, or impregnated materials, and the percent a.i. ranges from 0.8% to 99.9%. Two products, EPA Reg. Nos. 85249-1 and 85249-2, are the only products currently registered under PC code 072599 for nanosilver. The other five products, EPA Reg. Nos. 7124-101, 10324-18, 68161-1, 69681-35, and 83587-3 were classified as having the active ingredient silver (PC code 072501), but are now being reclassified as having a nanosilver active ingredient; as such, they will be included in the nanosilver registration review case #5042, as shown in Table 5.

Table 5 – Summary of Nanosilver Registered Products

PC Code*	EPA Reg. No.	Product Name	Percent a.i.	Formulation	Use
072599	85249-1	HeiQ AGS-20	19.3	Powder	Material Preservation
	85249-2	HeiQ AGS-20 U	19.3	Powder	
TBD	83587-3	Additive SSB	99.9	Powder	Material Preservation
TBD	10324-18	Algaesil	0.80	Liquid	Pools
	69681-35	Clor Mor Silver Algaecide	0.80	Liquid	Pools
TBD	68161-1	Algaedyn	0.80	Liquid	Pools
TBD	7124-101	Nu-Clo Silvercide	0.80	Liquid	Pools

*The Agency is considering creating different nanosilver names and PC codes for each unique nanosilver chemistry. Each row signifies what may be a unique type of nanosilver chemistry.

As the Agency continues to review existing and newly proposed silver pesticide products, there may be additional products with nanosilver chemistries (unique active ingredients) added to the nanosilver registration review case. Such products may contain particles in the nanoscale range, ingredients that enhance the stability of the particles, and/or have other properties that may exhibit unique size-related effects. The Agency has requested scanning and transmission electron microscopy (SEM and TEM) data for products subject to the registration review silver DCIs. Additionally, any new applications for registration of products that may contain a nanosilver chemistry will be asked to submit the same type of data.

1.5.2 Summary of Registered Uses

Table 6 includes a summary of the registered uses of products containing nanosilver that will be assessed in this registration review. The registered nanosilver products can be applied by the following application methods: open pour powder, open pour liquid, and closed loading.

Table 6 – Summary of Nanosilver Registered Uses

Use (EPA Reg Nos.)	Application Rate (as silver)	Application Methods
Material Preservative (83587-3, 85249-1, 85249-2)		
Adhesives and Sealants (83587-3)	753 to 9,990 ppm	Open Pour Powder
Ceramics, ceramics glazes, porcelain enamels (83587-3)	9,990 ppm	Open Pour Powder
Coatings, all types (83587-3)	9,990 ppm	Open Pour Powder
Plastic films, sheets, slabs and molded parts (83587-3)	753 to 9,990 ppm	Open Pour Powder
Textiles - Application method unspecified (83587-3)	753 to 9,990 ppm	Open Pour Powder
Textiles – Coated (85249-1, 85249-2)	19 ppm	Closed Loading
Textiles – Incorporated (85249-1, 85249-2)	100 ppm	Closed Loading
Swimming Pools (7124-101, 10324-18, 68161-1, 69681-35)		
Initial Treatment	0.05 to 0.1 ppm	Open Pour Liquid
Weekly Prevention Treatment	0.025 ppm	Open Pour Liquid

1.6 Regulatory History

In light of information suggesting that some existing silver-based pesticide products were registered before EPA began to make the distinction between nanosilver and non-nanosilver, EPA sent a letter in 2009 under authority of FIFRA Section 6(a)2 to each registrant with silver-based products. The letter requested confirmation as to whether their products contained any amount of silver in any form having a dimension that measured between 1 and approximately 100 nanometers. An example letter is in www.regulations.gov at EPA-HQ-OPP-2011-0370-0020. In response to this letter, four registrants, representing five registered products (EPA Reg Nos. 68161-1 73499-1, 73499-2, 75829-1, and 83587-3), stated that their products, which were registered using data for conventional silver (PC Code 072501), contained nanosilver. These five products were included in Table 1 "Registered Products – Nanosilver" of the nanosilver PWP. Since then, three of these products (EPA Reg. Nos. 73499-1, 73499-2, and 75829-1) have been voluntarily cancelled.

Also, in the nanosilver PWP, Table 2 identified three products that the Agency believed to contain nanosilver: EPA Reg. Nos. 49403-34, 49403-36 and 49403-38. Since then, the Agency has determined that products EPA Reg. Nos. 49403-34 and 49403-38, do not contain nanoscale silver, and EPA Reg. No. 49403-36 was cancelled September 18, 2013.

On December 1, 2011, EPA issued conditional registrations for two pesticide products containing a nanosilver chemistry as an active ingredient. The registrations were issued to HeiQ Materials Ag ("HeiQ") for the products HeiQ AGS-20, EPA Reg. No. 85249-1, and HeiQ AGS-20 U, EPA Reg. No. 85249-2, intended for use as a preservative in textile products. This information can be found at www.regulations.gov in docket EPA-HQ-OPP-2011-0370. As part of the conditional registration, HeiQ is required to provide the types of data identified in Table 7 of this document in addition to the conditional data requirements given during registration. Both of these products are included in this registration review case.

In addition, on May 15, 2015, EPA issued a conditional registration for another pesticide product containing nanosilver as an active ingredient. The registration was issued to Nanosilva, LLC for the product NSPW-L30SS, EPA Reg. No. 84610-2, for use as an antimicrobial additive and included data terms and conditions on the registration similar to the data required for the HeiQ products. The registration decision was challenged in the Ninth Circuit Court of Appeals, and the court vacated the registration. In response to the Court's mandate, EPA issued a cancellation order on July 20, 2017.

On February 29, 2012, EPA sent Data Call-In Notices (DCIs) to registrants with products included in the Silver and Compounds Registration Review case (Case No. 4082) that required generation and submission of, among other things, particle size data to determine if a silver product contained nanosilver. The Agency has received and reviewed data for most of the silver products, including those registered after the DCI was issued, and determined that seven products will be reclassified as having a nanosilver chemistry as the active ingredient. These seven products are included in the Nanosilver Registration Review case (Case No. 5042). The Agency will continue reviewing particle size data for the remaining silver products (approximately 36) and will provide notice for any new reclassified products (i.e., reclassified from silver to nanosilver-based) not otherwise noted in this document.

1.6.1 Tolerance Information

None of the products containing nanosilver are registered for food or food contact use.

1.7 Incidents

1.7.1 Human Health

The are no human health incidents listed for the nanosilver PC Code (072599) in the OPP Incident Data System (IDS) for the time period 1/1/1999 to 9/11/2018 when the search was conducted.

Because of the potential that some products that were initially classified as conventional silver were actually nanosilver, the incident database was also searched using the PC Codes for conventional silver. This search identified 64 incidents for the conventional silver PC Codes (072501 and 072503) for the time period 1/1/1999 to 9/11/2018. Most of the incidents (59) involved the use of a particular brand of drinking water treatment cartridge, four incidents involved the use of a swimming pool/spa product, and one incident involved the use of a surface disinfection product. The products that were associated with these incidents are not among the products that have been identified as containing nanosilver.

1.7.2 Ecological

No nanosilver ecological incidents have been reported in the OPP Incident Data System (IDS) for the time period 1/1/1999 to 6/4/2018.

2 Anticipated Data Needs

The studies listed in Table 7 are anticipated to be needed for the registration review of each of the unique nanosilver active ingredients identified in Table 5. The data are based on requirements listed in 40 CFR Part 158 W and include special non-guideline studies consistent with data required for previous nanosilver product registrations. While the Agency anticipates requiring data on each unique nanosilver active ingredient, in response to the DCI to be issued on this registration review case, registrants may cite to data in public literature and provide bridging rationales and waiver requests. EPA will consider such citations, rationales and requests, based on similarity of actives while keeping in mind the cautions in the SAP report about extrapolating from one nanosilver formulation to another.

While this listing is comprehensive, as with the two nanosilver registrations granted, there may be circumstances meriting reduction of the data required, taking into account the test notes of 158W, which are not repeated here. For example, a product applied using a closed mixing/loading system may not require inhalation studies, or a product that purportedly does not leach may not require all the aquatic animal testing or the down-the-drain studies.

Table 7 – Studies Anticipated as Needed for Nanosilver Registration Review

GLN	Study Name	Test Substance[1]	Time Frame (months)	Risk Assessment(s) Data Will Support	Use Site(s) Triggering Anticipated Data Requirement	Applicable Exposure Scenario(s)
830.1620/ 1650	Description of Production and Formulation	TGAI, TEP	7	All	All	All
830.1800	Enforcement Analytical Method	TGAI, TEP	7	All	All	All
830.7050	UV/Visible Light Absorption	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[2,6]	Particle Size and Diameter (Size) Distribution (DLS)	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[2,6]	Particle Size and Diameter (Size) Distribution (SEM)	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[2,6]	Particle Size and Diameter (Size) Distribution (TEM)	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[6]	Surface Area Determination	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[6]	Zeta Potential	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[6]	Stability to Sunlight, Detergents, Temperature, and Salinity	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[6]	Chemical Speciation	TGAI, TEP	7	All	All	All
Non-Guideline –Special Study[6]	Rate of Deposition	TEP	7	All	All	All
Non-Guideline –Special Study[6]	Dissolution Kinetics	TGAI, TEP	7	All	All	All
870.3100	90-Day Oral Toxicity (Rodent)	TGAI	24	Human Health Toxicology	All	Incidental oral Drinking water
870.3465	90-Day Inhalation Toxicity (Rat)	TGAI	24	Human Health Toxicology	All	Inhalation
870.3250	90-Day Dermal Toxicity	TGAI, TEP	24	Human Health Toxicology	All	Dermal

GLN	Study Name	Test Substance[1]	Time Frame (months)	Risk Assessment(s) Data Will Support	Use Site(s) Triggering Anticipated Data Requirement	Applicable Exposure Scenario(s)
870.4100	Chronic Oral Toxicity (Rodent)	TGAI	24	Human Health Toxicology	All	Drinking water
870.4200	Carcinogenicity (Two rodent species-Rat and mouse preferred)	TGAI	48	Human Health Toxicology	All	Drinking water, Inhalation, Dermal
870.3700	Prenatal Developmental Toxicity – Rat and Rabbit Preferred	TGAI	24	Human Health Toxicology	All	Inhalation, dermal, incidental oral
870.3800	Reproduction and Fertility Effects	TGAI	24	Human Health Toxicology	All	Inhalation, dermal, incidental oral
870.5100	Reverse Mutation Assay	TGAI	9	Human Health Toxicology	All	Inhalation, dermal, incidental oral
870.5300 and 870.5375	*In Vitro* Mammalian Gene Mutation	TGAI	9	Human Health Toxicology	All	Inhalation, dermal, incidental oral
870.5385 and 870.5395	In Vivo Cytogenetics	TGAI	9	Human Health Toxicology	All	Inhalation, dermal, incidental oral
870.7485	Metabolism and Pharmacokinetics	PAI or PAIRA	24	Human Health Toxicology	All	Inhalation, dermal, incidental oral
870.7800	Immunotoxicity	TGAI	12	Human Health Toxicology	All	Inhalation, dermal, incidental oral
875.1200[3]	Dermal Indoor Exposure	TEP or surrogate	24	Occupational and Residential Handler	All	Dermal
875.1400[3]	Inhalation Indoor Exposure					Inhalation
875.2300	Indoor Surface Residue Dissipation	TEP	24	Residential Post-Application	Textiles Plastics	Dermal, Incidental oral
Non-Guideline –Special Study[6]	Textile Attrition Study	TEP	24	Occupational and Residential Post - Application	Textiles	Inhalation
Non-Guideline	Pool Water Residues	TEP	24	Residential Post - Application	Swimming pools	Dermal, Oral

GLN	Study Name	Test Substance[1]	Time Frame (months)	Risk Assessment(s) Data Will Support	Use Site(s) Triggering Anticipated Data Requirement	Applicable Exposure Scenario(s)
–Special Study[6]						
850.2100	Avian Acute Oral Toxicity	TGAI	12	Ecological	All	Terrestrial Systems
850.2200[4]	Avian Dietary Toxicity	TGAI	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Terrestrial Systems
850.1010	Acute Freshwater Invertebrate Toxicity	TGAI	12	Ecological	All	Aquatic systems
850.1075	Acute Freshwater Fish Toxicity	TGAI	12	Ecological	All	Aquatic systems
850.1300	Aquatic Invertebrate Life Cycle	TGAI	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Aquatic systems
850.1400	Freshwater Fish Early-life Stage	TGAI	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Aquatic systems
850.1730	Fish Bioconcentration Factor	TGAI	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Aquatic systems
850.4500[5]	Algal Toxicity	TGAI	12	Ecological	All	Aquatic systems
850.4550[5]	Cyanobacteria toxicity	TGAI	12	Ecological	All	Aquatic systems
850.4400[5]	Aquatic plant toxicity, Lemna sp.	TGAI	12	Ecological	All	Aquatic systems
835.1110	Activated Sludge Sorption Isotherm	TEP, AIRTA	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Aquatic systems
850.6800	Modified Activated Sludge, Respiration Inhibition Test	TEP, AIRTA	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Aquatic systems
835.1230	Sediment and Soil Adsorption/Desorption	TEP, AIRTA	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Aquatic systems

GLN	Study Name	Test Substance[1]	Time Frame (months)	Risk Assessment(s) Data Will Support	Use Site(s) Triggering Anticipated Data Requirement	Applicable Exposure Scenario(s)
835.1240	Leaching and Adsorption/Desorption	TEP, AIRTA	12	Ecological	Paints, stains and coatings; Textiles; Swimming pools	Aquatic systems

TGAI – Technical Grade Active Ingredient
TEP – Typical End Use product
AIRTA – Active Ingredient Release from the Treated Article during leaching test
PAI – Pure Active Ingredient
PAIRA – Pure Active Ingredient, Radiolabeled

[1] If a nanosilver active ingredient is applied to textiles, studies may be required for an additional test substance: Active Ingredient Release from the Treated Article during leaching test (AIRTA). This determination will be made on a case-by-case basis.
[2] In the anticipated DCI, EPA will recommend particle sizing to be measured by all of the following techniques: dynamic light scattering (DLS), both secondary electron and backscatter electron scanning electron microscopy (SEM), and transmission electron microscopy (TEM). DLS particle size distributions should be measured before and after sonication. Provided micrographs should be representatives of the sample. It is suggested that the following micrographs be included with submissions: 1) A zoomed-out image showing potential larger-order structures (such as assemblies, aggregates, and agglomerates) of the particles, 2) A zoomed-in image of potential larger-order structures with note of the population distribution by size, and 3) A zoomed-in image of the particle showing the structure of the particle, along with population distribution by size. If more than one type of particle is present, each should have its own micrograph and population distribution by size. Please have digital copies of the SEM/TEM images available upon request.
[3] The anticipated DCI will identify dermal and inhalation handler exposure scenarios that include: Open pour liquids for pool treatment, Open pour solids for material preservation.
[4] Study 850.2200 can be waived if nanosilver determined by the Agency not to bioconcentrate based on study 850.1730.
[5] Green algae data are required. Additional aquatic plant testing under 850.4500 (freshwater diatom, marine diatom), 850.4550 (cyanobacteria), and 850.4400 (Lemna sp.) will be needed if the EC50 for the green algae is less than 1 mg a.i./L.
[6] The anticipated DCI will require that a protocol must be submitted prior to study submission.

3 Human Health Risk Assessment

The Agency anticipates the need to require generation and submission of human health hazard and exposure data and to conduct a human health risk assessment for nanosilver during registration review. The hazard characterization section cites findings from studies available in the scientific literature for nanosilver with certain size ranges and specified properties. This information provides a general understanding of the potential human health hazards of nanosilver; however, it may or may not apply to other nanosilver ingredients, such as those in the products identified herein.

3.1 Hazard Characterization

In the Agency's 2012 summary of the human health data for nanosilver, information was provided on one nanosilver material, HeiQ AGS-20, for conditional registration. The information presented on HeiQ AGS-20 is based on published literature studies with nanosilver materials that may not be similar in physical-chemical characteristics as the nanosilver materials in this registration review, and thus may or may not be relevant to the hazard of other nanosilver test materials included in this registration review. Hence, while the available information is summarized here, additional data for this product and other active ingredients in this registration review case, consistent with the data requirements identified in part 158W, are needed to fully characterize the hazard of the included nanosilver active ingredients. Whether there is any similarity in hazard and dose-response to the currently available information may be considered in well supported bridging arguments that are submitted to EPA. Study summaries and references cited below can be found in www.regulations.gov under document number EPA-HQ-OPP-2011-0370.

Acute toxicity testing of HeiQ AGS-20 showed that the acute toxicity was low; skin and eye irritation was either moderate or non-irritating. No skin sensitization was observed. Repeat dose oral toxicity studies with nanosilver (Kim et al., 2008; Kim et al., 2010; Park et al., 2010) reported effects in the liver (central vein dilation, bile duct hyperplasia, elevated aspartate and alanine transaminase enzymes, elevated alkaline phosphatase) and slight cell infiltrate in the kidneys of mice.

One repeat dose inhalation toxicity study with a nanosilver material with an average diameter of 18-19 nm (Sung et al., 2009) showed toxic effects in the liver (bile duct hyperplasia) and lungs (chronic alveolar inflammation and macrophage accumulation in lungs) of rats after inhalation of the nanosilver material for 13 weeks at a concentration of 515 $\mu g/m^3$. The Agency considers the effects in the liver and lung adverse. Significant increases in the amount of nanosilver in tissues, such as olfactory bulb, brain, kidneys, and blood, were also reported in this study. Females had two to three times more silver accumulation in their kidneys than males. This study indicates to the Agency that, if sufficient quantities of nanosilver become airborne, and if such nanoparticles display toxicity similar to the nanoparticles used in the Sung et al. (2009) study, then inhalation of nanosilver may result in adverse health effects. As a result, the Agency anticipates requiring additional data about what, if any, material is released from treated materials, and what, if any, effects are observed from longer term exposures to the nanosilver ingredients in the each of the products referenced.

There are no data available that examined developmental or reproductive toxicity of nanosilver, or neurotoxicity of nanosilver. Available data indicate that nanosilver can distribute to the brain and olfactory bulb after oral administration to rats, and *in vitro* studies suggest that nanosilver can cause depletion of the neurotransmitter dopamine and changes to inhibitory action potentials in hippocampal neurons (Hussain et al., 2006; Liu et al., 2012; Zhaowei et al., 2009).

There are no available studies on the chronic toxicity or carcinogenicity of nanosilver. Only one known study examined mutagenicity of nanosilver in the erythrocyte micronucleus assay in rats (Kim et al., 2008), and that study was negative for induction of micronuclei.

3.2 Dietary Exposure

A dietary risk assessment has not been conducted because none of the products mentioned in this workplan are registered for food contact use. However, there is a potential for drinking water exposure from discharges due to the materials preservative and swimming pool treatment uses. The Agency expects that the mammalian toxicology data anticipated to be required may be useful to evaluate this exposure potential.

3.3 Occupational and Residential Exposures

3.3.1 Residential Handler Exposures

Residential handler exposures are expected during use of the nanosilver swimming pool treatment product. Durations of exposure could range from short to intermediate term. The residential handler scenario that will be assessed is listed in Table 8. Indoor Dermal (875.1200) and Inhalation (875.1400) exposure studies are anticipated to be needed to assess this exposure scenario.

Table 8 – Residential Handler Exposure Scenarios for Nanosilver

Scenario	Exposure Route(s)	Duration
Open pour liquid for pool treatment	Dermal, Inhalation	Short and Intermediate Term

3.3.2 Residential Post Application Exposures

Residential post-application exposures are expected for nanosilver treated pools and treated articles manufactured from nanosilver preserved textiles and plastics. Infants and children as well as older individuals are also a potential subpopulation of exposure, based on residential use sites. The residential post-application scenarios that will be assessed are listed in Table 9. A pool water residue study (non-guideline special study) is anticipated to be needed to assess dermal and incidental oral exposure to treated pool water. Indoor surface residue dissipation studies (Guideline 875.2300) on plastics and textiles are anticipated to be needed to assess incidental oral and dermal exposures to plastics and textiles. A textile attrition study (non-guideline special study) is anticipated to be needed to assess inhalation exposures to textiles.

Table 9 – Residential Post-Application Exposure Scenarios for Nanosilver

Scenario	Exposure Route(s)	Duration
Swimming in nanosilver treated pools	Dermal Incidental Oral	Short and Intermediate Term

Scenario	Exposure Route(s)	Duration
Crawling and playing on flooring manufactured with nanosilver preserved plastics	Dermal Incidental Oral	Short and Intermediate Term
Mouthing household items and toys manufactured with nanosilver preserved plastics	Incidental Oral	Short and Intermediate Term
Wearing and mouthing textiles treated with nanosilver	Dermal Incidental Oral	Short and Intermediate Term
Machine drying textiles treated with nanosilver	Inhalation	Short and Intermediate Term

3.3.3 Occupational Exposures

Occupational handler dermal and inhalation exposures are expected when handling nanosilver products during pool treatment and materials preservation. This exposure duration could range from short to long term depending upon the specific use. The occupational handler scenarios that need to be assessed are listed in Table 10. Indoor dermal (875.1200) and inhalation (875.1400) exposure studies are anticipated to be needed to assess these exposure scenarios.

Table 10 – Occupational Handler Exposure Scenarios for Nanosilver

Scenario	Exposure Route(s)	Duration
Open pour liquids for pool treatment	Dermal, Inhalation	Short and Intermediate Term
Open pour solids for material preservation	Dermal, Inhalation	Short, Intermediate, and Long Term

3.3.4 Occupational Post-Application Exposures

Occupational post-application inhalation exposures are expected when handling treated textiles during commercial laundry operations. This exposure duration could range from short to long term depending upon the specific textile that is treated. The occupational post-application scenario that needs to be assessed is listed in Table 11. A textile attrition study (non-guideline special study) is anticipated to be needed to assess inhalation exposures to textiles.

Table 11 – Occupational Post-Application Exposure Scenarios for Nanosilver

Scenario	Exposure Route(s)	Duration
Laundering nanosilver treated textiles	Inhalation	Short, Intermediate, and Long Term

3.4 Aggregate and Cumulative Exposures

3.4.1 Aggregate Exposure

At this time, there is insufficient information to determine aggregate exposures to all nanosilver pesticidal products currently in the market place. The toxicity and exposure data, which are anticipated to be required for registration review, will allow the Agency to determine exposures to which pesticide products should be aggregated.

3.4.2 Cumulative Exposures

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding

between any form of nanosilver and any other substances, and nanosilver does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA assumes at this time that nanosilver does not have a common mechanism of toxicity with other substances including other forms of nanosilver. In 2016, EPA's Office of Pesticide Programs released a guidance document entitled *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis*.[3] This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and, if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[4] and conducting cumulative risk assessments (CRA).[5] During registration review, the Agency will utilize this framework to determine if the available toxicological data for nanosilver suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

4 Environmental Risk Assessment

The Agency plans to conduct an environmental risk assessment for the nanosilver uses, particularly focusing on materials preservative uses, such as plastics and textiles if the particular nanosilver chemistries are shown to leach, and swimming pool uses. Any of the other use patterns may also be subject to ecological assessment if the fate and product chemistry profiles indicate the potential for environmental exposures. The risk assessment integrates the environmental fate and effects data to determine if any uses pose risks to nontarget organisms. Potential risks to fish, aquatic invertebrates, aquatic plants, and birds and mammals will be assessed after the data gaps specified in Table 7 are satisfied and the relevant data are available.

4.1 Environmental Fate

Nanosilver may reside or persist in the environment for a significant period of time because it typically sorbs to sediments. There is also the potential for nanosilver to reach publicly-owned wastewater treatment and privately-owned septic systems. If reached, the nanosilver particles will most likely complex with sulfide and partition to biosolids where they may release ionic silver. The release of ionic silver may adversely affect microorganisms that are vital to the wastewater treatment process. Because there are contradictory reports in the scientific literature on the potential for nanosilver to impact wastewater treatment operations, EPA anticipates requiring data about the environmental fate of nanosilver and the impact to wastewater treatment processes.

4.2 Ecotoxicity

Ecological effects data are used as measures of direct and indirect effects to aquatic and terrestrial organisms. Acute and chronic toxicity data from registrant-submitted studies conducted in

[3] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework
[4] Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism Toxicity (1999)
[5] Guidance on Cumulative Risk Assessment of Pesticide Chemicals that have a Common Mechanism of Toxicity (2002)

accordance with the 850 OCSPP Harmonized Test Guidelines are used to evaluate the potential direct and indirect effects to plants and animals. Ecotoxicity guideline studies are not yet available for nanosilver. The anticipated data requirements are specified in Table 7. Ecotoxicity data are anticipated to be needed for freshwater fish (acute and chronic), freshwater aquatic invertebrates (acute and chronic), aquatic plants, and bioconcentration in fish. For aquatic plants, only green algae testing is initially required. However, if the EC50 for the green algae is less than 1 mg a.i./L (1 ppm), then additional testing will be needed with *Lemna*, diatoms, and cyanobacteria.

For potential terrestrial exposures, avian data are anticipated to be required. Acute avian data are needed to ensure appropriate precautionary labeling. Avian dietary data are included in case the fish bioaccumulation data shows the potential for the unique nanosilver chemistry to bioconcentrate in the food chain. If the bioaccumulation data show little potential for bioaccumulation, the avian dietary study will not be needed.

4.3 Endangered Species

The Agency has not conducted a risk assessment that supports a complete endangered species determination for nanosilver. The endangered species determination will allow the Agency to determine whether each use of the nanosilver has “no effect” or “may affect” federally listed threatened or endangered species (listed species) or their designated critical habitats. When an assessment concludes that a pesticide’s use “may affect” a listed species or its designated critical habitat, the Agency will consult with the U.S. Fish and Wildlife Service and/or National Marine Fisheries Services (the Services), as appropriate.

5 Endocrine Disruptor Screening Program (EDSP)

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decisions for nanosilver, EPA did not identify endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), nanosilver is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a “naturally occurring estrogen, or other such endocrine effects as the Administrator may designate.” The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA

will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. The Agency has reviewed all of the assay data received for the List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. A second list of chemicals identified for EDSP screening was published on June 14, 2013[6] and includes some pesticides scheduled for Registration Review and chemicals found in water. Nanosilver is not on either list. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines, and the Tier 1 screening battery, please visit our website.[7] In this final work plan, EPA is making no human health or environmental safety findings associated with the EDSP screening of nanosilver. Before completing this Registration Review, the Agency will make an EDSP FFDCA section 408(p) determination.

6 Label Changes

The Agency invites any label amendments that could be considered to eliminate the anticipated need to require certain data, reduce the possibility that EPA's planned risk assessments overestimate risk due to reliance on conservative assumptions, and/or improve label clarity.

7 Next Steps

A DCI is anticipated to be issued in 2018 requiring the data set out in Table 7 – Studies Anticipated as Needed for the Registration Review of Nanosilver of Section 2 of this document.

[6] See https://www.regulations.gov/document?D=EPA-HQ-OPPT-2009-0477-0074 for the final list of chemicals
[7] http://www.epa.gov/endo/

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Appendix A: Toxicity, Environmental Fate, Ecotoxicology Profile, Product Chemistry

While some registrants have submitted data on individual nanoscale products and some data are available from the open literature, the Agency anticipates requiring data on each of the nanosilver active ingredients to allow for more thorough human health and ecological assessments from the nanosilver in the listed pesticide products. The available data on nanosilver products and those in the open scientific literature cannot at this time be construed as being representative of the characteristics of the nanosilver active ingredients that are subject to the registration review,

especially in light of the known structural and physical/chemical differences among the active ingredients.

The summary of the available data on nanosilver that was cited in support of the HeiQ nanosilver products can be found at www.regulations.gov under docket number EPA-HQ-OPP-2011-0370. The summary of available data cited in support of the vacated registration of Nanosilva (NSPW-L30SS) can be found at www.regulations.gov under docket number EPA-HQ-OPP-2012-0594.

Appendix B: Public Comments Received Concerning the Preliminary Work Plan

Summary of Comments and Responses

On July 6, 2012, EPA published the PWP announcing the establishment of the registration review docket (EPA-HQ-OPP-2011-0370) for nanosilver, Case 5042 (77 FR 40048). During the 60-day comment period, 12 public submissions were received.

There were six submissions from groups concerned with impacts to wastewater treatment plants and surface water: 1) Chris Hornback, Senior Director, Regulatory Affairs, National Association of Clean Water Agencies (NACWA); 2) Janet B. O'Hara, Water Resources Control Engineer, San Francisco Bay Regional Water Quality Control Board; 3) James M. Kelly, Executive Director, Bay Area Clean Water Agencies (BACWA); 4) Richard Boon, Chair, California Stormwater Quality Association (CASQA); 5) Geoff Brosseau, California Stormwater Quality Association; and 6) Jackie Kepke, Vice Chair, Tri-Tac.

Two submissions were from silver trade groups: 1) Erin M. Tesch, Silver Task Force North America (STF NA) and 2) Bergeson & Campbell on behalf of Rosalind Volpe, Executive Director, Silver Nanotechnology Working Group (SNWG).

Two submissions were from non-governmental organizations: 1) Patricia L. Bishop, Research Associate, Regulatory Testing Division, People for the Ethical Treatment of Animals (PETA) and Kristie Sullivan, Director, Regulatory Testing Issues, Physicians Committee for Responsible Medicine (PCRM) and 2) Jaydee Hanson, Policy Director, International Center for Technology Assessment (ICTA).

There were two other commenters: 1) Nanobiosystems and 2) Larry Kesler, Senior Product Safety Chemist, Clariant Corporation.

General Response

Several commenters referred to "recent research" and some provided citations to support their comments. The Agency agrees that many researchers are studying nanomaterials, including various nanosilver chemistries. The citations provided in the comments generally refer to public literature information on nanomaterials, which typically differ from submitted pesticidal nanosilver chemistries sufficiently to make data comparisons invalid. We anticipate requiring studies for each unique registered nanosilver chemistry and will consider studies from the open literature, including those submitted by registrants, to the extent that appropriate comparisons are possible with respect to the chemistries and use patterns at issue.

Further, science and policies evolve over time and EPA is committed to using the best available science in our assessments. We are working with several stakeholders to reduce the number of animals needed for testing while maintaining integrity in our decisions. We will consider bridging

rationales based on open literature and non-animal testing as appropriate, while keeping in mind the cautions about extrapolating from one nanosilver formulation to another that were included in the FIFRA SAP report of the November 2009 meeting.

I. Storm and Wastewater Discharges

A. California Stormwater Quality Association (CASQA) (EPA-HQ-OPP-2011-0370-0012)

CASQA is concerned about the registration status of certain pesticide ingredients because on a recurring basis, uses of EPA-approved pesticides result in adverse impacts to water quality and aquatic life in urban runoff and receiving waters. In recent years, numerous studies have documented the presence of pesticides and pesticide-caused toxicity in both surface waters and sediments in California's urban waterways. CASQA members are concerned about products containing nano-scale particles that may be washed into stormwater and ultimately into surface waters, as we have detailed in previous comments related to nanomaterials. CASQA is specifically interested in this registration review because numerous uses detailed in Appendix A of the Summary Document ("Nanosilver Summary Document Registration Review Initial Docket," June 2012, pp. 20-32) may result in releases of nanosilver into stormwater.

1. **Comment:** What are the fate, transport and effects on aquatic life of nanosilver discharged directly to surface waters? Recent research found that a portion of poly(vinylpyrrolidone)-coated silver nanoparticles placed directly into simulated wetlands was mobile between environmental compartments and bioavailable. Another study indicated that particle size may affect bioavailability.

   Response: The workplan is designed to obtain additional data and other information in order to conduct risk assessments of potential exposures through registered uses of nanosilver products. The studies anticipated as needed for the registration review of nanosilver are summarized in Table 7. The information from these studies, existing information, and other data from the open literature will be used to characterize the aquatic risks, as appropriate. If CASQA is aware of specific studies that the Agency does not currently have, please submit them to the Chemical Review Manager identified in www.regulations.gov at EPA-HQ-OPP-2011-0370, for the nanosilver case.

2. **Comment:** What is the potential for nanosilver to accumulate in aquatic and terrestrial food chains? Recent research indicates that gold nanoparticles biomagnify in a terrestrial food chain.

   Response: There are presently insufficient data to prepare a more current assessment of these scenarios for each unique active ingredient included in this case. The workplan is designed to obtain data and other information sufficient to make this determination as part of the registration review risk assessment process.

3. **Comment:** Are nanoparticles able to deliver silver ions to new environmental locations, perhaps within organisms that take them up? For example, filter-feeding organisms have been shown to be more sensitive to nanosilver, perhaps because they are ingesting and accumulating the particles.

   Response: The workplan is designed to obtain data and other information, regarding silver nanoparticle/ion transport, and the potential sensitivity of filter-feeding organisms and other aquatic receptors as part of the risk assessment process.

4. **Comment:** What are the risks of nanosilver pesticides in final products? It is important that EPA evaluate the environmental risks associated with the final product that is sold to the consumer, including any carrier material. For example, nanoscale pesticides are used in products like treated wood and fabrics that are not ordinarily labeled as pesticides. In some of these products, the nanoscale material is created during the treatment of the material. In addition, EPA should also evaluate the impacts of disposal of final products treated with nanosilver, particularly products that consumers would not normally consider as hazardous, such as fabric. California's hazardous waste standard for total silver content is 500 milligrams per kilogram.

   Response: The planned assessment is intended to evaluate the risks of the specifically manufactured nanosilver particles as they are released from treated articles. Exposures from disposal of treated products is likely less than the maximum estimated exposures from direct use and thus such exposures are assessed as part of the broader assessment.

5. **Comment:** CASQA believes that the use of nanosilver in swimming pool algaecides, fabric treatments, and materials preservatives will result in nanosilver washing into stormwater systems.

   Response: The workplan is designed to obtain data and other information in order to conduct risk assessments of potential aquatic exposures through registered uses of nanosilver products.

6. **Comment:** We are concerned that the nanosilver registration review docket does not provide the level of detail often included in most OPP environmental risk assessment work plans. The Environmental Summary primarily focuses on fabric treatments, and does not address risks, data gaps or data requirements pertaining to other registered uses. Like BACWA, we encourage EPA to look to Registration Review Problem Formulation for Bifenthrin (Docket ID Number EPA–HQ–OPP–2010–0384) to develop a more robust and informative assessment plan for nanosilver that is consistent with the approach employed in other OPP pesticide registration review work plans.

   Response: The Environmental Summary of the PWP primarily focused on fabric treatments because at the time it was written, there was only one product registered as nanosilver, which was used for fabric treatments. This Final Work Plan includes more products and more uses (e.g. pool uses) and so has expanded the focus of the data

requirements and risk assessments accordingly. Also, the use of the bifenthrin work plan as an example is not appropriate for nanosilver because there are no previous assessments to rely upon for nanosilver. During registration review, all uses of all registered nanosilver products will be assessed. However, as with other pesticides, future nanosilver products will continue to be held to these same standards. Thus, if registrants wish to register new uses for their products, for example, the Agency will require data and other information consistent with that described in this FWP to address the proposed uses.

7. **Comment:** CASQA requests that EPA require the registrants to develop analytical methods with sufficiently low detection limits for nanosilver in surface water, sediment, and soil. In the Summary Document, EPA has noted that there are no impairments listed nor TMDLs developed for nanosilver (p. 11). This statistic is not surprising, given that there are no practical chemical analysis methods for nanosilver. However, it is notable that there are seventy-nine 303(d) listings and sixty-two TMDLs for silver. We encourage EPA to require registrants to develop appropriate analytical methods.

   Response: Existing analytical instrumentation/techniques are being modified for nanosilver detection in the above sample matrices. Most detection methods require a breakdown of the physical nanoparticle for quantitation. At the same time, not all detection methods are adequate for particle analysis. But, as research advances, as it has greatly in the past few years, more techniques will be either coupled or newly developed for nanosilver. Proposals and test protocols for non-standard test methods should be discussed with the Agency prior to being conducted.

8. **Comment:** Like BACWA, CASQA is concerned that toxicity related to nanosilver could be additive with other forms of silver pesticides, including silver nitrate, silver chloride, and colloidal and ionic silver. Because there is relatively little information about the effects of nanosilver on aquatic life, we support the ecological data requirements for freshwater and marine settings (Summary Document, p. 9).

   Response: The Agency concurs with this comment.

9. **Comment:** CASQA looks to EPA to ensure that pesticide regulatory processes adequately consider potential water quality impacts, so that in the future, water quality impacts are prevented before they result in CWA Section 303(d) impaired waters listings. Because local agencies in most states do not have authority to regulate pesticide uses or application patterns, it is the responsibility of federal and state pesticide regulators to control pesticide uses sufficiently to prevent surface water toxicity.

   Response: The Agency acknowledges your comment and plans to ensure that pesticide regulatory processes adequately consider potential water quality impacts to prevent potential for future incidents that lead to a change to impaired waters listings under the Clean Water Act Section 303(d).

B. Bay Area Clean Water Agencies (BACWA) (EPA-HQ-OPP-2011-0370-007)

Comment: The Bay Area Clean Water Agencies (BACWA) submitted many comments and recommendations, most of which overlapped similar submissions, including those from Tri-Tac. BACWA encourages the Agency to develop a more robust and informative assessment plan for nanosilver that is consistent with other pesticide registration review dockets including evaluating potential impacts to wastewater treatments facilities and evaluating risks of final products. The citation of other risk assessments – including that for PHMB, comparison data, conceptual models and abstracts are also submitted for consideration.

Response: The Agency acknowledges receipt of the questions and supporting documents submitted by BACWA and agrees that they may be appropriately addressed through registration review data requirements as part of the risk assessment.

C. National Association of Clean Water Agencies (NACWA) (EPA-HQ-OPP-2011-0370-0015)

1. **Comment:** While EPA has improved its assessment plans to ensure they better evaluate uses resulting in discharges to wastewater treatment facilities, the nanosilver registration review docket does not provide the level of detail often included in most Office of Pesticide Programs environmental risk assessment work plans. The docket primarily focuses on a single formulation (HeiQ) and does not address risks, data gaps or data requirements pertaining to other registered uses beyond fabric treatments. The docket also does not include critical elements such as problem formulations, risk hypotheses, conceptual models and analysis plans.

   Response: HeiQ was the only formulation covered in the PWP because it was the only registered product that was known to contain nanosilver at the time the PWP was released. The final workplan and corresponding DCI are designed to result in the submission of data and other information sufficient to assess the nanosilver active ingredients as part of the registration review risk assessment process.

2. **Comment:** NACWA encourages EPA to develop a more robust and informative assessment plan for nanosilver that is consistent with other pesticide registration review dockets.

   Response: Thank you for your comment. We believe this FWP is consistent with the work plans for other registration review cases.

3. **Comment:** All the uses listed in the Environmental Summary document may potentially result in discharges of nanosilver to the sewer system and NACWA requests that EPA conduct a thorough evaluation of nanosilver's impacts on these facilities. It is essential that EPA ensure that nanosilver uses will not result in exceedances of water quality standards,

impacts to biosolids management options, or interference with the microorganisms that are crucial for effective wastewater treatment.

Response: The Agency plans to conduct a thorough evaluation under FIFRA of nanosilver impacts on these facilities. Through the risk assessment process, the Agency anticipates being able to make determinations, for example, to ensure that registered nanosilver uses will not result in exceedances of water quality standards, impacts to biosolids management options, or interference with microorganisms, in order to maintain effective wastewater treatment.

D. San Francisco Bay Regional Water Quality Control Board (EPA-HQ-OPP-2011-0370-0013)

Comment: We concur with the comments on nanosilver registration review provided by the Bay Area Clean Water Agencies (BACWA) and the California Stormwater Quality Association (CASQA). These entities put significant effort and resources into pollution prevention, and they share the Water Board's concerns about the potential aquatic impacts from the increasing production and use of silver nanoparticle products. The Water Board is particularly concerned about the potential impacts of silver nanoparticles to aquatic life, including endangered fish species such as steelhead (*Oncorhynchus mykiss*), Chinook salmon (*Oncorhynchus tshawytscha*) and Coho salmon (*Oncorhynchus kisutch*). Attached is a very recent paper that suggests nanosilver can interfere with fish osmoregulation systems, which are critical for their survival. We urge EPA to fully evaluate these unique potential impacts of nanosilver before allowing its widespread use.

Response: The evaluation of submitted data entails analysis of both lethal and sublethal effects in fish. The submitted data will be considered as appropriate during the risk assessment process. The impacts of nanosilver on aquatic taxa will be evaluated in the risk assessment process.

E. Technical Advisory Committee for the California Association of Sanitation Agencies (Tri-TAC) (EPA-HQ-OPP-2011-0370-0008)

Comment: Tri-TAC, the Technical Advisory Committee for the California Association of Sanitation Agencies, the California Water Environment Association and the League of California Cities would like to add our support to the September 7, 2012, comment letter submitted by the Bay Area Clean Water Agencies (BACWA) regarding the subject Nanosilver Registration Review. Nanosilver has been found to be especially toxic to nitrifying bacteria, which are essential organisms for many wastewater treatment agencies. Tri-TAC agrees with BACWA that now is the time to identify the environmental impacts of nanosilver and develop appropriate regulations to guide its use.

Response: The Agency acknowledges your support of the comment letter submitted by the Bay Area Clean Water Agencies regarding nanosilver registration review. The toxicity

of the nanosilver active ingredients to nitrifying bacteria will be considered in registration review assessments.

II. Trade Groups

Comments in this section were provided by two trade groups: Silver Nanotechnology Working Group (SNWG) and the Silver Task Force, North America (STFNA).

A. Silver Nanotechnology Working Group (EPA-HQ-OPP-2011-0370-0010)

1. **Comment:** A large proportion of the existing data that OPP has utilized to support its existing risk assessment for silver was actually developed using substances that OPP would now deem to be nanosilver.

   Response: The SNWG is alleging that the human health endpoints that the Agency uses for conventional silver are based on studies that used nanosilver. The endpoints for conventional silver are based on clinical observations of argyria from the 1930s (*Argyria, The Pharmacology of Silver*, W.R. Hill and D.M. Pillsbury, Williams and Wilkens, Baltimore, 1939) when patients were exposed to colloidal silver that was used for medicinal purposes. The SNWG alleges that the colloidal silver used in the 1930s was nanosilver. Even assuming the colloidal silver used in the 1930s was a form of nanosilver, which is not established, one form of nanosilver is not considered to be chemically representative of all forms of nanosilver. As such, data on one unique nanosilver may not necessarily address the data needs for all other unique nanosilver ingredients. While the Agency anticipates requiring data on each unique nanosilver active ingredient, registrants may cite to data in public literature, and provide bridging rationales and waiver requests. EPA will consider such citations, rationales and requests, based on similarity of actives and keeping in mind the cautions in the SAP report about extrapolating from one nanosilver formulation to another.

2. **Comment:** Research since the SAP clearly demonstrates that the antimicrobial effects and other biological activity of nanosilver are attributable to silver ions released by the nanosilver particles, and that the particles themselves are not biologically active.

   Response: The Agency believes that while the referenced study (Xiu, Z., Zhang, Q., Puppala, H.L., Colvin,V.L., and Alvarez, P.J.J., "Negligible Particle Specific Antibacterial Activity of Silver Nanoparticles," Nano Lett. 12(8):4271-5, Aug. 8, 2012) may be correct in assessing the toxicity of the nanosilvers used in the study, there is currently insufficient data to conclude that one form of nanosilver is chemically representative of all forms of nanosilver. The Agency has determined that it is appropriate to follow the SAP recommendations for evaluation of nanosilver pesticides. In general, the SAP advised that the toxicity of nanosilver could differ from and might be higher than other forms of silver including the silver ion, and that the toxicity of nanoparticles may drastically change with minor alterations of such characteristics as size, shape, and surface chemistry.

3. **Comment:** New research also demonstrates that the toxicity of nanosilver is generally less than other silver compounds, so data developed with silver compounds can be appropriately used in a conservative unified risk assessment.

   Response: EPA agrees with the SAP that the current body of data indicates that the toxicity of nanoparticles may drastically change with minor alterations of such characteristics as size, shape, and surface chemistry, and that the toxicity of nanosilver could differ from and might be higher than other forms of silver, including the silver ion. EPA will consider any new research referenced by registrants, as well as any citation to data in public literature, bridging rationales and waiver requests, based on similarity of actives, while keeping in mind the cautions in the SAP report about extrapolating from one nanosilver formulation to another or relying on data on the silver ion alone.

4. **Comment:** Although the SAP recommendations support an inference that the risks of nanosilver pesticides should be evaluated separately from other silver pesticides, this should not preclude a unified risk assessment if OPP can now determine that the available scientific data no longer warrant this approach.

   Response: The Agency has determined that it is appropriate to follow the SAP recommendations for evaluation of nanosilver pesticides. In general, the SAP advised that the toxicity of nanosilver could differ from and might be higher than other forms of silver including the silver ion. EPA will consider any new research referenced by registrants, as well as any citation to data in public literature, bridging rationales and waiver requests, based on similarity of actives, while keeping in mind the cautions in the SAP report about extrapolating from one nanosilver formulation to another or relying on data on the silver ion alone. The Agency does not have sufficient data to justify a unified risk assessment at this time.

5. **Comment:** OPP has utilized materially differing definitions of nanosilver depending on the context.

   Response: The Agency has not adopted a "definition" of nanosilver. However, as previously stated, we generally agree with the SAP recommendations for evaluation of pesticides containing a nanosilver chemistry that is manufactured to retain properties that may be different from the bulk. Such properties include but are not limited to size, shape, charge, and surface coating. While the SAP concern focuses primarily on a size range of 1-20 nm[8] and various industries use the 1-100 nm range, there is no clear scientific evidence supporting these thresholds, for particles smaller or larger than these size ranges

[8] Bailey, J. (January 26, 2010). *Transmittal of meeting minutes of the FIFRA Scientific Advisory Panel meeting held November 3-5, 2009 on the evaluation of hazard and exposure associated with nanosilver and other nanometal pesticide product* [Memorandum]. Arlington, VA: Environmental Protection Agency. Retrieved from https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0683-0177

may also result in unique size-related effects.[9,10] The focus by EPA on pesticides with unique size-related properties is consistently reflected in each of the communications commenter references.

6. **Comment:** OPP has recommended that registrants use Dynamic Light Scattering (DLS) to characterize particle size without any apparent recognition that this technology will not yield data corresponding to the OPP definition of nanosilver, because if a sample is not sonicated to reduce agglomerates it will systematically overstate actual particle size. Thus, commenters note a decision to classify the product as nanosilver is meaningless and arbitrary if the DLS data serve as the basis for that decision.

   Response: As noted above, EPA has not adopted a definition of nanosilver. As recommended by the SAP, EPA is more closely evaluating pesticides with silvers that are manufactured to retain properties such as size in the nanoscale, shape, charge, and surface coating that may have the potential to impact the biological response to nanosilver. Thus, in determining whether a silver ingredient should be evaluated as nanosilver, EPA considers the chemical formulation, manufacturing process, and physical and chemical properties such as size, stability, surface chemistry, etc. and considers whether the product may exhibit unique size-related properties. With respect to data to characterize particle size, EPA further notes that Dynamic Light Scattering (DLS) is one technique that is useful in biological systems, as it gives information about how nanoparticles behave in/interact with solvent medium (proteins, biological molecules, etc.).[11] It also gives information about the particles' state of agglomeration/aggregation by comparing the size measurements taken before and after sonication, allowing for the determination of whether the particles exhibit enhanced stability compared to conventional (non-nano) products.

   DLS is not the only method by which a nanoparticle may be characterized. Other measurement techniques, such as SEM and TEM, may be necessary to complement DLS. Many methods for nanoparticle size determination can be found in the literature and several standardized methods from standardization organizations such as ISO/TR 13014 and ASTM E2859. EPA notes that as always, proposals and protocols for test methods should be submitted for review by EPA before test initiation.

7. **Comment:** Any decision by OPP to issue a DCI for nanosilver to an arbitrary subset of the registrants with products meeting the OPP definition of nanosilver, or to exclude existing colloidal silver data from the data that support nanosilver products, would be intrinsically arbitrary and would warrant immediate judicial relief.

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[9] SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks). (2010). Opinion on the scientific basis for the definition of the term "nanomaterial." Retrieved from https://ec.europa.eu/health/sites/health/files/scientific_committees/emerging/docs/scenihr_o_032.pdf

[10] European Commission. (2016). Questions and answers on the commission recommendation on the definition of nanomaterial. Retrieved from http://ec.europa.eu/environment/chemicals/nanotech/faq/questions_answers_en.htm

[11] Stetefeld, J., McKenna, S. A., & Patel, T. R. (2016). Dynamic light scattering: a practical guide and applications in biomedical sciences. *Biophysical Reviews, 8*(4), 409–427.

Response: As stated earlier, EPA has not adopted a definition of nanosilver. As recommended by the SAP, EPA is more closely evaluating pesticides with silvers that are manufactured to retain properties such as size in the nanoscale, shape, charge, and surface coating that may have the potential to impact the biological response to nanosilver. As noted, EPA is evaluating data submitted in response to the DCI for the silver registration review case to determine if those products contain silver in the nanoscale range. If, on the basis of data submitted, EPA determines that the silver ingredient is nanoscale and manufactured to retain that size property, EPA is reclassifying the product for registration review purposes and the product will then be reviewed as part of the nanosilver registration review case. Only products with silver ingredients meeting these conditions will be considered for inclusion in the nanosilver registration review case and subject to the DCI for that case. Thus, EPA's decision to reclassify a product is data-driven and consistent with the recommendations of the SAP on evaluation of nanoscale chemistries. Currently, there are seven reclassified products found to be of nano-size and they will be assessed in the nanosilver case and issued DCIs, and EPA is evaluating data for the remaining silver products. With respect to the comment on colloidal silver, the Agency agrees that some forms of colloidal silver could be of nano-size and has requested additional data appropriate to determine the size of these silvers. The Agency is still evaluating the data for these colloidal silvers as well as other remaining silver products.

8. **Comment:** OPP should defer registration review for nanosilver and extend the comment period to allow proper review of new scientific data that support a unified risk assessment for all silver compounds, and to assure that EPA utilizes defensible criteria and information in determining which registered pesticides contain nanosilver.

   Response: The Agency is evaluating data for products issued in the DCI under silver and silver ions to determine if products have been classified properly. Currently, there are several products found to be of nano-size that will be managed in the nanosilver case. There are not currently sufficient data to support conducting a unified risk assessment. Until such time as data or information sufficient to support a unified risk assessment for all silver compounds is evaluated and approved by the Agency, the Agency will continue to follow the recommendations of the SAP.

B. Silver Task Force North America (EPA-HQ-OPP-2011-0370-0014)

1. **Comment:** The first comment addresses the question of whether there is a real need to have separate registration reviews for silver-based antimicrobials and nanosilver-based antimicrobials. It is the opinion and belief of the STFNA that the science is clear that the biologically active moiety in all silver-based antimicrobials is the silver plus ion (Ag+).

   Response: The Agency believes there is a need to have separate registration reviews for silver-based antimicrobials and nanosilver-based antimicrobials at this time. In general, the SAP advised that the toxicity of a nanosilver ingredient could differ from and might be higher than other forms of silver including the silver ion.

The field of nanotoxicology is in its infancy. There are insufficient data at this time to conclude that the sole form of toxicity from every single form of silver-based antimicrobials is from the silver ion (Ag^+), especially nano forms whose properties may be altered or modified with different shapes, sizes, surface coatings, dopants, and other properties. Nanosilver may at times be used because it has unique size-related properties, some of which may result in unique size-related toxicological properties. Thus, contrary to the comment, there are no current data to demonstrate that the toxicity of all silver-based antimicrobials can be assessed on the basis of the silver ion.

2. **Comment:** The STFNA's second comment addresses the issue of appropriate due process to stakeholder involvement. The EPA has yet to publicly define what is "nanosilver" and what is not. Nor has the Agency provided a validated methodology for particle size determination that would assure equitable categorization of products with respect to size. While the Agency has identified a limited number of registrants as having registered products that the Agency believes to be nanosilver, the Summary Document states that the Agency is in the process of attempting to determine if any other registrants involved in the on-going Silver Registration Review and Data Call-In also contain nanosilver. Without a clear definition of what the Agency believes to constitute a nanosilver product and which registrants have registered products believed to be nanosilver, it is premature and not fair to seek comments from stakeholders on the Preliminary Work Plan. Affected registrants should have the ability to comment when they have been notified that they could potentially be affected by the Nanosilver Preliminary Work Plan.

   Response: The Agency has directly notified registrants with products that the Agency believes to contain nanosilver and, therefore, have been reclassified to the nanosilver case. While the European Union defines a nanomaterial as having at least 50% of the particles with one or more external dimension falling in the 1-100 nm range, there is no clear scientific evidence supporting these thresholds; a lower size distribution percentage (below 50%) or particles larger than 100 nm may also result in unique size-related effects.[12] However, although EPA has not specifically defined nanosilver, chemical formulation, manufacturing process, and physical and chemical properties, such as size, stability, surface chemistry, etc., are taken into consideration to determine whether the product may exhibit unique size-related properties. If there is potential for the product to have unique size-related properties, then the Agency may classify it as nanosilver.

3. **Comment:** The STFNA requests the Agency extend the comment period for the Nanosilver Preliminary Work Plan until such time that the Agency has notified registrants that their product(s) will be subject to the potential requirements identified in the Nanosilver Preliminary Work Plan.

[12] European Commission. (2017). Definition of nanomaterial. Retrieved from http://ec.europa.eu/environment/chemicals/nanotech/faq/definition_en.htm

Response: The Agency has notified registrants of silver products that their product(s) may be subject to the data requirements identified in the Nanosilver Final Work Plan if the data submitted in response to the silver DCI identifies the silver ingredient as nanosilver. In addition, registrants of products containing nanosilver have also been notified that their products will be subject to data requirements in the Nanosilver Final Work Plan. Although the Agency decided that the comment period for the Nanosilver PWP would not be extended, the Agency welcomes discussion with any registrants that have been notified that their product is believed by EPA to contain nanosilver.

III. NGO

Two sets of comments in this section were provided by non-government organizations (NGOs): A) International Center for Technology Assessment (ICTA) and B) People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM).

A. International Center for Technology Assessment (ICTA) (EPA-HQ-OPP-2011-0370-0016)

A. **Comment:** While we are glad that the EPA is finally reviewing the registration of some of the commercial products containing nano-silver, we urge the EPA to respond to our 2008 petition on nano-silver.

Response: EPA released its response to the ICTA Nanosilver petition in March of 2015. See EPA-HQ-OPP-2008-0650 at www.regulations.gov.

B. Comment: On June 17, 2011 in its Federal Register notice, EPA proposed using two different legal authorities contained in the Federal Insecticide and Rodenticide Act (FIFRA) to obtain information about nanopesticidal products. We agree with the EPA view that FIFRA section 6(a)(2) is the "most efficient and expedient administrative approach to obtaining information about nanoscale materials in pesticides." If a decision has been made not to proceed with issuing regulations under section 6(a) (2), EPA should say so explicitly.

Response: As addressed in EPA's 2015 ICTA petition response, the Agency believes that for existing registrations, compliance with FIFRA section 6(a)(2) and the existing implementing regulations at 40 CFR Part 159 should ensure that the EPA has access to any information that could be used to determine whether a previous decision to register a product remains a correct decision.

C. **Comment:** The Data Call In approach has only resulted in four companies identifying their products as containing nano-silver and the EPA has identified on its own only one additional company. This is a shockingly small number of companies given the large number of companies marketing their products as containing nano-silver.

Response: The Agency sought product chemistry data in response to the silver registration data call in to review. As of the writing of this FWP, we have received data

from the majority of silver registrants that received the DCI and silver based products registered after the DCI. If it is believed that a company is providing false or misleading content on their website, the information can be referred to EPA enforcement staff through https://www.epa.gov/enforcement/report-environmental-violations.

D. **Comment:** Human health effects, especially material released from treated textiles that accesses long term effects on the lungs, liver, kidneys, blood, and reproductive organs. The EPA should require a dietary risk assessment given the use of nano-silver in ways that will get into drinking water supplies and in dental treatments. The use of nanosilver treated fabrics can pose a long-term problem when infants are exposed to nano-silver and the EPA should require data to assess the likely exposure that infants would face in residential, daycare, and other settings. Specific data on carcinogenicity, mutagenicity, reproductive toxicity, developmental and neurodevelopmental toxicity, endocrine activity and acute toxicity are needed. The currently available data in all of these areas are lacking or insufficient for the EPA to make adequate judgments on the human health effects of these substances.

   Response: The Agency believes that the anticipated data requirements outlined in this FWP will provide adequate information to assess health risks, including those to infants, from the use of nanosilver products.

E. **Comment:** Occupational exposure is a special category related to human health effects. Workers could face the highest levels of exposure and special studies that focus on the effects of handling nano-silver in its various forms should be designed and required of registrants. Requiring data on the systemic toxicity, skin sensitization, skin irritation/corrosivity, eye irritation/corrosivity, and respiratory sensitivity are especially needed for worker safety. Few data are presently available for any nano-silver applications in these areas.

   Response: The workplan is designed to obtain data and other information in order to conduct risk assessments of potential occupational exposures through use of registered nanosilver products.

F. **Comment:** The scientific advisory panel (SAP) review of nano-silver warned that the toxicity of nano-silver might be different from and higher than other forms of silver. We support their recommendation that the existing data requirements for antimicrobial pesticides might need to be changed to accommodate data appropriate for assessing the fate, degradation, metabolism, mobility, dissipation, and accumulation of nano-silver. Moreover, the EPA should require specific data on the kinds of nano-silver and the formulations of nano-silver being used in an application.

   Response: As indicated in Table 7 of this FWP, the Agency has identified studies that are anticipated to be called in that are non-guideline/special studies, as the commenter suggests.

G. **Comment:** Confidential Business Information (CBI) should not be used to shield the description of the way the product was produced, or the formulation process or the production process. The intellectual property provisions of patent law should be sufficient to protect a company's interests. No health or safety data should be hidden under CBI.

Response: FIFRA section 10 requires the Agency to protect information that is entitled to confidential treatment under section 10(b). EPA confidentiality regulations at 40 CFR part 2 require that the Agency protect information claimed as confidential until EPA determines that the information is not entitled to confidential treatment (or some other specific disclosure authority is triggered). However, the Agency has the authority to use CBI in the development of its risk assessments. The Agency will include information regarding the product in the risk assessment to characterize potential exposures, as appropriate.

B. People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) (EPA-HQ-OPP-2011-0370-0017)

1. **Comment:** We would like to point out an inconsistency between the Nanosilver Summary Document Registration Review: Initial Docket (June 2012), which indicates the anticipated need for a 90-day oral toxicity study, and the Human Health Data Summary for Nanosilver Registration Review Document (June 22, 2012), which indicates that the existing literature data is sufficient.

   Response: The Human Health Data Summary for Nanosilver Registration Review (June 22, 2012) does not state that data from existing literature are sufficient to fulfill the need for a 90-day oral toxicity study from all forms of nanosilver, as no unified risk assessment currently exists. The document instead summarizes information presented in the decision document for the conditional registration for a specific nanosilver a.i. (AGS-20 by HeiQ) used as a materials preservative in textiles. At the time this document was written, this was the only a.i. registered specifically as a form of nanosilver. It does not state that this information is by default sufficient for all forms of nanosilver.

2. **Comment:** With a potential biological response dependent on numerous factors – and many of these factors lacking reliable means of measurement – it is impossible to generate meaningful information by conducting the above-mentioned animal tests. For example, it will undoubtedly prove technically challenging to deliver representative and appropriate doses of nanosilver to rats in the inhalation toxicity test being proposed for this pesticide registration review.

   Response: The Agency will utilize data generated in response to the registration review DCI for risk assessment purposes. In doing so, we will take into consideration uncertainty inherent in generation of animal data as part of our risk assessment calculations. Protocols for alternative test methods should be discussed with the Agency before using other testing methods.

3. **Comment:** In addition to the considerable uncertainty in toxic potential associated with the physicochemical variability of nanomaterials, there are many documented uncertainties in extrapolating from laboratory animal studies to the human situation. Certainly, some of these differences will make interpretation of the proposed inhalation study results challenging and given the likely unrealistic oral dosages and exposure times involved, it seems impossible that the rat reproductive/developmental toxicity test being called for in this pesticide registration review could provide meaningful data.

   Response: EPA agrees that there are uncertainties associated with extrapolating from animal studies to human effects and so includes the 10-fold safety factor for interspecies extrapolation. However, the understanding of how physiochemical properties, such as size, shape, surface area, surface chemistry, and reactivity, affect behavior and toxicity of nanomaterials is still ongoing. Research that has been reviewed by the Agency continues to support the same concerns identified in the 2009 SAP, that the hazards of nanosilvers cannot be fully characterized using data for the silver ion alone or by using only data on other nanosilver products. Therefore, the Agency believes that it is appropriate to utilize data generated in response to the registration review DCI for risk assessment purposes. Protocols for test methods should be discussed with the Agency before studies are conducted to reduce the added uncertainties as much as is feasible.

4. **Comment:** Furthermore, there is no clear rationale given in the Human Health Data Summary (HHDS) for conducting a 90-day inhalation study. Sung conducted a 90-day inhalation study using nanosilver particles that EPA notes were of similar size to the pesticide product under review, and a NOAEL of 133 ug/m^3 was determined. In addition, two 28-day inhalation studies are available. EPA states in the above document that dose-response was established from these studies and the data were sufficient for risk assessment.

   Response: As noted in the registration decision that was summarized as part of the HHDS, while the use of the point of departure (POD) from the Sung et al. (2012) study and the 10x database uncertainty ensures that the assessment is protective of potential inhalation effects, the uncertainty regarding the difference between physiochemical properties for purposes of assessing inhalation toxicity and taking into consideration the effects observed in the public literature inhalation study is best addressed by the 90-day inhalation study. Moreover, the HHDS does not state that data from existing literature are alone sufficient to fulfill the need for an inhalation toxicity study on all forms of nanosilver, as no unified risk assessment currently exists.

5. **Comment:** The EPA proposes to add several neurotoxicity assessment parameters to the inhalation study. This contradicts the discussion in the HHDS, which describes human data that does not indicate a concern that nano or bulk silver will interact with the central nervous system. We suggest that EPA investigate the potential for nanosilver to penetrate the human blood-brain barrier using an in vitro model; many are available. If EPA decides

to require these parameters, we suggest eliminating the 90-day inhalation study for the reasons given above and adding the neurotoxicity parameters to another study.

Response: The HHDS notes that there was a study of the silver nanoparticles used in bandages which made their way into human bodies, and it did not seem to be interacting with the central nervous system. However, that was the case for one product using one variety of nanoparticles, which does not represent the effects of the entire class of nanosilver. As discussed elsewhere in the HHDS, cited data show increases in the levels of silver in the olfactory bulb and/or brain after inhalation and oral administration of nanosilver in rats. While this silver was unidentified as either nanosilver or ionic silver, the HHDS also notes that there are in vivo studies, which report nanosilver crossing the blood brain barrier in rats and inducing brain edema. As the literature shows that this potential exists and minor changes to nanomaterial characteristics, such as surface chemistry, size, and shape, can have significant effect on the behavior and toxicity of nanomaterials, the Agency will continue to require such data.

6. **Comment:** It is also unclear why EPA is requiring a 90-day dermal toxicity test be done on animals given the existing dermal absorption data, which include results of a recent in vitro study using human skin and a recent human clinical study that measured silver levels in blood after application of burn wound dressings containing nanosilver. EPA even states that they will use the dermal absorption factor (DAF) to conduct a risk assessment; why then are they asking for a new animal test?

   Response: There are *in vitro* techniques available that allow determination of dermal penetration of chemicals through isolated animal or human skin. However, the Agency does not rely on *in vitro* dermal absorption study data as the sole basis for deriving dermal toxicity. As noted in the HHDS, "…it is unknown if the doses used in the *in vitro* studies would approximate *in vivo* levels" (pg. 7). In addition, while there exists some data for a particular form of nanosilver, the Agency cannot at this time make a unified risk assessment for nanosilver, so toxicity data generated from one form of nanosilver cannot be said to be representative of all nano forms of silver.

7. **Comment:** Lacking information on the characterization and presence of nanosilver in the environment, data on amounts and forms being released from all types of products, and a clear understanding of the possible interactions with the surrounding environment, it is difficult to see how a realistic hazard assessment and exposure scenario can be determined for the few products subject to this pesticide registration review.

   Response: The workplan and DCI, which is to be issued consistent with the workplan, is designed to obtain data and other information in order to conduct risk assessments relating to use of registered nanosilver products. The Agency takes into consideration uncertainty inherent in generation of data as part of its risk assessment calculations. Similar data will be required for new products containing unique nanochemistries.

8. **Comment:** Due to the physicochemical complexity, and possible ubiquity, of nanosilver in the environment, EPA must approach its assessment in a comprehensive manner, rather than requiring animal tests on individual products. The EPA's own Nanomaterial Research Strategy focuses on a tiered approach based on in vitro toxicity testing methods and recognizes the critical differences in assessing nanomaterials and bulk chemicals. We recommend that instead of applying unproven and unvalidated animal based methods used to test bulk chemicals, EPA consider nanosilver as a nanomaterial first and foremost and allow for the safety testing of nanosilver using available in vitro nano-specific testing methods.

   Response: While the Agency is moving towards more cell-based and other in vitro systems, these technologies are still in the preliminary stage of development, with the exception of certain systems designed for acute toxicity endpoints. The Agency continues to use those studies which it thinks will be most effective in determining the hazard and risk posed by a given chemical. For now, the Agency will use the current data requirements provided in the workplan.

9. **Comment:** Because nanomaterials differ from traditional chemicals and have proven difficult to test using some of the animal-based methods used for traditional chemicals, it makes more sense to apply an Integrated Testing Strategy (ITS) that takes into account the data available for the nanomaterial of interest (in this case, for nanosilver) and provides a rational testing strategy to satisfy regulatory needs while minimizing animal testing. Methods that have proven most efficient and sensitive to nanomaterials include in vitro methods using bacterial, fungal, and algal toxicity tests as well as human cell-based toxicity tests to assess human safety for these nanoparticles.

   Response: The FIFRA Scientific Advisory Panel (SAP) considered the issue of nanosilver toxicity in its November 2009 meeting. In general, the SAP advised that the toxicity of nanosilver could differ from and might be higher than other forms of silver. While additional research has been conducted and published on intercellular and intracellular transport and toxicity of nanomaterials, including different nanosilvers since the 2009 SAP, the understanding of how physiochemical properties, such as size, shape, surface area, surface chemistry, and reactivity, affect behavior and toxicity of nanomaterials is still in its infancy. Research published subsequent to 2009 continues to support the same concerns identified in the 2009 SAP, that the hazards of nanosilvers cannot be fully characterized using data for the silver ion alone or by using only data on other nanosilver products. Because there is insufficient research defining how the characteristics of different nanosilvers affect behavior and toxicity, the data specified in the FWP are needed for each pesticide product containing a unique nanosilver material.

10. **Comment:** Another promising approach is described in a report focused on elucidating the impact of ingesting silver nanoparticles using a novel in vitro digestion model that has been accepted to the journal of *Nanotoxicology* (publication date is to be determined).

This study assessed nanoparticle effect after coming into contact with artificial saliva, gastric, and intestinal solutions. Because of the model's specificity to nanosilver and its ability to assess the nanoparticles as they traverse the digestive system, we request that EPA consider this method for further use in risk assessment as well.

Response: We have located what we believe to be the report ("Behavior of silver nanoparticles and silver ions in an *in vitro* human gastrointestinal digestion model") that was published by Walczak et al., in the November 2013 issue of *Nanotoxicology*. We will review the report during the draft risk assessment (DRA) phase of registration review. We are also aware of a previous article by Rogers et al. ("Alterations in physical state of silver nanoparticles exposed to synthetic stomach fluids") that was published in Volume 420 of *Science of the Total Environment*.

11. **Comment:** In order to most efficiently regulate nanomaterial-containing pesticides, EPA must require manufacturers to develop in vitro, human and environmentally-relevant methods that are high throughput, efficient and flexible enough to handle the infinite variations that are possible with a nanomaterial-based product. If the Agency decides to require additional registration and testing of products containing true nanosilver according to antimicrobial pesticide regulations, then manufacturers should be encouraged to assess these risks using a human-relevant intelligent testing scheme that relies on high-throughput, reliable, in vitro methods rather than resorting to the problematic animal-based methods used for traditional pesticides.

    Response: The EPA and other agencies both domestic and international are currently developing guidances, guidelines, and protocols to address concerns regarding the unique potential toxicities of nanomaterials. Where possible, the Agency aims to reduce the use of animals for toxicological testing. The Agency will utilize data generated in response to the registration review DCI for risk assessment purposes. Protocols for alternative test methods should be discussed with the agency before using other testing methods.

12. **Comment:** It makes little sense to require animal testing on a product-by-product basis. EPA should delay decisions on toxicity testing requirements until nanosilver products can be characterized and compared for similarities and differences, and until realistic exposure levels can be determined. We disagree with Scientific Advisory Panel recommendations that bridging opportunities may be limited among nanosilver products and request that a full examination of the physicochemical properties be completed before requiring any animal tests.

    Response: The Agency thanks you for your comment but continues to agree with the recommendations from the Scientific Advisory Panel. The Agency will consider citations by applicants and registrants to relevant data on a similar unique nanosilver chemistry covered by the data requirement, with explanations of the similarities (i.e., bridging rationales). However, citing to data on a nanosilver chemistry that is not similar may not be sufficient to satisfy the outstanding data requirement. The Agency will utilize data

generated in response to the registration review DCI for risk assessment purposes. Proposals for alternative test methods should be discussed with the agency before conduct using other testing methods.

IV. Other commenters

A. NanoBioSystems (EPA-HQ-OPP-2011-0370-0006)

1. **Comment:** In establishing a Nanosilver Registration Review (Case No. 5042), the EPA is taking action on policy considerations found in the 2011 document, "Policies Concerning Products Containing Nanoscale Materials" (EPA–HQ–OPP–2010–0197) and on technical conclusions by the FIFRA Scientific Advisory Panel. Commentary on the proposed work plan (EPA-HQ-OPP-2011-0370-0004) offers the Agency and the Public the opportunity to examine the meaning of chemical "equivalence" in a context combining current concerns about nanotechnology with past data submitted to (and actions taken by) the EPA and its predecessor agencies.

   Response: The Agency acknowledges and thanks NanoBioSystems for their comment.

2. **Comment:** The EPA should undertake a separate and parallel examination of what may constitute "equivalence" for future use with the Nanosilver Registration Review submissions. The phrase "substantially similar" is used in copyright law, which along with patent law, has a rich judicial history in addressing claims of equivalency (a.k.a. infringement).

   Response: The Agency thanks NanoBioSystems for their suggestion and will take it under advisement.

3. **Comment:** The experience gained with patent law on the Doctrine of Equivalence and on the Reverse Doctrine of Equivalence should be considered in such an examination.

   Response: The Agency thanks NanoBioSystems for their comment and will take it under advisement.

B. Clariant Corporation (EPA-HQ-OPP-2011-0370-0009)

1. **Comment:** Clariant strongly disagrees with this reclassification. None of the products manufactured and registered by Clariant contain nanoscale particles. All products contain particles of the composite of silver chloride (20%) on titanium dioxide (80%) as already described by Clariant Corporation in 2003. The active chemical entity of Clariant's products is the silver ion released from the silver chloride in aqueous media. A metal ion in aqueous solution is a cation and not to be classified as a nanoscaled particle. Clariant Corporation is requesting that EPA withdraw this listing as it is not scientifically justified.

   Response: The Agency reviewed data from Clariant for two products submitted in response to the silver DCI of 2012, in order to make a classification determination. The third product, EPA Reg. No. 49403-36, was cancelled. The Agency determined that the

Clariant products, EPA Reg. Nos. 49403-34 and 49403-38, do not contain nanoscale silver.

2. **Comment:** The Agency requested microscopy of the JMAC Composite PG particles with appropriate scale to confirm the size measurements. Clariant is currently working with an outside lab, recognized in the field of nanotechnology, to provide this data. This data will not be available until late 2012. Clariant Corporation is confident that this data will confirm that our material does not fall into what is globally considered nano range.

   Response: The Agency reviewed data from Clariant submitted in response to the silver DCI of 2012 in order to make a classification determination. The Agency determined that the products, EPA Reg. Nos. 49403-34 and 49403-38, do not contain nanoscale silver.