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USDA-AMS-NOP
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**Docket ID # AMS-NOP-18-0071-0001**

**Re. HS: Silver dihydrogen citrate**

These comments to the National Organic Standards Board (NOSB) on its Spring 2019 agenda are submitted on behalf of Beyond Pesticides. Founded in 1981 as a national, grassroots, membership organization that represents community-based organizations and a range of people seeking to bridge the interests of consumers, farmers, and farmworkers, Beyond Pesticides advances improved protections from pesticides and alternative pest management strategies that reduce or eliminate a reliance on pesticides. Our membership and network span the 50 states and the world.

## Nanosilver?

Citric acid/citrate is used to control the size and shape of silver nanoparticles.[1] Although the petition does not mention nanotechnology, the petitioned material appeared to be nanosilver. The NOSB, noting universal public opposition to the use of nanotechnology and engineered nanomaterials in organic production, voted to exclude engineered nanomaterials in

[1] Rycenga, M., Cobley, C.M., Zeng, J., Li, W., Moran, C.H., Zhang, Q., Qin, D. and Xia, Y., 2011. Controlling the synthesis and assembly of silver nanostructures for plasmonic applications. *Chemical reviews*, *111*(6), pp.3669-3712. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3110991/pdf/nihms280337.pdf. Henglein, A. and Giersig, M., 1999. Formation of colloidal silver nanoparticles: capping action of citrate. *The Journal of Physical Chemistry B*, *103*(44), pp.9533-9539. https://pubs.acs.org/doi/abs/10.1021/jp9925334.

2010.[2] NOP did not follow the recommendation, but said that petitions for nanomaterials would be treated as any other petitions.[3]

The petitioner disputes the idea that silver dihydrogen citrate is nanosilver and states that it is ionic silver. However, much of the research on the toxicity of nanosilver is pertinent to ionic silver. One cause of the toxicity of nanosilver is the fact that it provides a slow-release form of ionic silver. In the Fall of 2018, the HS recommended annotation, "limited to particle sizes greater than 300nm," will prevent products that do contain nanosilver from being used if this petition is approved. However, there are problems with ionic silver *per se* that should result in a denial of this petition. In addition, ionic silver would appear to be excluded with the proposed annotation.

## Silver dihydrogen citrate is hazardous to humans and the environment

There is ample evidence, as we expected to be documented in a technical review, that both ionic silver and nanosilver are toxic not only to microbes, but to other species as well.[4] It is disappointing that the TR relied so heavily on conclusions drawn by EPA and FDA, which operate under different laws, with different standards—weaker in many ways than the Organic Foods Production Act (OFPA).

### Toxicity

Studies show that the toxicity of nanosilver is at least partly due to the toxicity of ionic silver.[5] Ionic silver is released by the nanoparticles, and thus nanosilver serves as a sustained-

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[2] NOSB Recommendation, "Guidance Document -- Engineered Nanomaterials in Organic Production, Processing and Packaging." October 2010. https://www.ams.usda.gov/sites/default/files/media/NOP Materials Final Rec Engineered Nonomaterials.pdf. See also: NOSB, 2009. Nanotechnology in Organic Production, Processing, and Packaging.
https://www.ams.usda.gov/sites/default/files/media/Nano%20NOSB%20Materials%20Committee%20Recommendation%20%282009%29.pdf.

[3] NOP Policy Memorandum 15-2, "Nanotechnology" March 24, 2015.
https://www.ams.usda.gov/sites/default/files/media/NOP-PM-15-2-Nanotechnology.pdf.

[4] See, for example, Hadrup, N. and Lam, H.R., 2014. Oral toxicity of silver ions, silver nanoparticles and colloidal silver–a review. *Regulatory Toxicology and Pharmacology*, *68*(1), pp.1-7; Beer, C., Foldbjerg, R., Hayashi, Y., Sutherland, D.S. and Autrup, H., 2012. Toxicity of silver nanoparticles—nanoparticle or silver ion?. *Toxicology letters*, *208*(3), pp.286-292.
https://s3.amazonaws.com/academia.edu.documents/40028264/Toxicity_of_silver_nanoparticles-Nanopar20151115-30668-wuznkt.pdf?AWSAccessKeyId=AKIAIWOWYYGZ2Y53UL3A&Expires=1534088201&Signature=U%2FOUnlTRyPcN%2FRdM9MHqQ5LCzqo%3D&response-content-disposition=inline%3B%20filename%3DToxicity_of_silver_nanoparticles_Nanopar.pdf; Aitken, R.J., Hankin, S.M., Ross, B., Tran, C.L., Stone, V., Fernandes, T.F., Donaldson, K., Duffin, R., Chaudry, Q., Wilkins, T.A. and Wilkins, S.A., 2009. EMERGNANO: A review of completed and near completed environment, health and safety research on nanomaterials and nanotechnology Defra Project CB0409. *Institute of Occupational Medicine Report TM/09/01*; Senjen, R. and Illuminato, I., 2009. Nano and biocidal silver: Extreme germ killers present a growing threat to public health. Friends of the Earth, Victoria, Australia. https://foe.org/resources/nano-biocidal-silver/.

[5] Lubick, N., 2008. Nanosilver toxicity: ions, nanoparticles –or both? *Environ. Sci. Technol.*, 42 (23), pp 8617–8617.; Kawata, K., Osawa, M. and Okabe, S., 2009. In vitro toxicity of silver nanoparticles at noncytotoxic doses to HepG2 human hepatoma cells. *Environmental science & technology*, *43*(15), pp.6046-6051; Beer, C., Foldbjerg, R., Hayashi,

release form of ionic silver.[6] As summarized by a news story in *Environmental Science and Technology*, "[Sam] Luoma, who recently authored the Woodrow Wilson International Center for Scholars' Project on Emerging Nanotechnologies report, *Silver Nanotechnologies and the Environment: Old Problems or New Challenges?* … says that 'baseline risk comes from the amount of silver that's in the environment —the amount of silver ions. Nanoparticles can then add to that risk,' whether by facilitating ions' behavior or disrupting cell activity on their own."[7] Other research has pointed to nanoparticle-specific mechanisms of toxicity of nanosilver.

In view of the position taken by the NOSB on engineered nanomaterials, the board should not list silver dihydrogen citrate without the proposed annotation prohibiting nanosilver. However, regardless of whether it is an engineered nanomaterial, there are sufficient demonstrated health and environmental hazards associated with silver dihydrogen citrate as a source of ionic silver to reject the petition.

Silver is deposited in many or all organs, and there is evidence that it may persist in the body for weeks to months.[8] The accumulation of silver in soft tissues is responsible for the most widely known effect, argyria, which lends a grayish hue to the skin—but silver is also deposited in the liver, spleen, adrenal glands, muscle tissue, and brain.[9] High doses can be lethal.[10] Other health effects that have been documented include weight loss, hypoactivity, altered neurotransmitter levels, altered liver enzymes, altered blood values, enlarged heart, and immunological effects.[11] Reproductive and developmental impacts include testicular and sperm toxicity in males, ovarian histopathology in females, reduced reproductive success, and effects on the neurological development of offspring, and behavioral changes.[12] Since silver accumulates in the body, it is dangerous to discount these effects as being associated with higher doses than would be predicted by exposure to silver dihydrogen citrate as petitioned.

## Antimicrobial resistance

The spread of antimicrobial resistance is a health care crisis of major proportions. The Centers for Disease Control and Prevention (CDC) call it "one of the world's most pressing

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Y., Sutherland, D.S. and Autrup, H., 2012. Toxicity of silver nanoparticles—nanoparticle or silver ion?. *Toxicology letters*, *208*(3), pp.286-292; Hadrup, N. and Lam, H.R., 2014. Oral toxicity of silver ions, silver nanoparticles and colloidal silver–a review. *Regulatory Toxicology and Pharmacology*, *68*(1), pp.1-7.

[6] Hadrup, N. and Lam, H.R., 2014. Oral toxicity of silver ions, silver nanoparticles and colloidal silver–a review. *Regulatory Toxicology and Pharmacology*, *68*(1), pp.1-7.

[7] Lubick, N., 2008. Nanosilver toxicity: ions, nanoparticles –or both? *Environ. Sci. Technol.*, 42 (23), pp 8617–8617.

[8] Hadrup, N. and Lam, H.R., 2014. Oral toxicity of silver ions, silver nanoparticles and colloidal silver–a review. *Regulatory Toxicology and Pharmacology*, *68*(1), pp.1-7.

[9] Lansdown, A.B.G., 2007. Critical observations on the neurotoxicity of silver. *Critical reviews in toxicology*, *37*(3), pp.237-250.

[10] Hadrup, N. and Lam, H.R., 2014. Oral toxicity of silver ions, silver nanoparticles and colloidal silver–a review. *Regulatory Toxicology and Pharmacology*, *68*(1), pp.1-7.

[11] Hadrup, N. and Lam, H.R., 2014. Oral toxicity of silver ions, silver nanoparticles and colloidal silver–a review. *Regulatory Toxicology and Pharmacology*, *68*(1), pp.1-7.

[12] Ema, M., Okuda, H., Gamo, M. and Honda, K., 2017. A review of reproductive and developmental toxicity of silver nanoparticles in laboratory animals. *Reproductive Toxicology*, *67*, pp.149-164.

public health problems."[13] Many bacterial infections are becoming resistant to the most commonly prescribed antibiotics, resulting in longer-lasting infections, higher medical expenses, and the need for more expensive or hazardous medications. The development and spread of antimicrobial resistance is the inevitable effect of the use of antimicrobials.[14] Microbes evolve quickly, and antimicrobials provide strong selection pressure for those strains with genes for resistance.

Silver is used on surgical sites—commonly in dressings—and surgical sites are a common entry point for dangerous antibiotic-resistant infections (including methicillin resistant *Staphylococcus aureus* (MRSA)).[15] It is important that we maintain options—including ionic silver—for preventing and treating MRSA and other opportunistic infections in surgery. A recent review article[16] found, "The declining efficacy of existing antibiotics potentially jeopardises outcomes in patients undergoing medical procedures." In particular, the study found:

> We estimate that between 38·7% and 50·9% of pathogens causing surgical site infections and 26·8% of pathogens causing infections after chemotherapy are resistant to standard prophylactic antibiotics in the USA. A 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 120 000 additional surgical site infections and infections after chemotherapy per year in the USA (ranging from 40 000 for a 10% reduction in efficacy to 280 000 for a 70% reduction in efficacy), and 6300 infection-related deaths (range: 2100 for a 10% reduction in efficacy, to 15 000 for a 70% reduction).

Silver is an antimicrobial with medical uses, so it is important to avoid unnecessary use that could lead to resistance. The TR states that bacterial resistance to the petitioned substance has not been reported, but we found several research papers documenting resistance to silver ions. Sütterlin et al. found, "Despite a restricted consumption of silver-based products in Swedish health care, silver resistance genes are widely represented in clinical isolates of *Enterobacter* and *Klebsiella* species. To avoid further selection and spread of silver-resistant bacteria with a high potential for healthcare-associated infections, the use of silver-based products needs to be controlled and the silver resistance monitored."[17] Davis et al. isolated two

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[13] CDC, "Get Smart: Know When Antibiotics Work." http://www.cdc.gov/getsmart/antibiotic-use/fast-facts.html.

[14] Thomas F. O'Brien, 2002. Emergence, Spread, and Environmental Effect of Antimicrobial Resistance: How Use of an Antimicrobial Anywhere Can Increase Resistance to Any Antimicrobial Anywhere Else, Clinical Infectious Diseases 2002; 34(Suppl 3):S78–84.

[15] Engemann, J.J., Carmeli, Y., Cosgrove, S.E., Fowler, V.G., Bronstein, M.Z., Trivette, S.L., Briggs, J.P., Sexton, D.J. and Kaye, K.S., 2003. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. *Clinical infectious diseases*, *36*(5), pp.592-598. Krieger, B.R., Davis, D.M., Sanchez, J.E., Mateka, J.J., Nfonsam, V.N., Frattini, J.C. and Marcet, J.E., 2011. The use of silver nylon in preventing surgical site infections following colon and rectal surgery. *Diseases of the Colon & Rectum*, *54*(8), pp.1014-1019.

[16] Teillant, A., Gandra, S., Barter, D., Morgan, D.J. and Laxminarayan, R., 2015. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *The Lancet infectious diseases*, *15*(12), pp.1429-1437.

[17] Sütterlin, S., Dahlö, M., Tellgren-Roth, C., Schaal, W. and Melhus, Å., 2017. High frequency of silver resistance genes in invasive isolates of Enterobacter and Klebsiella species. *Journal of Hospital Infection*, *96*(3), pp.256-261.

silver-resistant strains of *Enterobacter cloacae* from infected teeth containing dental restorations; both were also resistant to ampicillin, erythromycin, and clindamycin.[18] Larimer et al. easily induced resistance to silver ions and nanosilver in the laboratory, and the resulting resistant bacteria also showed increased resistance to the antibiotic isoniazid.[19] The researcher Silver documents widespread resistance to silver and its genetic basis, with the warning, "The wide and uncontrolled use of silver products may result in more bacteria developing resistance, analogous to the world-wide emergence of antibiotic- and other biocide-resistant bacteria."[20] Hobman and Crossman document a long history of resistance to silver and other heavy metals – often carried on the same genetic elements as antibiotic resistance— and conclude, "The continuing widespread presence of antimicrobial metal resistance genes often intimately associated with other antimicrobial resistance genes suggests that it is unlikely that they are going to go away soon, and we must take resistance gene co-carriage and co-selection into account when we think about strategies to combat antimicrobial and antibiotic resistance. Persistence of these metal resistance genes points to what the future for antibiotic resistance gene persistence could be." [21]

Considering the medical uses of silver and evidence of the existence of genes for silver resistance—and especially the fact that silver- and antibiotic-resistant genes are frequently transmitted together—it is important to avoid promoting unnecessary uses of silver that can increase the spread of resistance.

While silver dihydrogen citrate is petitioned for use on food, the NOSB must also consider possible impacts on the environment from discharges and food waste. Microbial life in the soil is important to organic production, and waterways provide a breeding ground for resistant microbes.[22]

## Ancillary substances

The petition lists as ancillary substances:

- Citric acid: this substance is a component of the solution and is used as a stabilizer and pH control agent.
- Sodium lauryl sulfate: this substance is intentionally added during manufacturing to act as a stabilizer for the solution.

Since these have a technical or functional effect in the final product (stabilizers, pH control), they are ingredients, not ancillary substances, and should be evaluated.

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[18] Davis, I.J., Richards, H. and Mullany, P., 2005. Isolation of silver-and antibiotic-resistant Enterobacter cloacae from teeth. *Oral microbiology and immunology*, *20*(3), pp.191-194.

[19] Larimer, C., Islam, M.S., Ojha, A. and Nettleship, I., 2014. Mutation of environmental mycobacteria to resist silver nanoparticles also confers resistance to a common antibiotic. *BioMetals*, *27*(4), pp.695-702.

[20] Silver, S., 2003. Bacterial silver resistance: molecular biology and uses and misuses of silver compounds. *FEMS microbiology reviews*, *27*(2-3), pp.341-353.

[21] Hobman, J.L. and Crossman, L.C., 2015. Bacterial antimicrobial metal ion resistance. *Journal of medical microbiology*, *64*(5), pp.471-497.

[22] Icgen, B. and Yilmaz, F., 2014. Co-occurrence of antibiotic and heavy metal resistance in Kızılırmak river isolates. *Bulletin of environmental contamination and toxicology*, *93*(6), pp.735-743.

## Chemical interactions

> The petition says,
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> Ionic silver rapidly reacts with chlorides and some other anions that will result in low solubility silver salts. This reaction would potentially affect stability of the product. We recognize that two chloride salts, calcium and potassium, are permitted for use in organic processing, but the chloride salts are not expected to be used during the early processing stages. Therefore, the silver dihydrogen citrate would not be anticipated to have the opportunity to react with those substances and adversely impact the stability of the product.

The technical review states, "Silver dihydrogen citrate is incompatible with aluminum sulfate, aluminum ammonium chloride, aluminum orthophosphate, chlorides, sequestering agents designed to remove transition metals from solution, ethylenediaminetetraacetic acid (EDTA, above 1.5%), and calcium hardness above 300 ppm. These substances are not on the National List for organic handling."

The following chlorides are on the National List, §205.605: calcium chloride, potassium chloride, and magnesium chloride. In addition, sodium chloride (table salt) is implicitly allowed by OFPA and may be present during processing and in the finished product. It is possible that the presence of these chlorides poses no problem through interaction with silver dihydrogen citrate, but that is something to be established rather than ignored.

# Silver dihydrogen citrate is not essential to organic production and handling.

The petitioner has not argued in the petition justification that silver dihydrogen citrate is essential to organic production and handling. It has presented arguments of the benefits of the material –arguments that should be considered in a comprehensive review of cleansers, disinfectants, and sanitizers. Only through such a review—which would establish the need for such materials in organic production and handling, as well as the relative benefits of available materials—can the essentiality of a petitioned sanitizer be established. Information in the petition and technical review is not sufficient.

The TR says, "When processing agricultural products, biocides like SDC are paramount in ensuring the safety of consumer. There is no reported literature describing other antimicrobial practices that are available for direct and indirect food contact sanitization in the processing of agricultural products other than the application of biocide solutions."[23] However, national and international agencies stress the importance of non-chemical sanitation measures. These practices begin with construction of facilities to be "cleaning friendly," meaning that easy access is provided to all surfaces and equipment and that surfaces are smooth and made of materials that can be easily cleaned. Rodents and insects should be excluded, rather than poisoned. Such facilities can be cleaned by physical methods and may often be disinfected with

[23] TR lines 385-388.

steam or hot water rather than biocides. Clean facilities offer fewer opportunities to contaminate food.[24] Sanitizers used in disinfecting food production facilities offer fewer possibilities for contamination of food than do chemicals used directly on food.

## Silver dihydrogen citrate is incompatible with organic production.

Ionic silver is inconsistent with organic production because it has not been shown to be in compliance with other applicable criteria.[25]

## Conclusion

Beyond Pesticides agrees with the Handling Subcommittee in opposing the petition for silver dihydrogen citrate. Silver dihydrogen citrate poses health and environmental risks – particularly the risk of increasing resistance to antibiotics and silver-based medications. The technical review has many flaws, some of which have been pointed out above. The petition for SDC must be denied to protect the effectiveness of remaining antimicrobial medications.

Thank you for your consideration of these comments.

Sincerely,

Terry Shistar, Ph.D.
Board of Directors

[24] Food and Agriculture Organization, 2007. Meat Processing Technology. http://www.fao.org/docrep/010/ai407e/AI407E00.htm; USDA Cooperative Extension, 2010. Meat Plant Sanitation, http://articles.extension.org/pages/27418/meat-plant-sanitation.

[25] NOSB Guidance on Compatibility With a System of Sustainable Agriculture and Consistency With Organic Farming and Handling, NOSB Recommendation Adopted April 29, 2004.