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BEFORE THE
EUROPEAN COMMISSION
SCIENTIFIC COMMITTEE ON EMERGING AND NEWLY
IDENTIFIED HEALTH RISKS (SCENIHR)

Re: Nanosilver: Safety, Health and Environmental Effects and Role In Antimicrobial Resistance

COMMENTS OF THE SILVER NANOTECHNOLOGY WORKING GROUP
FOR REVIEW BY THE EUROPEAN COMMISSION
SCIENTIFIC COMMITTEE ON EMERGING AND NEWLY IDENTIFIED HEALTH
RISKS (SCENIHR)

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SILVER NANOTECHNOLOGY WORKING GROUP

Comments on Nanosilver: Safety, Health and Environmental Effects and Role in Antimicrobial Resistance

Nanotechnology is widely recognized as being an emerging field which in recent years has prompted unprecedented levels of interest from scientists, the public, policy makers and environmental advocacy groups. Implicit in much of the dialogue on nanotechnology is that it is new and so must have unknown effects to humans and the environment.

Nanosilver is a material that is finding increasing use in a wide range of market sectors ranging from medical devices to textiles. The key distinction between 'nano' and 'conventional' silver is particle size; nanosilver refers to silver particles that range below one micron, although recent focus has been on particle sizes below 100 nanometers. Although today's nanosilver has many alternative nomenclatures and historical aliases including 'colloidal silver,' the underlying material is the same-extremely small particles of silver. Contrary to many common assumptions, nanosilver materials have a long historical record of demonstrated safe use together with a long period of formal and successful regulatory oversight. The use of very high doses of colloidal silver at the beginning of the 20th century sparked a vast amount of research on the toxicology of nanosilver resulting in the first exposure limits for silver and subsequent regulations on its use. In addition, multiple studies show the transformation of nanosilver particles to benign silver sulfide in real environmental media. This is directly analogous to the well-known speciation of silver ions.

Thus, historical data relevant to risk assessment is readily available on nanosilver and needs to be tapped by regulators when making policy decisions. New research can help to refine knowledge to modern requirements but assessment should also take historical data into perspective. In this regard, development of bacterial resistance to silver has often been presented as a concern for silver *use* *in general.* The decision to focus on nanosilver for an issue presented as general for silver illustrates a bias that is not justified. Bacteria have been exposed to sub-inhibitory levels of Ag+ for over four billion years and no widespread resistance has been evident to date, whereas widespread resistance to antibiotics has developed within the last 60 years [1]

Nanosilver has been made and used by man for decades.

The earliest rational synthesis of nanosilver to our knowledge was by Carey Lea in 1889 [2]. Throughout the early 1900"s nanoscale silver was one of the earliest materials that formed the basis of colloid science - the discipline focused on the synthesis and characterization of extremely small particles [3]. In the first half of the last century, nanoscale silver was referred to as "millimicron silver" or "colloidal silver". Colloidal nanosilver was widely and successfully used as a topical disinfectant throughout the first decades of the 20th century until antibiotics took over as the technology of choice [4]. Colloidal nanosilver continued to be applied to new applications throughout the 20th century and found widespread use as an algaecide for swimming pools and in drinking water purification systems. In the last two decades, nanosilver has been used for numerous medical applications and in engineered articles such as textiles, coatings and plastics. Not only is nanoscale silver demonstrably NOT a new material, it must surely be one of the oldest manufactured materials used by humans – nanosilver has been in continual use throughout a period of at least 12 decades.

It is estimated that today about 320 tons/year of nanosilver are produced and used worldwide [5, 6]. This is a very minor component of overall silver volumes. Nanosilver comprises about 8-10 million ounces of silver in a market that has over a billion ounces a year of supply and equal demand. Thus, new applications of nanosilver are not expected to have a significant impact on the level of silver demand over the next ten to fifteen years, even though many end-users may in fact achieve significant commercial success. If nanosilver does replace conventional silver in many traditional and emerging applications the fact that the use of nanosilver requires far less of the metal than does conventional uses dispels the notion that significant growth in this sector over the next decade will lead to increased demand in the silver market [7].

Nanoscale silver products have been safely regulated in the U.S. since the 1950s. The false assumption that nanosilver is new leads to an equally false assumption that antimicrobial nanosilver products have not been regulated. Reality shows that, particularly in the United States, there is a long history of safe commercial use of nanoscale silver registered under enacted biocide regulations. The very first silver product registered under the FIFRA regulations (USEPA Office of Pesticide Programs) was a colloidal nanosilver algaecide product that has been safely used for over fifty years. Every EPA silver registration between 1970 and the 1990 was in fact a colloidal nanosilver or nanosilver-composite product. Significantly, the very first NON-nanosilver product registered by EPA was not registered until 1994. An overall analysis reveals that today over 50% of all EPA registered silver products are based on nanoscale silver [8]. Throughout a period of five decades the EPA has not recorded any incidents of significance on the EPA's formal incident reporting database (EPA OPP IDS) indicating that thorough monitoring of real-life use supports the safety of nanosilver products.

Nanosilver has been safely used in direct aquatic applications for decades. Colloidal nanosilver algaecides and composite materials have been in wide consumer use in the US since the 1950s. These products have been safely used for swimming pools and municipal and domestic drinking water purification continually since the 1970s. Both swimming pools and drinking water are applications with direct exposure to high volumes of water that ultimately pass to sewerage treatment facilities and natural aquatic systems. The reason for this long history of low impact is that there is a demonstrated tendency of silver particles to be strongly passivated by ubiquitous natural environmental complexing agents such as sulphur, chlorides, phosphate and dust [9, 10]. Furthermore, this tendency of silver nanoparticles to speciate in a similar manner to the well recognized environmental passivation of silver ions is further supported by recent scientific research [11, 12, 13]. The ecological fate and toxicity of environmentally passivated silver, typically forming silver sulphide, is a thoroughly investigated topic, particularly from the long history and high volume of photographic use of silver [14, 15].

Nanosilver is safely used in dermal wound care for decades.

Studies have shown that nanosilver does not penetrate unbroken skin. Moreover, medicinal research on nanosilver clearly demonstrates that there are no ill effects even when it is used directly on wounds and broken skin. FDA approved nanosilver dermal wound care ointments and bandages are used in thousands of hospitals every day to promote skin repair by reducing inflammation and such products often save lives by preventing infections [16].

Exposure is far less than to conventional silver products and synthetic chemical antimicrobials

The latest human health, environmental health, and life-cycle risk assessments for nanosilver can be found in the "Proposed Decision Document for the Registration of HeiQ AS-20 as a Materials Preservative in Textiles." [17]

The assessment of risk is a balance between potential for harm (toxicology) and exposure. An analysis of exposure patterns for nanosilver would reveal that most products employ miniscule amounts of nanosilver (tens of parts per million by weight of treated article) and in all cases this is employed in forms that are bound and secured in plastic matrices and/or coatings. Nanoparticles cannot exist as discrete particles, since they will agglomerate and they therefore need to be in a matrix to allow them to exist discretely and react appropriately. Furthermore, an exposure analysis in comparison to conventional silver products and synthetic chemical antimicrobials shows significantly lower quantities of active substance are required for nanosilver to achieve an equivalent effect. Such analysis shows a compelling potential for less chemicals to be used to treat consumer products and less pollution of the environment.

Nanosilver Benefits Consumers

Antimicrobial products bring benefit to millions of consumers every year. Products such as plastics, textiles, and cosmetics last longer and provide better value for money and increased utility to consumers. This is a market that has been served by many different synthetic and inorganic materials over multiple decades, only a small portion of which is served by silver additives, of which nanosilver is just one form.

Antimicrobial treatments can bring a number of functionalities to consumer articles, including longer shelf life (e.g. cosmetics) giving more safety, less waste and ultimately lower prices for consumers; plastics that are protected against the degrading action of bacteria (e.g. discoloration); and textiles that are protected against colonization of bacteria that can lead to odors (e.g. sports clothing), ultimately giving greater comfort and prolonged use. Additional benefits such as reduced washing frequency at lower temperatures can give significant water and energy savings. Antimicrobial treatments, of which nanosilver represents less than 0.1% of the numerous materials available for this purpose, therefore serve a broader purpose giving benefits to numerous consumer goods every day.

Bacterial resistance?

The concern regarding potential for bacterial resistance development from widespread use of silver as a justification for recommending against the use of nanosilver in consumer goods is unfounded. This concern is based on a selective review and interpretation of the literature that disregards multiple publications that state the risk of microorganism resistance to silver in reality is low. A notable example is provided by Percival et al. who state that *"it is important to note that bacteria have been exposed to subinhibitory levels of Ag+* [silver ions] *for over four billion years and no widespread resistance has been evident to date"* [1]. Humankind in all types of societies have processed and used silver for thousands of years without ill effects. It is important to recognize that silver is a natural element that is prevalent throughout the world at low concentrations with no evidence to support a concern for widespread bacterial resistance. All silver antimicrobials act against bacteria through a silver ion (Ag^+) mode of action, which is broad-spectrum (bacterial aerobes, anaerobes-gram-positive and gram negative rods and cocci, and fungi-molds and yeasts), and thought to be attributed to silver cations interfering with electron transfer and binding to the following negatively charged moieties in the target cell: cell wall, cell membrane, DNA. This will induce structural changes and cell lysis [18, 19]. To single out nanosilver in order to address a concern over silver resistance in general is not right. To highlight nanosilver when other silver materials are used and will continue to be used in often higher volumes makes no sense.

Up to this point there has been very limited documentation of silver resistance and these have been in isolated *in vitro* studies [20, 21, 22, 23]. No silver resistance has actually been seen in the natural environment or in a real clinical setting. The overall consensus is that silver resistance is rare due to its multiple target sites. Since silver has multiple points of attack, the development of a series of mutations that result in resistance to all mechanisms of action in a single generation is unlikely [24, 25, 20, 1]. No transfer of silver resistance has been reported in the natural environment. In addition, silver demonstrates antimicrobial action in resistant bacteria including MRSA, VRE and bacteria with silver resistant genes [26, 27, 28, 19]. It may be prudent over the long-term to develop and standardize silver MIC levels or breakpoint levels (Minimum Inhibitory Concentration or the minimum concentration at which an antibiotic will inhibit the growth of an microorganism), but indeed current evidence indicates that the clinical threat is very low and rare outside of selected and isolated *in vitro* settings [20].

Based on the information available for silver, regulatory offices within EPA, other federal agencies and international organizations have established safe levels for regulating silver in food, water, and air. These organizations have relied on the use of the Gaul and Staud (1935) [29] or Pillsbury and Hill (1939) [30] studies and have concluded that argyria (a cosmetic blue-grey discoloration of the skin) is the endpoint of concern for humans exposed to silver. By regulating to prevent this effect, reasonable protection is provided for the population from other toxicological risks from silver that would be expected to occur at higher levels [31]. In addition, it should be noted that adverse effects attributable to silver including argyria (a cosmetic endpoint and not considered of toxicological concern) upon which many of the EPA, OSHA, FDA, and USDA human health standards are based [32, 33, 18, 34]) are exceedingly rare [33].

In their presentation at the German Federal Institute of Risk Assessment Workshop on Nanosilver (February 9, 2012), the EPA cited Chopra (2007) [20] and concluded that there is a low threat of bacterial resistance to silver in the clinical setting. Also, in a 30 day dosing of 1 mg/L nanosilver to estuarine sediment cores, the EPA [34] noted that there was no impact to the microbial community and no increase in antibiotic resistance to the bacterial population in the sediment [35, 36].

Unusual behavior of nanosilver?

The justification for acting against nanosilver boils down to the conviction that due to the small particle size nanosilver must be new and accordingly must behave differently to conventional silver. Macro forms of silver ("macro" particles or conventional silver materials) are rarely employed in the market – silver ion and silver salt materials dominate the antimicrobial treatment market. Regardless of form, all silver substances have antimicrobial properties. In this way, nanosilver is fundamentally no different from any other antimicrobial silver materials available in the marketplace e.g. silver-glass, silver-zeolites, silver salts etc. This is particularly true for applications where the silver is embedded in a substrate as is typically the case for plastics, coatings and textiles. The mode of action is therefore not unusual in comparison to other silver forms employed in the marketplace or used throughout history. Singling out nanosilver in this manner is not scientifically justified and is based on a flawed understanding of silver materials and nanosilver in particular.

Moving Beyond Fear

It would be a mistake to ignore the accumulated knowledge of our scientific and regulatory heritage in a mistaken bid to declare nanosilver materials as new chemicals, with unknown properties and automatically harmful simply on the basis of a change in nomenclature [5].

What is needed now is no more of this fear mongering campaigning against very important emerging nanotechnologies. We need a clear, reasonable, and responsible path for registration.

It is hoped that regulatory agencies will ultimately no longer impose unwarranted barriers to these emerging nanotechnology industries, but instead nourish the benefits these can provide while screening finished products claiming pesticidal properties on a case by case basis for any environmental risk. We need a sensible path forward for registering nanopesticides worldwide that is not burdensome for either the government or industry and allows consumers to enjoy their benefits.

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