Ionic Silver Textile Products and their Effects on Skin Microbes

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Part of a series of white papers commissioned by Noble Biomaterials, Inc. that review the literature and address the human and environmental safety of ionic silver textiles, including Noble’s product X-STATIC.
Background

Noble Biomaterials, Inc. (Noble) has commissioned a series of white papers that review the literature and address the safety of ionic silver in apparel products. Specifically, the company seeks to increase its knowledge of the body of literature that can provide insights on the effects of the small amounts of ionic silver released from fiber on both consumers and the environment. The form of silver used as a coating on the polymer substrates of its products is pure metallic silver. Metallic silver changes form when it comes in contact with moisture; the form of silver that is ultimately diffused from the fiber is ionic. This is in contrast to other silver technologies based on nano-scale silver particles that potentially release metallic silver from the substrate they are applied to. Much of the literature evaluating silver diffusion and potential safety issues is based on nano-silver.

These white papers will evaluate and assess the following issues:

1. What is the effect of ionic silver in apparel on skin bacterial populations? Is there any negative health impact to the disruption of the skin microbe population?
2. What are the resistance patterns of microbes when exposed to ionic silver? What is the current state of microbes that have developed a resistance to ionic silver (that were previously sensitive to ionic silver)? Does ionic silver cause cross-resistance to commonly used antibiotics?
3. Does ionic silver contribute to the potential for bioaccumulation in the body and the environment? If so, what is the impact?
4. Does ionic silver negatively impact wastewater treatment (by impacting the microbes used to break down organics)?

The first of these papers focuses on bacterial populations in skin. It examines the following questions:

- What is the effect of ionic silver in apparel on skin bacterial populations?
- Is there any negative health impact to the disruption of the skin microbe population? (Are so-called “good” bacteria being killed along with “bad” and if so, does that raise concerns?)
Summary: Silver Coated Textiles and Skin Microbes

Much of the literature reviewing silver and its efficacy and safety covers metallic silver and nano-silver particles. The technological advance of being able to manufacture ionic silver-coated textiles has developed over the past 12 years and represents a small but growing body of research on apparel products in the marketplace. There are important distinctions between and among types of silver. Ionized silver has demonstrated benefits over the other forms of silver. This review is focused on ionic silver. Literature on nano and other forms of silver in textiles is not included in this document.

Several in vitro studies and three clinical studies were reviewed which focus specifically on the ionic form of silver in textiles. In vitro studies include the “soaked fabric test,” in which a perspiration soaked ionic silver coated fabric is exposed to skin cultures. These tests show that ionic silver is diffused through apparel when activated by perspiration only in the areas of the body in direct contact with the fiber. The researchers’ conclude that because only a few textile fibers are in contact with the skin and only briefly, no dramatic change in skin flora could be anticipated.

Three separate clinical studies with a total of 60 patients with atopic dermatitis/eczema showed no dermal side effects to silver-coated apparel even after two weeks or greater of constant, direct exposure. In these studies, the microbe skin populations (both good and bad bacteria) colonized and grew back normally within 7 days. There were no adverse dermal effects because the “good” bacteria were temporarily killed. There was no elevation of silver in blood serum and no argyria.

New technologies and biological test systems make it possible to scientifically determine the interactions between textiles and the skin accurately and to recognize and evaluate potential benefits and risks. These methods can be used as safety tests for textiles with antimicrobial activity. Clinical studies of long-term wear and its safety and efficacy would need to be conducted to conclusively answer the questions related to impact on skin microbes including “good bacteria”. However, experts agree that the 1) 12 years of in vitro and in vivo studies; 2) long-term use in military populations with tens of millions of applications; 3) widespread applications in healthcare medical devices; and 4) extensive use in consumer goods for more than 15 years, do not point to any evidence that skin microbe disruption (including disruption to “good” bacteria) is a safety concern to individuals wearing ionic silver coated apparel.

Brief History on Silver in Apparel Products

Silver has been used as an antimicrobial agent for hundreds of years. It was used in its solid elemental form in ancient times to sterilize drinking water and in modern times to prevent and manage infections, including wounds. It has been used as a solution of salts to cleanse wounds, in the form of antibiotic creams and ointments to treat bacterial infections and as an anti-bacterial coating on medical devices such as catheters. Textile manufacturers discovered its antimicrobial benefits in hospital garments and curtains. The number of bio-functional textiles with antimicrobial activity has increased considerably over the past several years. The differences between metallic silver and ionized silver are becoming better understood. Increasingly, the anti-odor benefits of silver coated textiles are being recognized and the new anti-microbial fiber technologies that release ionic silver have enabled the manufacture of antimicrobial clothing. Anti-microbial apparel products can reduce the odor that develops in garments from human perspiration.

The four main objectives for antimicrobial solutions in textiles are to: 1) avoid loss of performance properties as a result of microbial fiber degradation; 2) limit incidence of bacteria; 3) reduce formation of odor as a result of microbial degradation of perspiration; and 4) avoid transfer and spread of germs. Antimicrobials are applied to fibers in three different ways: 1) spinning mass; 2) fiber surface; or 3) manufactured fiber is coated with a finishing agent. Antimicrobial fibers come in two forms: active and passive. Passive fibers do not contain any type of antimicrobial additives. The bacterial cells themselves are not affected but the micro-organisms are prevented...
from adhering to the fiber surface or are attacked by non-leaching surface compounds. Active antimicrobials represent the majority of textiles. They contain finishes with specific antimicrobial substances that act upon microorganisms, either on the cell membrane during metabolism or within the core substance (genome). These textiles work via diffusion principles. The bioactive substance diffuses out at a variable rate from the finish or from within the fiber by ion exchange or by the substitution of cations created from exposure to perspiration. (Antimicrobial Textiles-Evaluation of Their Effectiveness and Safety, Höfer, 2006.)

**Not all Bacteria are Created Equal**

The skin is a complex organ and can protect itself from infection naturally. Bacteria are always found on healthy skin. This colonization of microbes protects the skin. There are Gram-positive micro-organisms such as staphylococci and some types of corynebacteria, and Gram-negative bacteria such as Klebsiella pneumoniae or Escherichia coli. These bacteria found in skin flora (local) and in hydrolipid film have a pH value of between 5.4 and 5.9. With the presence of moisture, bacteria increase their number by cell division rapidly with or without oxygen. Antimicrobial tests are conducted on both Gram-positive and Gram-negative microbial strains. (Antimicrobial-Finished Textiles Three-Dimensional Structures, Heide, 2006.) Microorganisms of skin flora support a low pH of the acid mantle by breaking down organic compounds of sweat and the hydrolipid layer. The pH of the acid mantle wards off Gram negative bacteria from surface of skin. Eccrine sweat contains the body’s own antimicrobial substances including lysozyme (an enzyme which attacks the bacterial wall) and dermicidin, a peptide that exerts anti-microbial influence. Under the skin’s horny layer, living cells produce antimicrobial substances. Finally, pathogenic germs are kept away from the surface of the skin by antimicrobial peptides emitted for defense of microorganisms of the skin flora. Resident germ populations can defend the skin from germs such as Staphylococcus aureus. Antimicrobials assist the natural defense mechanisms of bacteria.

**Silver as an Antimicrobial: How Does it Work?**

In its metallic form, silver is inert and cannot kill bacteria. To become a bactericidal agent, silver atoms must lose an electron to become positive charged silver ions, also called cations (Ag+). The silver cations convey antimicrobial effects. Elemental silver ionizes when exposed to moisture. Silver ions are highly reactive and affect multiple sites within bacterial cells ultimately causing cell death. They bind to the bacterial cell membranes causing disruption of the bacterial cell wall and cell leakage. Silver ions transported into the cell disrupt cell function by binding to proteins and interacting with energy production, enzyme function and cell replication. Ionization of silver metal is proportional to the surface area of the particle exposed. (Silver in Health Care: Antimicrobial Effects and Safety in Use, Lansdown, 2006.)

Silver does not act via cell receptors and therefore there is no immune response and no bacterial resistance. Silver ions are active against a broad range of bacteria, fungi, and viruses, including antibiotic resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococci (VRE). Studies of the effects of silver dressings on experimental models of biofilms (complex microbial community containing bacteria and fungi embedded in the protective polysaccharide matrix) show that they kill bacteria within the matrix and increase susceptibility of bacteria to antibiotics. Silver release is measured in parts per million or ppm (one part per million, equivalent to 1 mg/L). Silver is found naturally at low concentrations in individuals without prior exposure to silver, although it has no known physiological function (we don’t know why it occurs naturally in the body). Reported concentrations of silver are as follows: blood <2.3 µg/L; urine 2 µg/L; liver 0.05 µg/g; wet tissue and kidneys 0.05 µg/g (Silver in Health Care: Antimicrobial Effects and Safety in Use, Lansdown, 2006.)
What is known about the Effects of Antimicrobials on Skin?

In the past, dermatologists and hygienists have raised concerns about the safety of textiles treated with antimicrobial agents, primarily nano-silver. What is known about the chemical toxic effects of biocide agents on skin is that these influences are dependent on the specific human toxicological properties of the relevant substance used as the agent. Most silver textile processors want to demonstrate no reservations about human toxicity. (Antibacterial Textiles, Skin-Borne Flora and Odour, Dirk Höfer, 2006.) The majority of clinical studies with silver coated textiles are conducted in patients with atopic dermatitis/eczema.

The metal on silver coated textiles oxidizes with moisture release silver ions. These silver ions interact with the body’s biology, skin flora and microbes. Investigations with silver nitrate and bacteria showed a detachment of cytoplasmic membrane from the cell wall. Like other biocides, silver is non-specific in action and cannot discriminate between pathogenic bacteria and healthy bacteria—in both cases the DNA loses its replication ability and the protein becomes inactivate after silver treatment. Although absorbed silver interacts with other metals and tissue proteins, these interactions do not appear to be harmful with the exception of the skin discoloration known as argyria, a cosmetic problem.

Argyria is a process of silver granule deposition in skin leading to a blue-grey skin discoloration. There is no tissue injury. The effect is cosmetic only and reverses when exposure is discontinued. The most common causes of systemic argyria, as noted in the literature, were not from medicinal use of silver but rather the constant exposure to silver either as a chemist, silver miner or from long term use of silver cups and plates for eating and drinking. The term "blue blood," used to describe Royalty, came from the finding of mild argyria in European nobility from the constant use of silver place settings, silverware, and silver cups. As the silver was ingested it built up over time, leading to a bluish skin color. Silver granules can be found in all organs including the skin, indicating that the silver aggregates are not completely cleared. It would therefore appear that any form of silver if ingested in large quantities can be a causative factor for argyria. Local exposure to nano-silver can cause mild argyria. Silver itself has been shown to be harmless to normal human tissue. Toxicity results solely from the salt or complexes which are used to deliver the silver. (www.burnsurgery.org). There are no reports of argyria in individuals exposed to ionic silver coated textiles.

Summary of Findings

In vitro studies demonstrate that silver causes a significant reduction in bacteria and its cytotoxic effect is low. In vivo studies demonstrate benefits of silver coated textiles on dermatologic conditions like eczema with no side effects after two weeks of treatment. Study findings are summarized below:

- Clinical studies of silver coated apparel have been performed on patients with atopic dermatitis (AD) and atopic eczema. SCORAD Assessment (Scoring Atopic Dermatitis). SCORAD is a validated tool for the objective assessment of the severity of dermatitis, incorporating surface area involvement. Because of its ease of use, reproducibility and standardization, the SCORAD index provides an accurate picture of current skin status and progress and makes it possible to compare the severity of skin disease within a patient pool.
  - A clinical study conducted by Gauger compared treatment with silver-coated textiles on one arm to that of cotton on the other arm for 7 days followed by 7 days without treatment in 15 patients with local generalized Atopic Dermatitis. The silver reduced bacterial burden (S. aureus) for 7 days before re-colonization began. At the same time, toxicology side effects appear to be limited to system absorption through dermal wounds. No broad spectrum antibiotic resistance was found. (Silver-Coated Textiles in the Therapy of Atopic Eczema, Gauger, 2006.)
  - A clinical study conducted by Juenger evaluated the efficacy and safety of a special silver textile (X-Static® by Noble) in a study of 30 patients suffering from AD. Safety assessment consisted of monitoring and recording all adverse events, including monitoring hematology, blood chemistry,
and urinalysis values. Special emphasis was placed on monitoring silver in 24-h urine (detection limit 0.9 µg/L), the physical examination of patients for silver deposits in skin and mucous membranes on Days 14 and 28 and on canvassing patients about local reactions such as burning sensation, pain or metallic taste in the mouth. At no point in the study were silver deposits found in any of the patients during the physical examination, when the examiners checked for argyria in the skin, fingernails, conjunctiva or mucous membranes. The blood parameters of all patients were regular and not influenced during the study period. On Day 28 1 µg/L of silver was detected in one patient’s urine. A urine examination of this patient was without pathological findings on Day 56. No silver was detected on Day 56.

- Two clinical studies of atopic eczema (AE) in children were conducted by Nomura. In two studies comparing silver-coated textiles with cotton, one an open side by side comparison and the other a placebo controlled study, the antibacterial effect of silver coated textiles on S. aureus colonization was tested on the elbows of 15 patients (in each study) diagnosed with localized AE over 14 days. During the studies, no side effects related to the study textiles were noted. Random blood samples taken from patients wearing the textiles beyond the study conditions with their consent revealed no elevation of the serum silver level. A possible systemic absorption of silver because of a disrupted skin barrier has to be considered but was not noted. Irritation levels were low. (Silver-Coated Textiles in the Therapy of Atopic Eczema, Gauger, 2006.)

• In clinical studies in which an area of skin is disinfected before an operation, it can be seen that germ population is reduced temporarily but doesn’t disappear and in fact the germs regrow to make up deficit in skin flora. From a scientific point of view, the same effect is anticipated from wearing antimicrobial textiles. (Bacterial adaptation and resistance to antiseptics, disinfectants and preservatives is not a new phenomenon, Russell, 2004.)

• In vitro results show that the germs killed off are in very close and direct contact with fibers treated with the antimicrobial agent. Bacteria are found in parts of textiles where nutrients are attached—skin flakes, foodstuffs. These data suggest that human skin flora can only be influenced where skin is in direct and permanent contact with treated fiber. Extensive wear trials with antimicrobial textiles show odor reducing effect of the textile, but no adverse effects to the skin of the wearer. This is due to passive soaking effect, attaching sweat, skin germs and their substrates into the fabric and onto active fibers. (Antimicrobial Textiles, Skin-Borne Flora and Odour, Höfer, 2006.)

• Textiles with antimicrobial agents test to be worn close to the body. If one considers that depending on design and type of fiber, only a few textiles fibers are in direct contact with the skin, and only briefly, the results presented here show that no dramatic change in skin flora should be anticipated. However, long term wearing tests with treated textiles carried out under consideration of dermatological qualification should further underline safety of the application. (Antimicrobial Textiles, Skin-Borne Flora and Odour, Höfer, 2006.)

• Toxicological side effects of silver-coated textiles appear to be limited to systemic absorption through dermal wounds. Further studies are needed of people wearing silver coated textiles and silver absorption. (Silver in Health Care: Antimicrobial Effects and Safety in Use, Lansdown, 2006.)

• The incidence of silver allergy is not known (silver sensitivity tests are not routinely conducted except for diagnostic purposes). Clearly, evidence of silver allergy is contra-indicated for using any silver products therapeutically and avoiding silver-containing textiles which come into direct contact with the body. (Silver in Health Care: Antimicrobial Effects and Safety in Use, Lansdown, 2006.)

• In a review of risk levels in Control of Substance Hazardous to Health (UK), consumers exposed to silver in textiles are expected to be a minimal risk. Silver is not absorbed through intact skin, even in moist areas, to any great extent. It will be considerably lower than seen in patients exposed to 1% silver sulphadiazine
cream (30% Ag) or would dressings releasing at least 100 mg Ag cm\(^{-2}\). (Silver in Health Care: Antimicrobial Effects and Safety in Use, Lansdown, 2006.)

- Valid test methods have been developed and are required by the FDA to ensure safety of silver when used in products. Basis of safety tests for textiles is EN ISO 10993, the biological evaluation of medical devices. (International Standards association). Cytotoxicity, irritation and sensitivity tests are required by the FDA for 510k and PMA approvals. (Antimicrobial Textiles – Evaluation of Their Effectiveness and Safety, Höfer, 2006.)

Appendix and References

Noble’s Antimicrobial Solution

Noble’s antimicrobial technologies have been used in a variety of textiles since 1999. It is used by NASA, the US Military and Olympic athletes. The technology has been used in products for treating wounds and burns for more than seven years in brands such as KCI and Systagenix.

The Noble technology uses pure metallic silver permanently bonded as a thin uniform coating on the surface of a flexible polymer. It does not change the properties of the underlying material. The antimicrobial properties are inherent in the fabric and active for the life of the product. Within one hour of contact of the fabric, 99.9% of the bacterial and fungi organisms will be reduced. With this technology, no metallic silver is released – only silver ions. These silver ions continuously release throughout the life of the product, naturally inhibiting and reducing contamination.

- Noble has 10 years of usage experience with hundreds of thousands of wound care applications for chronic indications. Many applications are used for 7 days or longer in duration. There have been no reports of safety or dermal issues. Application of its X-Static® wound care products are conducted in clinical and hospital settings.

- Noble has more than 40 medical device applications (licensees) globally using X-Static®. It has under gone evaluation and been certified by the US FDA in 510k and PMA registrations; European CE mark and Envisa (Brazil) registrations.
  - ISO Intracutaneous Study showed no evidence of significant irritation
  - ISO Maximization Sensitization Study showed no evidence of causing delayed dermal contact sensitization
  - Cytotoxicity Study using ISO Elution Method reported mild cell lysis or toxicity

- Noble has 10 years of long-term wear test data through the US Military Boot Sock program with no safety or dermal complaints.
How are Effectiveness and Safety Measured in Antimicrobial Textiles?

Test systems have been developed to record and quantify reduction of bacteria by antimicrobial textiles. The two main international test methods are the agar diffusion test and the suspension or challenge test. The common procedure test and calculation and assessment test are noted below as well (Antimicrobial Textiles, Skin-Borne Flora and Odour, Höfer).

- The agar diffusion test is used for passive antifungal activity on textiles. It tests antibiotic resistance of germs. A probe is placed directly on the surface of a germ-containing agar plate. In textile research this method can be recommended as a quick and preliminary qualitative method to distinguish between active and passive antimicrobial principles (zone of growth inhibition around probe). It is considered the best test for antimicrobial activity and efficacy.

- The suspension test records growth inhibition. Because no fabric has contact points with all parts of body at all times, a test is used called the adhesive force index. It looks at skin soaked sweat in contact with fiber. Only long term use is really able to predict low risk. However, in the JIS 1902-2002 Suspension test, after 18 hours of incubation some textiles achieve growth inhibition of germs of around 10^3.

- Studies conducted to look at effective range of treated textiles and therefore the influence exerted on skin flora. PA fibers were impregnated with silver and placed in a bacterial colony and studied to look at area where bacteria were killed.

- The common procedure test measures specific antibacterial activity. It starts with log culture of bacteria diluted with sodium chloride to a definite suspension with 10^5 CFU (colony forming units). Common procedure tests for general antibacterial activity. In the absence of a reference material with same chemical and physical properties, the internal growth control material can be used as a reference.

- The calculation and assessment test measures the reduction value in the growth of microorganisms. Reduction (R) is calculated which expresses the differences in bacterial growth between sample material and reference material RM over 18 hours. It is expressed in log stages as bacterial growth inhibiting antibacterial activity.

What are the Various Definitions of Metals?

Occasionally, questions are raised about the term heavy metal. A heavy metal is a member of a loosely defined subset of elements that exhibit metallic properties. It includes the transition metals, some metalloids, lanthanides, and actinides. Many different definitions have been proposed—some based on density, some on atomic number or atomic weight, and some on chemical properties or toxicity. The term heavy metal has been called a misinterpretation in a report issued by the International Union of Pure and Applied Chemistry (IUPAC). It cited the contradictory definitions and its lack of a coherent scientific basis. (“Heavy metals,” a meaningless term, Dulfus, 2002.) There is an alternative term toxic metal, for which no consensus of exact definition exists. Depending on context, heavy metal can include elements lighter than carbon and can exclude some of the heaviest metals. Heavy metals occur naturally in the ecosystem with large variations in concentration. In modern times, anthropogenic sources of heavy metals, i.e. pollution, have been introduced to the ecosystem. Waste-derived fuels are especially prone to contain heavy metals, so heavy metals are a concern in consideration of waste as fuel. (Zevenhoven, Control of Pollutants in Flue Gases and Fuel Gases, Espoo, 2001.)
References

Antimicrobial Textiles, Skin-Borne Flora and Odour by Dirk Höfer
2. Ibid
3. Ibid
Silver Coated Textiles in the Therapy of Atopic Eczema. Anke Gauger pp 152-164
4. Ibid
5. Ibid
6. Ibid
Silver in Health Care: Antimicrobial Effects and Safety in Use. Lansdown, Alan pp 17-34