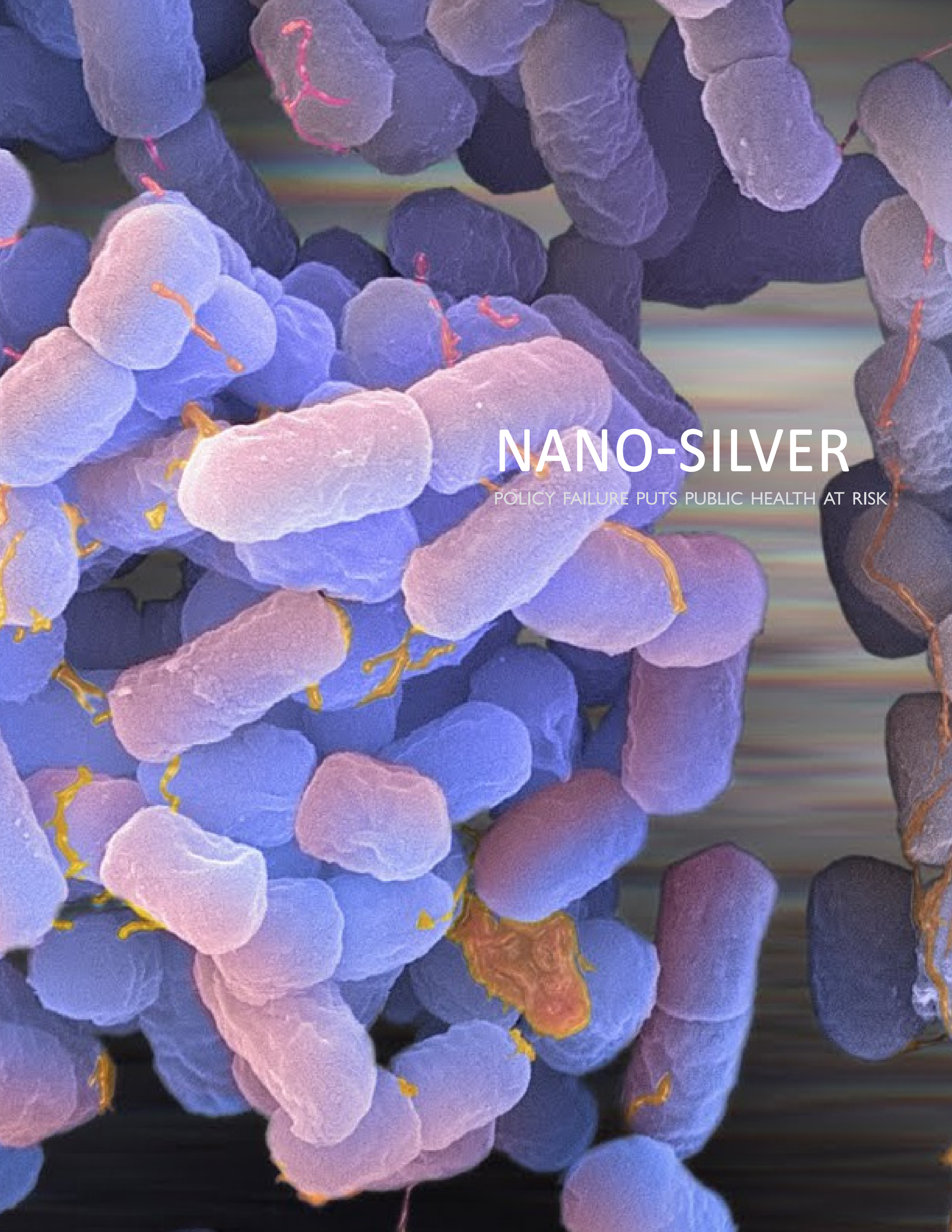
NANO-SILVER

POLICY FAILURE PUTS PUBLIC HEALTH AT RISK



Friends of the Earth

nano-silver

policy failure puts public health at risk

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We would like to extend our sincere thanks to the scientific, health and legal experts who participated in interviews for this report.

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nano-silver: policy failure puts public health at risk

executive summary

Two of the greatest health problems of our time — antibiotic resistance and the allergy epidemic — share a very important link.

The numbers of deaths caused by bacterial resistance to antimicrobials and antibiotics in hospitals continues to rise. Hospital-associated infections kill around 100,000 people in the United States and 150,000 people in Europe each year.

At the same time, we are experiencing an epidemic in allergic diseases and asthma in industrialized countries. Nearly 40% of children in Australia live with an allergy. In the United States, the figures are even worse – more than 54% of all U.S. citizens test positive to one or more allergens; more than half of U.S. households have at least six detectable allergens.

Compelling new scientific research connects these two serious and complex problems to the misguided 'war on bacteria' in every aspect of our life.

Now, a growing number of experts warn that the rapidly expanding use of nano-silver in bacteria-killing products could make both of these problems a lot worse.

For nearly a century, we have waged a war on bacteria. We have learned to fight off these 'enemies' by using stronger and stronger weapons. As the bacteria have found ways to resist the lethal effects of one antimicrobial weapon, we have been forced to unleash another. There is now a real worry that we may be running out of options to tackle resistant bacteria.

The medical community has been turning to nano-silver as an antimicrobial of last resort. Yet at the same time, many companies have seen a marketing advantage in including nano-silver as an ingredient in everyday products.

Nano-silver is found internationally in toothpastes, pet shampoos, fabric softeners, bath towels, cosmetics, deodorants, baby clothes, baby bottles, refrigerators, food storage containers, kitchen cutting boards, underwear, ATM buttons, industrial disinfectants, agricultural pesticides and handrails for buses. Here in the United

States, people are already coming into contact with nano-silver every day.

In interviews for this report, experts warn that the use of such a powerful antimicrobial in these everyday products is not only unnecessary, but dangerous.

As with antibiotics, the overuse of nano-silver will promote resistance to this important antimicrobial. Already, there is early evidence of bacterial resistance to silver in some clinical settings.

What's worse, experts warn that nano-silver will also promote resistance to antibiotics and other antimicrobials.

As concern grows about our allergy epidemic, scientists have realized that in addition to breeding resistance in bacteria, our unchecked use of antimicrobial compounds like nano-silver might carry another hidden cost.

Along with other experts surveyed for this report, Nobel laureate Professor Peter Doherty agrees that childhood interactions with bacteria are essential to develop strong immune systems in children.

The widespread use of a powerful bacteria killer such as nano-silver in everyday products could further increase the incidence of allergies.

Research into another antimicrobial used widely in both households and hospitals - triclosan - has revealed both the mechanisms for bacterial resistance and widespread incidence of triclosan-resistant bacteria in hospitals.

Experts agree that regulators need to halt the excessive and unnecessary use of powerful antibacterials in everyday products. This is necessary to maintain the effectiveness of antimicrobials and antibiotics for clinical use and to counteract the allergy epidemic.

Yet existing regulation not only fails to recognize that nano-silver presents new and often greater toxicity risks than the same substance in bulk form, there is no provision at all for assessment of public health threats – including the capacity to drive development of more powerful resistance in bacteria.

Friends of the Earth United States is calling on the government to act now to seriously restrict the use of nano-silver in consumer, industrial and environmental products.

introduction

Definition of nanotechnology

Nanoparticles are commonly defined as particles with at least one dimension less than 100 nanometers (1 nanometer = 1 billionth of a meter). Nanoparticles show novel physicochemical properties compared to larger sized particles of the same substance.

Some of these new properties include:

- greater surface area to react with their targets
- greater chemical and biological reactivity
- higher bioavailability, including uptake into individual cells and even cell organelles

Historical uses and properties of silver

Better known for its uses in photography and jewellery, it has also long been established that silver can kill microorganisms. The release of silver ions from different silver compounds can cause damage to fungi, algae, bacteria and viruses, preventing their growth. This property has long been exploited in the use of silver as an antimicrobial (Wijnhoven, et al. 2009). As an antimicrobial, silver has offered the ability to disinfect while seemingly presenting few, if any, acute harmful effects to human beings, other than in large doses (Luoma 2008, Wijnhoven, et al. 2009).

Some commentators have suggested that there is no cause for concern about the safety of silver, given that it was used as an antimicrobial in ancient Rome. Let's not forget that historical use is no proof of safety - the ancient Romans, Greeks and Egyptians also used lead, copper, arsenic and mercury in cosmetics!

Nano-silver is an even more effective antimicrobial than silver

Nano-silver is much more efficient as an antimicrobial than bulk silver (Marambio-Jones and Hoek 2010). The rate of ion release is generally proportional to a particle's surface area; nano-silver appears to be more efficient than bulk silver at generating silver ions (Wijnhoven, et al. 2009).

In addition to this greater release of silver ions, nano-silver presents new properties, including:

- the ability to cross many biological barriers

- increased production of reactive oxygen species
- capacity to efficiently deliver silver ions to the surface of bacteria (Marambio-Jones and Hoek 2010)

Nano-silver is also more readily manipulated into commercial products than bulk silver. Due to the ability to manufacture nano-silver as spheres, particles, rods, cubes, wires, film and coatings, it can be embedded into a range of substrates, such as metals, ceramics, polymers, glass and textiles (Wijnhoven, et al. 2009).

Commercial use of nano-silver is expanding rapidly

In 2009 the estimated worldwide market size of nano-silver was 320 tons/yr (Gottschalk, et al. 2010), although this is expected to expand rapidly. This volume may appear small, although its toxicological burden might easily be the equivalent of 32,000 tons/yr of bulk silver, or even much greater (as per calculations in Maynard 2006).[1]

The Consumer Products Inventory at the Project on Emerging Technologies lists nano-silver as the most commonly used manufactured nanomaterial in consumer products (PEN 2011). Of the 1317 products listed here, there are over 300 products containing nano-silver. These products include toothpastes, pet shampoos, water filters, fabric softeners, bath towels, shoes, socks, computer keyboards, cosmetics, deodorizers, baby clothes, baby bottles, baby toys, refrigerators, food containers, kitchen cutting boards, electric shavers, curling irons, wrist bands and much more. These nano-silver products include the common brand names Crocs and Remington (Appendix). In preparing for this report, a brief web search for products in the United States whose manufacturers acknowledge use of nano-silver revealed that the Consumer Products Inventory is only the tip of the iceberg. Without mandatory labelling of nano-ingredients, it is impossible for either the public or regulator to quantify the true scale of commercial use of nano-silver.

In addition to its use in consumer products, nano-silver has been applied as an antimicrobial to a range of industrial products, including disinfectants, food packaging, water purification, powder coatings (coating door knobs), wall paints and air conditioning. It has also been used as a disinfectant coating throughout Hong Kong subways (Appendix).

Early examples in agriculture may include the use of nano-silver as a "nanobiotic" in poultry production (Clement 2009). Asian agricultural chemical companies also advertise nano-silver for use as a fungicide, foliar spray and disinfectant for fish farming (Gih Hwa 2011). It is unclear whether the authors are referring to nano-silver as opposed to a colloidal or bulk silver suspension.

Significantly, nano-silver has important applications within a clinical setting, lining wound dressings and as coatings for medical devices, such as catheters and stents (Silver, Phung and Silver 2006). Given growing resistance to other antimicrobials, nano-silver is used increasingly as an antiseptic, disinfectant and for external wound treatment.

Most experts agree that antimicrobials in everyday products are completely unnecessary

While recognising that the use of nano-silver in certain clinical settings is of great value, most experts interviewed for this report agreed the current widespread use of nano-silver in household products may be excessive and unnecessary.

Professor Stuart Levy, Professor of Molecular Biology and Microbiology and of Medicine, and Director of the Center for Adaptation Genetics and Drug Resistance at Tufts University School of Medicine in the United States, suggested in 2001 that the dramatic rise in household products containing antimicrobial agents was a cause for concern. He cautioned that this could select for resistant bacteria, alter our microflora and ultimately our immune systems. Levy states: "*Although we need to control pathogens when they cause disease, we do not have to engage in a full-fledged 'war' against the microbial world*" (Levy, 2001).

Professor Andrew Maynard, then Chief Science Advisor to the Project on Emerging Nanotechnologies at the U.S. Woodrow Wilson Center, now Director of the Risk Science Center and Professor of Environmental Health Sciences at the University of Michigan's School of Public Health, cautioned in a 2008 radio interview that companies selling nano-silver products were doing so without considering the repercussions. "*It's almost as if manufacturers are like kids in a toy store at the moment. They've got new technology nanosilver and they're just putting it everywhere they are so excited*

1 Comparing a "conventional" material made up of 2 mm diameter particles, to a nanomaterial comprised of 20 nm diameter particles, and assuming hazard is associated with either particle number or surface area, not mass *about it, but nobody's really thinking about the long term consequences of that*" (Living on Earth 2008).

In an interview for this report, Dr. Samuel Luoma, Emeritus at the U.S. Geological Survey and John Muir Institute of the Environment at the University of California, Davis, informed that: "*The biggest environmental danger with nano-silver and probably for human health as well is if hundreds of these products are used by millions of people. If it's used wrong [nano-silver] and if it's over-used, then you could indeed find resistance. There are a large amount of products with unknown and unproved effectiveness and unproven necessity – their presence on the market is a way of unnecessarily increasing risk"* (S. Luoma, phone interview 6/21/11).

A further interview for this report, with Dr. Kristen Kulinowski, a Faculty Fellow in the Department of Chemistry at Rice University and Director for External Affairs for the Center for Biological and Environmental Nanotechnology (CBEN), and currently serving as the Director of the International Council on Nanotechnology (ICON), stated: *"I think the value to society of the use of nano-silver in a clinical setting is greater than the value to society of its use in a consumer product where there's no potential health benefit"* (K. Kulinowski, phone interview 6/27/11).

In another interview for this report, Professor John Turnidge, warned that: *"It's a market that created itself. In a sense, that they just use fear of bacteria as a marketing tool to introduce products that are unnecessary"* (J. Turnidge, phone interview 3/17/11). Professor Turnidge is Clinical Director of Microbiology and Infectious Diseases, SA Pathology, Professor of Paediatrics, Pathology and Molecular and Biomedical Sciences, University of Adelaide and current president of the Australian Society for Microbiology.

Nano-silver may exert both ionic and particle-mediated toxicity

This report focuses on the public health challenges raised by nano-silver, rather than its toxicity to humans or the environment. Toxicity issues are therefore discussed only briefly below. For detailed reviews on these subjects see Aitken, et al. (2009), Batley and McLaughlin (2010), Luoma (2008) or Wijnhoven et al. (2009).

Recent studies have found that nano-silver exerts both ion and nanoparticle-mediated toxicity. Nano-silver delivers silver ions to exposed organisms even more effectively than bulk silver (Luoma 2008). Nano-silver also produces reactive oxygen species (ROS) at the particle surface (Hussain, Hess, et al. 2005).

The toxicity of nano-silver is different to and has been observed to be greater than that of silver ions alone, in both bacteria (Luoma 2008) and zebrafish used by regulators as a model test species (Asharani, et al. 2008). *In vitro* study has also shown that nano-silver can act as a developmental neurotoxicant, exerting a toxicity that is distinct from that of silver ions, and related to factors including particle size, coating and chemical composition, in addition to ion release (Powers, et al. 2011).

Nano-silver can show higher bioavailability and different accumulation in exposed animals than silver in ionic form (Asharani, et al. 2008, Griffitt, et al. 2009). Even where a solution of nano-silver contains a substantial number of aggregates and agglomerates >100nm in size, the bioavailability can be far higher than that of silver ions alone (Griffitt, et al. 2009).

For a more detailed discussion of ionic versus particle-mediated toxicity please see Senjen and Illuminato (2009).

The loss of nano-silver from products into waste streams may be rapid

A recent study revealed that nano-silver used in some clothing can easily leak into wastewater during washing. Two brands of socks lost nearly 100% of their silver content within four washings (Benn and Westerhoff 2008).

The majority of nano-silver may be removed from wastewaters and deposited in sludge or biosolids by waste treatment (Benn and Westerhoff 2008). Biosolids could then reach the environment as agricultural fertilisers, dumping in landfills or oceans, or via incineration (Kiser, et al. 2009).

However it is possible that anionic and uncharged nanomaterials could pass through into sewage effluents and not be retained in sewage biosolids (Batley and McLaughlin 2010). Inevitably, the more nano-silver in incoming wastewater, the more nano-silver will be lost to the environment in treated effluent (Luoma 2008). Swiss researchers recently modelled the environmental concentrations of several commercially used nanoparticles. They predicted that nano-silver in sewage treatment effluents and surface waters may already pose risks to aquatic organisms (Gottschalk, et al. 2010).

Nano-silver could increase greenhouse gas emissions from wastewater treatment

Nano-silver has been shown to impair the function of bacteria in activated sludge, resulting in four times the normal quantity of nitrous oxide being released (Knight 2010). Nitrous oxide is 310 times more effective at trapping heat in the atmosphere when compared to carbon dioxide over a 100-year time period, which makes it an extremely potent greenhouse gas (UNFCCC n.d.).

Nano-silver is toxic to non-target bacteria

Microorganisms are the foundation of all ecosystems and provide key environmental services ranging from primary productivity to nutrient cycling and waste decomposition (Klaine, et al. 2008).

Early studies have shown that nano-silver can reduce the activities of microbes employed in treating wastewater (Choi, et al. 2008, Knight 2010). Nano-silver contaminated effluent released into natural waterways could also disrupt critical bacteria-driven processes. If biosolids containing nano-silver are applied to agricultural soil, it could also reduce soil fertility on farms.

Early studies suggest nano-silver presents new toxic risks

At realistic environmental exposure levels (below 0.19 nM) nano-silver impaired the reproduction of zebrafish and caused deformities (Lee, et al. 2007). A high-level international review has concluded that evidence for nano-silver's environmental toxicity is sufficient to require precautionary action (Aitken, et al. 2009).

The potential toxicity to humans is very poorly understood and inadequate to undertake human risk assessment (Wijnhoven, et al. 2009). Nonetheless, i*n vitro* studies have found that nano-silver was toxic to mammalian liver cells (Hussain, Hess, et al. 2005), stem cells (Braydich-Stolle, et al. 2005) and even brain cells (Hussain, Javorina, et al. 2006).

In their review of nano-silver toxicity, Wijnhoven et al. (2009, p25) conclude that long-term study of nano-silver's potential toxicity to humans is required: "Developmental toxicity and neurotoxicity will have dramatic consequences and given the equivocal carcinogenicity effects, additional information on these long-term endpoints is needed."

Nano-silver could promote mitochondria-related disease

Each human cell contains ancient forms of tiny symbiotic bacteria called mitochondria – our cells' energy producers.

Early *in vitro* studies have already demonstrated that exposure to nano-silver can reduce mitochondrial function (Hussain, Hess, et al. 2005, Hussain, Javorina, et al. 2006).

The number of diseases associated with mitochondrial malfunction is ever-increasing and includes Parkinson's, Alzheimer's and Huntington's disease (Schapira 2006). It appears plausible that a long-term increased exposure to nano-silver could result in increased incidence of these types of diseases.

bacterial resistance:
an emerging crisis in public health

"There is no question that the resistance to bacteria in hospitals is a very scary issue."

Dr. Samuel Luoma, Emeritus at the U. S. Geological Survey and John Muir Institute of the Environment at the University of California, Davis (S. Luoma, phone interview 6/21/11).

Clinical and microbiological professionals agree that we are in serious trouble. As a result of the overuse and abuse of antibiotics, in recent decades antibiotic resistance has increased in bacterial pathogens. This has led to treatment failures in both human and animal infectious diseases (WHO 2010). In a recent interview with *The Age* (AAP 2011), Professor Peter Collignon, Director of Infectious Diseases & Microbiology at the Canberra Hospital and Australian National University Medical School, stated, "*We've got resistant bacteria causing infections in people that are either untreatable or close to being untreatable*."

In the United States, 1 in 17 hospital infections kill. The U.S. Center for Disease Control and Prevention estimates that each year, roughly 1.7 million hospital-associated infections, from all types of bacteria combined, cause or contribute to 99,000 deaths. In Europe, hospital-associated infections are thought to cause or contribute to 147,000 deaths each year (WHO 2010).

Significantly, the World Health Organisation dedicated this year's World Health Day (April 7, 2011) '*Antibiotic resistance: No action today, no cure tomorrow*' in an effort to raise the general awareness about this problem.

The importance of nano-silver in hospitals

The rapid rise in antibiotic resistance has required the increased use of other antimicrobials in disinfectants and antiseptics within clinical settings. These include hypochlorites, quaternary ammonium compounds, nano-silver and triclosan. Of these antimicrobials, nano-silver is also used in wound dressings, especially for burns, and to control bacteria on catheters and stents. Given growing resistance to other antimicrobials, nano-silver is of key importance.

Professor Roy Kimble of the University of Queensland and director of burns and trauma at the Royal Children's Hospital in Brisbane observed in 2009 that: "*The vast majority of burns surgeons in Australia use* *silver dressings."* Professor Collignon has previously advised that nano-silver is very useful in stopping the growth of bacteria on medical devices without relying on antibiotics (Salleh 2009).

In 2008 Professor Andrew Maynard was explicit about the need to safeguard such clinical use: "*At the moment silver is one of our last defenses against some of these bugs these microbes that are resistant to many other forms of antimicrobial agents. If we give the secret of our last best defense away, silver, it leaves us with very little else to kill these harmful agents… It literally is the silver bullet and I think we have to use it judiciously*" (Living on Earth 2008).

In interviews for this report, other experts agree. Dr. Kulinowski cautions, *"It's safe to say that over use of any type of antimicrobial raises the potential for resistance. Therefore, in choosing which type of antimicrobial therapy to apply or if it's even needed, for example outside of a clinical setting, resistance really needs to be taken seriously"* (K. Kulinowski, phone interview 6/27/11).

Furthermore, despite widespread recognition of the clinical utility of silver wound dressings and other applications, there is some concern about potential toxicity to patient host cells. It has been suggested that this could delay wound healing or pose localised toxicity (Luoma 2008). There is also a risk that widespread clinical use of nano-silver (for example, in cleaning products, soaps and sheets) could contribute to more rapid development of resistance (see below). This suggests that clinical use of nano-silver should be limited to patients and anti-microbial applications of most value, where alternative disinfectants are not effective.

In an interview for this report, Assoc. Prof. Faunce, Australian Research Council Future Fellow at the Australian National University, recommended that hospital and health care providers should establish guidelines to restrict clinical use of nano-silver for critical applications and patients (T. Faunce, phone interview 3/15/11).

What doesn't kill bacteria makes them stronger

Figure 1: Selection of bacterial resistance to antimicrobials, based on a diagram by GreenFacts (2009).

Widespread use of nano-silver in low ion release consumer applications may be especially problematic

To minimise development of resistant bacteria in clinical settings, experts recognise that wound dressings must release high levels of silver ions in an attempt to kill all bacteria present (Chopra 2007).

It therefore appears likely that widespread household use of products that release lower levels of silver ions, for example dish cloths, baby mats or computer keyboards, may be especially problematic breeding grounds for bacterial resistance.

Early evidence of nano-silver resistance has already emerged

It is difficult to know how widespread bacterial resistance to silver might already be in our hospitals and broader society (Chopra 2007). Nonetheless, there are already several reports describing bacterial resistance to silver. As cited by Gupta, et al. (2001) "*The first report on the genetic and molecular basis for* Ag^+ *[ionic silver] resistance concerned a* Salmonella typhimurium *isolate, from the Massachusetts General Hospital, that killed several patients and required the closing of the burn ward in 1975 (McHugh et al. 1975).*"

Silver-resistant bacteria have been repeatedly found in hospital burn wards (examples listed by Chopra 2007), where the silver compound silver-sulfadiazine has been used for decades to treat burns patients. In particular, a 2003 investigation in a Chicago hospital found more than 10% of clinical isolates had silver resistance genes (Silver 2003). A relatively recent study also reported strains of bacteria able to survive high concentrations of silver nanoparticles (Lok, et al. 2007).

Exposure to silver can also promote bacterial resistance to many other antimicrobial compounds

Selection of bacteria with the ability to resist silver also selects for other antimicrobial resistance genes. Genes conferring antimicrobial resistance regularly travel quickly and widely due to the presence of mobile genetic (DNA) elements, such as plasmids, viruses, transposons and integrons. Resistance genes to silver have been found on a range of plasmids, notorious for containing multiple antibiotic resistance genes (Gupta, et al. 2001, Silver 2003).

Professor Stokes warns that the risk we face is not just silver resistance, adding "*the one thing that I'd put money on is that silver resistance is very closely linked in a genetic sense to other types of antimicrobial compounds, like antibiotic resistance genes. It's kind-of like a double whammy"* (H. Stokes, phone interview 3/10/11).

Widespread consumer and industrial use of nano-silver will promote rapid development of nano-silver resistant bacteria

In an interview for this report, Dr. Luoma cautions that: *"The biggest danger posed by nano-silver to the environment, and probably to human health as well, is if hundreds of products are used by millions of people"* (S. Luoma, phone interview 6/21/11).

Experts interviewed for this report agreed that the widespread use of nano-silver in consumer, agricultural and industrial settings is likely to breed further antimicrobial resistance.

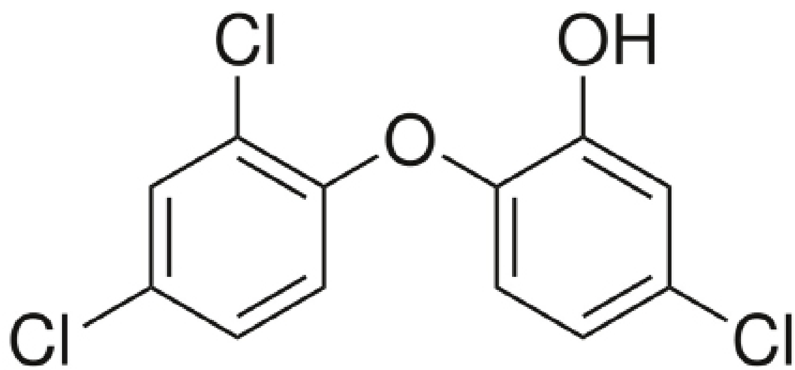
Professor Stokes warned "*the use of antimicrobials outside of the clinical context indirectly facilitates and further raises the possibility that such resistance genes are going to make their way into very serious pathogens, and at that point , it becomes a major health problem….and if we start using nano-silver quite broadly in the environment, then not only will we have bacteria that are resistant to nano-silver, then I would bet that they'll already be multi-drug [antibiotic] resistant as well."* (H. Stokes, phone interview 3/10/11)

Professor Turnidge suggested that "*prudence and restraint are probably the critical factors largely missing from what we do. We use [antimicrobials] much, much more than we need to as a society*" (J. Turnidge, phone interview 3/17/11).

In evidence to a U.S. House Committee on Energy and Commerce in 2010, Professor Stuart Levy observed that misguided use of antibiotics has contributed directly to the development of 'superbugs': "…*the widespread use – and misuse – of antibiotic drugs has spawned the evolution of life-threatening bacteria that render our current antibiotics useless*" (APUA 2010). It is to be hoped that we do not repeat such a mistake with nano-silver.

the case of triclosan:

a cautionary lesson for nano-silver



"The usage of nano-silver is equally as frustrating, bizarre and stupid as the use of triclosan in consumer products, which is very widespread now. Antiseptics in toothpaste, washing powder, god knows what else. It's a market that created itself. In a sense, that they just use fear of bacteria as a marketing tool to introduce products that are unnecessary. And nano-silver in consumer products is equally loony."

Professor John Turnidge, Clinical Director of Microbiology and Infectious Diseases, SA Pathology, Professor of Paediatrics, Pathology and Molecular and Biomedical Sciences, University of Adelaide and current president of the Australian Society for Microbiology (J. Turnidge, phone interview 3/17/11).

Triclosan offers a cautionary experience for nano-silver. Just like nano-silver, triclosan is another major antimicrobial agent now widely found in both consumer products and clinical settings. This has led to high resistance levels, compromising its clinical use and posing new public health threats.

The history of triclosan

The compound triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether) was first developed and introduced as an antimicrobial and preservative in the 1960s. Since this time, triclosan has been used in clinical settings as an antiseptic, but also within a vast range of domestic products, including hand soaps, toothpastes, mouthwash, deodorants, cutting boards, wound disinfectants, facial tissues, plastic utensils, socks and toys (Yazdankhah, et al. 2006). Like nano-silver, triclosan is a non-specific antimicrobial - that has the ability to kill (almost) all of the good microbes as well as the bad (Saleh, et al. 2010). Also, similar to nano-silver, triclosan has demonstrated toxicity to a range of higher life forms such as aquatic algae (Tatarazako, et al. 2004) and has been shown to interfere with nitrogen cycles in soil (Waller and Kookana 2009).

Widespread triclosan use has driven bacterial resistance to both it and other clinically useful antibiotics

The use of antimicrobials like triclosan selects for bacteria with genes resistant to antibiotics. Several studies have also demonstrated the prevalence of triclosan resistance within bacteria (Yazdankhah, et al. 2006, Bailey, et al. 2009, Chen, et al. 2009). Clinical surveys have revealed widespread triclosan-resistant bacteria that are also resistant to clinically important antibiotics. This has led scientists to caution against the indiscriminate use of triclosan (Mima, et al. 2007, Chen, et al. 2009).

Triclosan disrupts the development of the immune system

Researchers have found that people age 18 and under with higher levels of triclosan in their urine were significantly more likely to report diagnosis of allergies and hay fever (Clayton, et al. 2011). This research utilised data from thousands of individuals from the National Health and Nutrition Examination Survey (NHANES) collected in the United States. This is the first time that exposure to an antimicrobial has been strongly linked to alteration of the development of the human immune system.

Governments agree on the serious potential for triclosan to cause harm, but say there is insufficient evidence to regulate

Regulatory bodies in the United States, Europe and Australia have all conducted recent reviews into triclosan, focussing on different aspects of its toxicity and potential for bacterial resistance (U.S. EPA 2008, NICNAS 2009, SCCS 2010). All reviews warn of the environmental toxicity hazard, as well as risks involved in human handling and overexposure to this chemical. Nonetheless, they all effectively concluded that there was not enough scientific evidence to restrict the widespread use of this compound. The one exception has been a ruling by the European Union to restrict the contact of triclosan with food (SCCP 2006). Even in Europe, which prides itself on precaution-based chemicals regulation, a lack of full scientific certainty (and the complexity of conducting non-laboratory based experiments that demonstrate causality) is being used as the reason to indefinitely delay regulation.

The failure of regulators to restrict the use of triclosan is striking in light of their explicit recognition of the problems triclosan has brought.

Reason demands we act now

There are many similarities between triclosan and nano-silver. The weight of laboratory evidence and expert opinion suggests that the widespread use of these antimicrobials could increase bacterial resistance to multiple antimicrobials within pathogenic bacteria, whilst eradicating the beneficial bacteria around us. We may never gather enough causal data to comprehensively identify and quantify the public health risks. We should instead apply precaution to restrict the widespread use of these powerful antimicrobials.

allergy epidemic:
are we too clean for our own good?

"The concept that you should kill every bacteria is a myth, no person with any knowledge of the literature of how resistance works or the function of the human body would suggest that. We survive because of the beneficial bacteria that help us—taking a big dose of antibiotics is one of the most dangerous things that you could do—there is no foundation for that at all."

From a June 21st 2011 interview with Dr. Samuel Luoma, Emeritus at the U.S. Geological Survey and John Muir Institute of the Environment at the University of California, Davis.

"...Putting yet another consumer product out to kill 'germs' is exactly the wrong thing. Germs are good for you. We actually need to promote the message that the immunologists are now putting out – that almost all germs are good for you. The more good germs you get exposed to the less bad germs and allergies you will have."

Professor John Turnidge, Clinical Director of Microbiology and Infectious Diseases, SA Pathology, Professor of Paediatrics, Pathology and Molecular and Biomedical Sciences, University of Adelaide and current president of the Australian Society for Microbiology (J. Turnidge, phone interview 3/17/11).

With most wars children are often the first to bear the consequences and the war on bacteria is no exception. Allergies and asthma have rapidly become a major public health problem in industrialised countries.

Scientists have looked to explain this rapid increase in allergies in terms of inheritable genes or industrial pollutants, but have ruled these out (Table 1). It now appears that our use of antimicrobial compounds like nano-silver might carry a hidden price.

What is causing this epidemic?

The 'hygiene hypothesis' was first proposed in 1989 to explain the rapidly increased incidence of hay fever in England (Strachan 1989). This idea suggested that decreased exposure to infectious agents early in life (owing to increased use of antibiotics, vaccination and sanitation) results in unbalanced immune responses to antigens later in life, causing allergies. More recently, this hypothesis has been modified to the 'microflora hypothesis' (Noverr and Huffnagle 2005) or the 'old friends' hypothesis (Rook and Brunet 2005). These new names shift the focus to the need for humans to be exposed to environmental microbes like bacteria and fungi during our childhood to help prime our immune systems. Too little exposure to these microbes prevents the development of a well-balanced immune system, leading to a range of potential diseases, allergies and disorders later in life.

The double-edged sword of disease

The rise of modern sanitation and antibiotics has led to a dramatic decrease in infectious diseases (such as pneumonia and diarrhoea) as well as other positive health indicators like lowered infant mortality. However, autoimmune diseases and allergies which were virtually unknown to medicine before the 20th century have now become common.

Humans have co-evolved with a wide range of microbes, both ‘good’ and ‘bad’ (pathogenic). There is a growing body of compelling evidence that suggests that many of these microbes - both on us and inside us - play an important role in the development of our immune system and in protecting us from immune-related diseases (Mazmanian and Kasper 2006).

Exposure to microbes strengthens childhood immune systems

The occurrence of allergies and immune diseases like asthma in industrialised countries continues to rise. Interestingly, not all children are equally at risk.

A 2007 Canadian survey of over 13,000 children found that children who grow up on farms have less than half the risk of developing asthma than other rural children and children in cities (Midozi, et al. 2007). A similar trend was found in European children, where a greater diversity of microbes present in children’s home environments was significantly linked with a lowered risk of asthma (Ege, et al. 2011).

In a recent interview (Saggin 2011), Professor Peter Sly from the Queensland Children’s Medical Research Institute agreed with these findings:

“*Exposure to bacterial products, particularly from animals and farming-related activities, helps educate the immune system as to what to ignore in the environment and that helps to protect [against] the development of allergies and asthma, whereas in the city, kids don’t get quite the same sort of bacterial exposures*” he said.

Other comparative studies into autoimmune and allergic diseases add further support to the idea that we, in the industrialised world, have become too clean (Table 1).

Nobel laureate Professor Peter Doherty agrees that childhood interactions seem to benefit our immune system and adds “*Kids need to play in the dirt, and on the floor.*” (Pers Comm 3/24/11).

Friendly bacteria have a key role in health

Recent research suggests that many skin bacteria are not just harmless – they are actually beneficial to our health (Lai, et al. 2009, Cogen, et al. 2010). Even before we are born, maternal exposure to microbes appears critical for protecting offspring from asthma (Conrad, et al. 2009).

Nano-silver: its widespread use in the 'war on bacteria' could prove a great mistake

Nano-silver is an unselective antimicrobial - meaning that it efficiently kills both good and bad microbes. By placing this potent antimicrobial in close contact with our bodies, we reduce our body's exposure to good bacteria - compromising our immune system and increasing the chance of contracting immune diseases and allergies.

Table 1: A comparison of the research looking at the incidence of autoimmune and allergic diseases with human lifestyles. This table demonstrates that the increasing trend towards these diseases cannot easily be linked to industrial pollutants or genetics. It also suggests a protective role in the sharing of microflora between children.

Findings	Implications	Study
Children who grow up on farms are much less likely to have asthma than other non-farming rural and city children	Dismisses the role of urban industrial pollutants in allergies Strongly suggests a protective role in the sharing of microbes	Midozi, et al. (2007) Ege, et al. (2011)
Upon the fall of the Berlin Wall, rates of asthma were higher in West Germany than in East Germany - even though air pollution was worse in the East	Dismisses the role of urban industrial pollutants in allergies	von Mutius, et al. (1994)
Having one or more older siblings significantly lowered the incidence of hay fever, asthma, Type I diabetes and multiple sclerosis	Strongly suggests a protective role in the sharing of microbes	Strachan (1989); Ponsonby, et al. (2005); Cardwell, et al. (2008)
Child care during first 6 months lowered incidence of asthma and eczema	Strongly suggests a protective role in the sharing of microbes	Ball, et al. 2000)
Auto-immune diseases are rare in rural Asia and Africa, but rise sharply when immigrants from those countries come to the developed world	Dismisses the role of genetics in the inheritance of allergies	Detels, Brody and Edgar (1972); Symmons (1995)
Type I diabetes was 6 times more prevalent in Finland than in neighbouring Russia, in spite of similar genetic backgrounds	Dismisses the role of genetics in the inheritance of allergies	Kondrashova, et al. (2005)

nano silver:
still immune to regulation

Truck-sized gaps leave nano-silver effectively unregulated

In the Unites States, Europe, and Australia, regulations are primarily focused on the assessment of “new” chemicals. To date, despite widespread recognition that the toxicity of a nanoparticle cannot be predicted from the known toxicological properties of the same chemical in bulk form, nanoparticles are not recognised as “new” (Bowman and Hodge 2006). This means that although many nanoparticles present new and often greater toxicity risks than larger (bulk) particles of the same composition, they do not trigger new assessment. This leaves nano-silver effectively unregulated, with no requirements for companies to conduct and submit risk assessments before use. Manufacturers are still not required to identify nanoparticle ingredients on product labels or conduct nano-specific safety tests on these ingredients.

However, in June of 2011 the U.S. Environmental Protection Agency (EPA) took the first step towards regulating nanoscale silver and other nanoscale pesticide products (EPA 2011). EPA has broad authority under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) over all substances intended to kill pests, including germ killers, but has not addressed until now the growing nano-silver market or most other nanochemicals. EPA’s new proposed regulations detail two approaches for gathering environmental and health information about nanoscale materials in pesticide products. In addition, the notice proposes a new approach for how EPA will determine on a case-by-case basis whether a nanoscale ingredients is a “new”

Experts warn nano-silver is a policy failure

Most Australian experts interviewed for this report - Professors Turnidge, Stokes and Faunce - agreed that the absence of effective nano-silver regulation amounts to a policy failure.

active or inert ingredient, even when an identical, non-nanoscale form of the ingredient is already registered. Nevertheless, the recent notice released by the EPA gives no indication that the agency intends to consider the issue of antimicrobial resistance in addition to toxicity for its proposed regulations.

The proposed rules released in June 2011 are in response to a legal petition filed with the EPA by the International Center for Technology Assessment and the Center for Food Safety (CFS) in May 2008, on behalf of a coalition of 12 other public interest organizations including Friends of the Earth, calling on EPA to regulate nano-silver products as pesticides. The petition called on EPA to categorize nanoscale pesticide products as new active ingredients. Under pressure from various NGOs, the U.S. EPA (Environmental Protection Agency) decided to regulate what they called silver-ion generating devices such as washing machines. If the manufacturer declared that the aim of the device is to kill bacteria, the device would be considered a pesticide. The EPA was at pains to point out that this notice was not an effort to regulate nanotechnology; it was the silver's bactericidal effect rather than its size that led to their decision.

In an interview for this report, Dr. Diana Bowman, Senior Research Fellow in the Melbourne School of Population Health at The University of Melbourne, emphasized that nanoparticles not triggering assessment was a key regulatory gap. However, even if this trigger were activated, there is still no requirement or mandate for regulators to assess public health implications of widespread nano-silver use – for example regarding antimicrobial resistance. Dr. Bowman agreed that the narrow remit of regulators was a key barrier to effective regulation of nano-silver (D. Bowman, interview 3/11/11).

Following the release of the 2009 Friends of the Earth report, *Nano & Biocidal Silver – Extreme Germ Killers Present a Growing Threat to Public Health* (Senjen and Illuminato 2009), prominent Australian microbiologists including Professors Hatch Stokes and Peter Collignon warned that the widespread use of nano-silver could drive an increase in antimicrobial resistance. Since that time no action has been taken by relevant regulatory bodies to halt the widespread use of this antimicrobial. In interviews for this report, Professors Turnidge, Stokes and Faunce agreed that the absence of effective nano-silver regulation amounts to a policy failure.

When asked if he was disappointed in the government's response to expert calls to regulate nano-silver in terms of generating antimicrobial resistance, Professor Turnidge responded "*Yes, but it's in keeping with the whole antibiotic resistance story. Recent meetings have highlighted that a decade of cage rattling has had virtually no positive effect. When asked, the government put up a few phantoms and say we're doing this and we're doing that - but they're not doing anything. It's classic bureaucratic whitewash, sadly*" (J. Turnidge, phone interview 3/17/11).

Professor Andrew Maynard, Director of the Risk Science Center and Professor of Environmental Health Sciences at the University of Michigan's School of Public Health expressed that: *"If there is a policy failure anywhere, it is in the control of how antimicrobial agents are used, whatever the nature of the agent. That said, it has been remarkably easy for companies to use nano-silver without much consideration being given to possible long term consequences. Given the questionable benefits to consumers of some of these uses, and the possible knock-on impacts to efficacy in a clinical setting, I would argue that there is still a need for more informed and responsible use of such materials - whether guided by government policy or business codes of conduct" (A. Maynard, interview response via email 6/30/11).*

Lip service to the precautionary principle – but no precaution in practice

A precautionary approach to managing nanotechnology risks has been advocated by high level groups elsewhere. The German Federal Institute for Risk Assessment (BfR) has twice considered the challenges of nano-silver toxicity and bacterial resistance. The BfR concluded that an assessment of health risks was not yet possible, recommending that manufacturers avoid the use of nano-silver compounds in food and everyday products until the data are comprehensive enough to allow for a conclusive risk assessment to ensure products are safe for consumer health (BfR 2009, BfR 2011). Similarly, the United Kingdom's Royal Society and Royal Academy of Engineering have recommended that due to their novel risks, nanoparticles should be regulated and assessed as new chemicals before their commercial use, and face mandatory labelling (UK RS/RAE 2004). The management of nanotechnology in the United States has been anything but precautionary. Nano-silver remains effectively unregulated; the Royal Society's recommendations have been ignored.

Dr. Luoma is explicit about the need for regulation to curb over-use of nano-silver. Dr. Luoma states that: "*My feeling is that nanomaterials represent a brand new challenge for regulators. A stronger regulation of how nano is used with the explicit goal of making sure its use is limited to those situations where it's of great value or great benefit is a way to keep society from over using it [nano-silver]"* (S. Luoma, phone interview 6/21/11).

Assoc. Prof. Faunce suggests that regulators should take control of nano-silver seriously and act strongly: "*All we're really asking is for … regulators to take on world's best practice – and that they try to understand the precautionary principle. There are enough studies out there that show that there is a distinct effect of nano-silver at small sizes. In that sense, the product nano-silver needs to be regulated in its own right and not simply regarded as another version of silver*" (T. Faunce, phone interview 3/15/11).

Experts agree that we cannot consider the risks of nano-silver based solely on laboratory-based toxicology, but must also assess broader implications for public health

Professor Stokes expressed his surprise that the government was not more concerned to curtail the widespread use of nano-silver given the cost implications of antibacterial and antibiotic resistance: *"The cost of managing antibiotic resistance in hospitals is enormous...I would have thought from a government perspective that they would be looking at the problem, if only from self-interest"* (H. Stokes, phone interview 3/10/11).

Dr. Bowman believes that there is definitely a need to look beyond the laboratory when considering risk, however recognises that the scope of the legislative remit restricts how broadly regulators can assess the risk of nano-silver. "*It is not surprising that one of the things we have found when talking to regulators is that there may have been things we'd like them to look at, but their hands are tied*" (D. Bowman, interview 3/11/11).

Conclusion

The widespread use of nano-silver carries a great potential to cause harm. Based on current trends, it is reasonable to suspect that widespread use of nano-silver will contribute to:

- greater numbers of deaths related to antimicrobial resistant bacteria in hospitals
- an increase in immune-related diseases and conditions in the community, and
- further damage to the wider environment

Friends of the Earth calls on the United States Congress to act to ensure that regulators in the United States have the power to limit the widespread use of nano-silver.

appendix

Examples of nano-silver products available online or within the United States

Note: all products were viewed on March 31, 2011.



Product	Manufacturere	Nano-silver claim	Website
Baby bottle	GoBiz	"Feeding bottles and mug cups developed with this technology, help protect babies with weak immunity from ge[r]ms, the source of all diseases. Through new Nano-poly technology [1/1000,000,000m], and cutting-edge science, for the first time in the world, this perfectly prevents Secondary Virus Inflammation by control[l]ing germs, and acting as an anti-bacterial deodorant, and maintaining freshness up to 99.9% without additional disinfecting by boiling and sterilization."	http://www.gobizkorea.com/blog/ProductView.do?blogid=dream21&id=860332
Baby toothbrush	GenEzentials	"This toothbrush is made of safe and clean non-toxic silicon, contains silver nano (Ag+), and the negative ions released from the bristle inhibit bacteria, viruses and fungi."	http://genezentials.com/genezentials-products/baby-silicon-finger-toothbrush/silicon-finger-toothbrush
Shoes	Crocs	"Croslite Ag+™ material expands upon the comfort attributes inherent to Croslite™ material while adding anti-bacterial, anti-fungal and odor resistant nano-Silver ceramic crystals."	http://www.crocsrx.com/sCloud.html http://company.crocs.com/news-releases/top-us-government-agency-validates-benefits-of-croslite%E2%84%A2-material/
Food storage container	Prepology Kitchenware	"Each container in this nine-piece set features silver nano technology that's embedded in the polypropylene lid. This helps to slow down the introduction and buildup of bacteria."	http://www.qvc.com/qic/qvcapp.aspx/view.2/app.detail/params.item.K30602.desc.Prepology-9piece-Nano-Silver-Food-Storage-Set?&cookie=set
Food storage container	Kinetic	"Approved Nano Silver Technology that keeps your foods fresher up to 3 times longer than conventional plastic food storage."	http://www.kinetic-cookware.com/product.asp?cat=59&subcat=113

Product	Manufacturere	Nano-silver claim	Website
Epilator	Remington	“Depilation head with Nano Silver which inhibits the growth of micro-organisms on the head.”	http://www.drugstore.com/products/prod.asp?pid=210106&catid=45531
Industrial disinfectant for Hong Kong trains and subway	MTR	“99.9% effective in killing a wide range of viruses and bacteria under a laboratory-controlled environment. The coating lasts for about three years after application and MTR will conduct checks every eight months to ensure the bacteria-fighting powers remain intact.”	http://www.mtr.com.hk/eng/corporate/file_rep/PR-06-084-E.pdf
Agricultural fungicide	NSM	“Strong anti-fungal properties have found extensive usage in the agriculture sectors to improve germination and to accelerate growth and development without the use of chemical.”	http://www.nanosilver.com.my/ecs.asp
Aquaculture disinfectant	Gih Hwa Enterprise	“Eliminate the diseases caused by bacteria, virus and fungi, such as *Aeromonas hydrophila*, *Edwardsiellosis*, Red spot disease, mold, and *Streptococcus*”	http://www.gihhwa.com/en/nano_silver.html

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"The biggest environmental danger with nano-silver and probably for human health as well is if hundreds of these products are used by millions of people. If it's used wrong [nano-silver] and if it's over-used, then you could indeed find resistance. There are a large amount of products with unknown and unproved effectiveness and unproven necessity – their presence on the market is a way of unnecessarily increasing risk."

Dr. Samuel Luoma, Emeritus at the U.S. Geological Survey and
John Muir Institute of the Environment at the University of California, Davis

"I think the value to society of the use of nano-silver in a clinical setting is greater than the value to society of its use in a consumer product where there's no potential health benefit."

Dr. Kristen Kulinowski, a Faculty Fellow in the Department of Chemistry at Rice University and Director for External Affairs for the Center for Biological and Environmental Nanotechnology (CBEN), and currently serving as the Director of the International Council on Nanotechnology (ICON)

"If we start using nano-silver quite broadly in the environment, then not only will we have bacteria that are resistant to nano-silver, then I would bet that they'll already be multi-drug [antibiotic] resistant as well."

Professor Hatch Stokes, The ithree Institute (University of Technology Sydney) and
former president of the Australian Society for Microbiology

"The usage of nano-silver is equally as frustrating, bizarre and stupid as the use of triclosan in consumer products, which is very widespread now. Antiseptics in toothpaste, washing powder, god knows what else. It's a market that created itself. In a sense, that they just use fear of bacteria as a marketing tool to introduce products that are unnecessary. And nano-silver in consumer products is equally loony."

Professor John Turnidge, Clinical Director of Microbiology and Infectious Diseases, SA Pathology, Professor of Paediatrics, Pathology and Molecular and Biomedical Sciences. University of Adelaide and current president of the Australian Society for Microbiology

"For some reason, Australian regulators seem to be more sympathetic to industry wanting to use these particles – more than the environment. There seems to be a sort of inertia to take into account environmental and health hazards of nano-silver."

Associate Professor Thomas Faunce, Australian Research Council Future Fellow
at the Australian National University

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