NANO-SILVER

POLICY FAILURE PUTS PUBLIC HEALTH AT RISK

Friends of the Earth

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nano-silver

policy failure puts public health at risk

By Dr. Gregory Crocetti and Georgia Miller
Friends of the Earth Australia

Design and Layout
Natalie Lowrey

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Front cover image of ***E. coli*** bacteria from
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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. More than 7,000 similar deaths occur annually in Australia.

At the same time, we are experiencing an epidemic in allergic diseases and asthma in industrialised 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 US citizens test positive to one or more allergens; more than half US 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.

Australian health experts surveyed for this report, including Professor John Turnidge, Professor Hatch Stokes and Associate Professor Tom Faunce, 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 Australia, people are already coming into contact with nano-silver every day.

In interviews for this report, medical experts warn that using 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 interviewed for this report warn that nano-silver will also promote resistance to antibiotics and other antimicrobials.

As concern grows about our allergy epidemic, scientists have realised 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.

Widespread use of nano-silver carries the great potential to 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.

In interviews for this report, Professors Turnidge, Stokes and Faunce have described existing regulation (or non-regulation) of nano-silver as a policy failure.

Friends of the Earth Australia call on the government to restrict the use of nano-silver in consumer, industrial and environmental products.

Reponses from expert panel to questions relating to nano-silver

	Prof. Hatch Stokes	Prof. John Turnidge	Dr. Diana Bowman	Assoc. Prof Tom Faunce
Do you regard silver as an important antimicrobial in Australian hospitals – in the context of treating serious burns?	✓	✓	✓	✓
Are you concerned with the level of antibiotic resistance?	✓	✓	✓	✓
Do you agree that the widespread use of nano-silver in consumer products is excessive and unnecessary?	✓	✓	?	✓
Do you agree that the regulation of nano-silver has been a policy failure?	✓	✓	?	✓
Do you think that regulators need to look at chemicals like nano-silver in terms of public health, in addition to toxicity?	✓	✓	✓	✓

introduction

Definition of nanotechnology

Nanoparticles are commonly defined as particles with at least one dimension measuring less than 100 nanometres (1 nanometre = 1 billionth of a metre). Nanoparticles show novel physico-chemical 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, short-term 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 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 the surface area of a particle; 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 deliver silver ions efficiently to the surface of bacteria (Marambio-Jones and Hoek, 2010)

Nano-silver is also more readily manipulated into commercial products than bulk silver. Because nano-silver can be manufactured 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). This has led to a proliferation of its use in consumer and industrail products.

Commercial use of nano-silver is expanding rapidly

The estimated worldwide market size of nano-silver was 320,000 kg/yr in 2009 (Gottschalk *et al*., 2010), although this is expected to expand rapidly. This volume may appear small, however its toxicological burden might be 100 times, or even 10,000 times as great as this volume of bulk silver (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 nanomaterial in consumer products (PEN, 2011). Of the 1317 products listed, over 300 products contain nano-silver. These include toothpastes, pet shampoos, water filters, fabric softeners, bath towels, shoes, socks, computer keyboards, cosmetics, deodorisers, baby clothes, baby bottles, baby toys, refrigerators, food containers, kitchen cutting boards, electric shavers, curling irons, and much more. Manufacturers include big name brands Crocs, Samsung, LG, Remington and Vidal Sassoon (Appendix). Our brief web search for products in Australia 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 the public or regulators to quantify the true scale of commercial use of nano-silver.

In addition to its use in consumer products, nano-silver is used as an antimicrobial in a range of industrial products, including disinfectants, cleaning agents, powder coatings (coating door knobs), wall paints and air conditioning. It has 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).

Significantly, nano-silver has important applications within a clinical setting, particularly lining wound dressings and as coatings for medical devices, such as catheters and stents (Silver *et al*., 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 value, all experts interviewed for this report agreed the current widespread use of nano-silver in household products is excessive and unnecessary (Table 2).

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 warned 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, 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 about it, but nobody's really thinking about the long term consequences of that*" (Living on Earth, 2008).

In an 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 17/3/11). 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 discussed only briefly here. 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 ionic 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 *et al*., 2005).

The toxicity of nano-silver is different to that of silver

1. Comparing a "conventional" material made up of 2 µm diameter particles, to a nanomaterial comprised of 20 nm particles, and assuming hazard is associated with either particle number or surface area, not mass.

ions. Toxicity was greater 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 >100 nm in size, the bioavailability can be far higher than that of silver ions alone (Griffitt *et al*., 2009).

For more detail 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

Nano-silver used in some clothing can easily leak into waste water 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 some 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 predicted that nano-silver in sewage treatment effluents and surface waters may already pose risks to aquatic organisms (Gottschalk *et al*., 2009).

Toxicity 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 used in treating wastewater (Choi, 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, they could reduce soil fertility on farms.

Nano-silver could increase greenhouse gas emissions from wastewater

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.).

New risks for people and environment

At realistic environmental exposure levels (below 19 ng/L), nano-silver impaired the reproduction of zebrafish and cause deformities (Lee, 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, *in vitro* studies have found that nano-silver was toxic to mammalian liver cells (Hussain *et al*., 2005), stem cells (Braydich-Stolle *et al*., 2005) and even brain cells (Hussain *et al*., 2006; Powers *et al*., 2011).

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 cell's energy producers.

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

"Bacterial resistance to antibiotics is one of the biggest challenges of the 21st century"

Professor Hatch Stokes at The ithree Institute (University of Technology Sydney) and former president of the Australian Society for Microbiology (H.Stokes, phone interview 10/3/11)

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, 2007). Professor Peter Collignon, Director of Infectious Diseases and Microbiology at the Canberra Hospital and Australian National University Medical School, warned recently: *"We've got resistant bacteria causing infections in people that are either untreatable or close to being untreatable"* (AAP, 2011).

In the United States (US), 1 in 17 hospital infections kill. The US 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). In Australia, the 7,000 deaths annually from hospital-associated infections is four times greater than our road toll.

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 awareness about this problem.

Nano-silver's role in hospitals

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

There is widespread - albeit not universal - recognition of the clinical utility of silver wound dressings (Salleh, 2010). Professor Roy Kimble of the University of Queensland and director of burns and trauma at the Royal Childrens Hospital in Brisbane has observed that, *"The vast majority of burns surgeons in Australia use silver dressings"* (Salleh, 2010). 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).

However concern exists that nano-silver could adversely affect patient host cells. This could delay wound healing or pose localised toxicity (Luoma, 2008). This, in addition to concerns about promoting bacterial resistance (see below), 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. The potential for nano-silver's widespread clinical use (for example, in cleaning products, soaps and sheets) to drive more rapid develop of bacterial resistance to nano-silver also suggests a need for restrained use.

Faunce and Watal (2010) recommend that hospital and health care providers should establish guidelines to restrict clinical use of nano-silver for critical applications and patients.

What doesn't kill bacteria makes them stronger

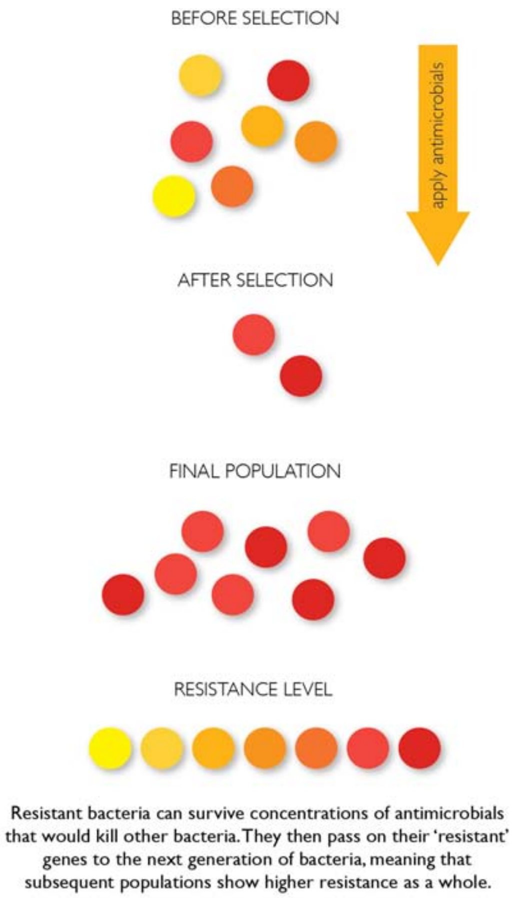


Figure 1: Selection of bacterial resistance to antimicrobials, based on diagram by GreenFacts (2009).

Widespread use of nano-silver outside clinical settings may promote rapid development of resistance

Experts recognise that to minimise development of resistant bacteria in clinical settings, 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 mattresses, toothbrushes or computer keyboards, may be especially problematic breeding grounds for bacterial resistance.

In 2008, Professor Andrew Maynard warned explicitly that widespread consumer and industrial use of nano-silver could compromise its medical role: "*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. Professor Stokes warns *"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 10/3/11).

Professor Turnidge suggests 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 17/3/11).

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 its emergence. As cited by Gupta (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).

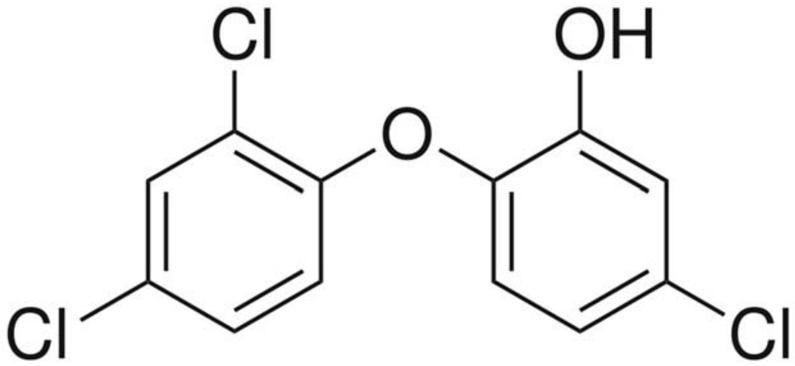
Exposure to silver can promote resistance to many other antimicrobial compounds as well

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 10/3/11).

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 17/3/11).

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). And, like nano-silver, triclosan is a non-specific antimicrobial - it has the ability to kill 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 demonstrated the prevalence of triclosan resistant bacteria (Yazdankhah *et al.*, 2006; Bailey *et al.*, 2009; Chen *et al.*, 2009). Clinical surveys have also found widespread triclosan resistant bacteria that are also resistant to clinically important antibiotics. This has led scientists to caution against the indiscriminate use of triclosan (Yazdankhah *et al.*, 2006; 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 used data from thousands of individuals from the US National Health and Nutrition Examination Survey. 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 that triclosan has serious potential to 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 (USEPA, 2008; NICNAS, 2009; SCCS, 2010). All reviews warn of the environmental toxicity hazard, as well as risks involved in human handling and over-exposure 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 these 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?

"There's been an epidemic increase in allergic diseases - such as asthma, food allergies, dermatitis - over the last 40 or 50 years, such that now in Australia as many as 40% of children will have an allergy to something and many of those will go on to develop diseases."

Winthrop Professor Susan Prescott, from University of Western Australia's School of Paediatrics and Child Heath (ABC Stateline, 2004).

"... 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 17/3/11).

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 hayfever 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 '*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 the 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 that 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 of the risk of developing asthma than other rural children and children in cities (Midodzi *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 Professor Peter Sly from the Queensland Children's Medical Research Institute agreed with these findings (ABC, 2011):

"*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 24/03/11).

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).

Deploying nano-silver in the every day 'war on bacteria' could prove a great mistake

Nano-silver is an unselective antimicrobial - it efficiently kills both good and bad microbes. Widespread use in consumer products means routinely placing this potent antimicrobial in close contact with our bodies. In addition to promoting microbial resistance, this will reduce our body's exposure to good bacteria, potentially 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 as other non-farming rural and city children	Dismisses the role of urban industrial pollutants in allergies Strongly suggests a protective role in exposure to diverse microbes	Midodzi *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 worst in the East	Dismisses the role of urban industrial pollutants in allergies	Von Mutius *et al.*, 1994
Having one or more older siblings significantly lowers 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 lower incidence of asthma and eczema	Strongly suggests a protective role in exposure to diverse 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 *et al.*, 1972; Symmons, 1995
Type I diabetes is 6 times more prevalent in Finland as 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

As with the EU and US systems, Australian regulations are primarily focused on "new" chemicals. To date, Australian legislation fails to recognise that nanoparticles present new and often greater toxicity risks than larger (bulk) particles of the same composition (Bowman and Hodge, 2006; Faunce and Watal, 2010). This leaves nano-silver effectively unregulated, with no requirements for companies to conduct and submit risk assessments before use.

In an interview for this report, Dr. Diana Bowman, Senior Research Fellow in the Melbourne School of Population Health at The University of Melbourne, emphasised 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. Dr. Bowman agreed that the narrow remit of regulators to assess broader implications was a key barrier to effective regulation of nano-silver (D. Bowman, interview 11/3/11).

Following the release of the 2009 FoE report, *Nano & Biocidal Silver – Extreme Germ Killers Present a Growing Threat to Public Health* (Senjen and Illuminato, 2009), prominent microbiologists, including Professors Hatch Stokes and Peter Collignon, warned that the widespread use of nano-silver could drive antimicrobial resistance. In a recent review, Faunce and Watal (2010) call for nano-silver to be regulated as a new chemical, for mandatory registration of use, for post-market surveillance and for guidelines to limit the clinical use of nano-silver. Yet, no action has been taken by relevant regulatory bodies or the Australian government to halt its widespread use.

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.

When asked if he was disappointed in the government's response to experts' calls to regulate nano-silver to prevent 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 17/3/11).

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

The Australian Government was a signatory to the most widely accepted version of the Precautionary Principle - the Rio Declaration on Environment and Development (UNEP, 1992), which states:

"*In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*".

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 aspects of nano-silver toxicity and bacterial resistance. It concluded that a reliable 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, in the United Kingdom, the Royal Society and Royal Academy of Engineering have recommended that nanoparticles should be regulated and assessed as new chemicals and face mandatory labelling due to the seriousness of nanotoxicity risks (UK RS/RAE, 2004).

On 11 July 2008 Senator Kim Carr, the Minister for Innovation, Industry, Science and Research, released the Australian Government Objectives for the Responsible Management and Oversight of Nanotechnology. This document claimed the Australian Government will "*Protect the health and safety of humans and the environment*", by continuing to "*apply a precautionary approach consistent with Australia's international obligations, including the Rio declaration*" (DIISR, 2008).

The Australian Government Department of Health and Ageing has also recognised the precautionary principle as being "particularly relevant" within the context of administrative policy (DHA, 2001).

However, in spite of these commitments, the management of nanotechnology in Australia has been anything but precautionary. Nano-silver remains effectively unregulated; the Royal Society's recommendations have been ignored.

Assoc. Prof. Faunce, Australian Research Council Future Fellow at the Australian National University, suggests that regulators should take control of nano-silver seriously and act strongly "*all we're really asking is for Australian 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 15/3/11).

Illustration by Maude Farrugia

Australia's nanotechnology business friendly regulatory environment

In stark contrast to the precautionary principle, a recent Australian Government nanotechnology report touts praise by the OECD for our lax regulation (DIISR 2011,8):

"*In 2006, the OECD cited Australia's approach to regulation as a best practice benchmark for other OECD countries. Australia was identified as having the fewest restrictions on product markets of the 30 OECD countries, the least public ownership of business and the least restrictive impact of business regulation on economic behaviour. Australia has been ranked as the third fastest place in the world to start a business*".

Assoc. Prof. Faunce suggests that "*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 the environmental and health hazards of nano-silver*" (T. Faunce, phone interview 15/3/11).

Table 2. Reponses from expert panel to questions relating to nano-silver during interviews between March 10-17, 2011.

	Prof. Hatch Stokes	Prof. John Turnidge	Dr. Diana Bowman	Assoc. Prof Tom Faunce
Do you regard silver as an important antimicrobial in Australian hospitals – in the context of treating serious burns?	✓	✓	✓	✓
Are you concerned with the level of antibiotic resistance?	✓	✓	✓	✓
Do you agree that the widespread use of nano-silver in consumer products is excessive and unnecessary?	✓	✓	?	✓
Do you agree that the regulation of nano-silver has been a policy failure?	✓	✓	?	✓
Do you think that regulators need to look at chemicals like nano-silver in terms of public health, in addition to toxicity?	✓	✓	✓	✓

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 as to why 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 10/3/11).

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 11/3/11).

All Australian experts interviewed for this report agree there is a pressing need to act to manage the public health threats from the widespread use of nano-silver (Table 2). This is a key challenge for the regulatory body National Industrial Chemicals and Assessment Scheme (NICNAS), as it considers new regulations to control nano-silver and other nano-forms of existing chemicals.

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 Ministers for Innovation and Health, Kim Carr, Catherine King and Nicola Roxon to act to ensure that Australian regulators have the power to limit the widespread use of nano-silver.

appendix

Examples of nano-silver products available online or within Australia

Product	Manufacturer	Nano-silver claim	Website
Soap	COR	"The particles of Cor soap's active ingredients, including silver, sericin, collagen and chitosan, are dramatically reduced in size, reaching deep below the surface, killing bacteria, minimizing wrinkles, moisturizing and feeding vital nutrients to the skin".	http://www.skincarestore.com.au/cor-silver-soap-30g-p-5907.aspx
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 controling 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
Ladies Cycling Jersey	Scody	"Silpure is a state-of-the-art antimicrobial. Silpure® utilizes the natural ability of silver to limit the growth of odor-causing bacteria and represents a new generation antibacterial technology for topical application to textiles."	http://www.rebelsport.com.au/ecom/rebel/product_detail.aspx?id=32697&cat=2410

Product	Manufacturer	Nano-silver claim	Website
Cleaning cloth	E-CLOTH	"The cloth incorporates natural nano-silver to kill bacteria caught in the cloth. Further tests showed that, after a rinse with warm water, E-cloths re-introduced just 0.01% of bacteria back onto a sterile surface".	http://www.everten.com.au/product/E-Cloth-Antibacterial-Cloth.html
Socks	AgActive	"Through a process of Nanometer Technique, our clothing destroys many of the bacteria, fungi and viruses that cause infection, odour, itchiness and sores".	http://www.healthychannels.com.au/
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/
Sports jacket	ASAT	"Nano Silver technology kills bacteria to virtually eliminate human odour. Anti-microbial formula requires no special activation and will not wash away in the laundry".	http://www.abbeyarchery.com.au/p/ASEBLZ3XL/ASAT+Elite+Extreme+Layer+Zip+Mock.html
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
Bed mattress	Therapedic	"The border fabric contains "Silver Nano Technology" – Traces of real silver, known for its anti-microbial and anti-static properties".	http://www.sleepytime.com.au/Therapedic-pg10573.html http://www.snuggle-inaustralia.com.au/Mattresses/Therapedic/Hourglass/tabid/94/Default.aspx
Refrigerator	Samsung	"Silver Nano particles coated on the inner walls of the refrigerator stop bacteria from multiplying, helping keep the inside of the refrigerator clean and hygienic".	http://www.samsung.com/au/consumer/home-appliances/refrigerator/side-by-side/RS23HDURS1/XSA/index.idx?pagetype=prd_detail
Vacuum cleaner	LG	"The hygienic Nano-Silver technology minimises the growth of bacteria in the dust container for a healthier environment".	http://www.lge.com.au/vacuum/download/Vacuum_Range_Brochure.pdf

Product	Manufacturer	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
Hair brush	Lady Jayne	"The Lady Jayne Salon Professional range has a unique gel grip handle for comfortable styling, ionic technology for strong, smooth hair and nano silver for its antibacterial agents".	http://www.beautyheaven.com.au/hair/hair-accessories/16137-brush-ceramic-radial
Hair straightener	Vidal Sassoon	"Nano silver – combines micro particles of ceramic and silver (antibacterial element) for enhanced shine and healthy looking hair"	http://www.vssassoon.com.au/lib/Products/straighteners/VS2085A/pdf/mf1596.pdf
Pool cleaner	Zodiac	"Silver Nano Technology for ultimate bacteria fighting capabilities".	http://www.zodiac.com.au/products/mineral-purification-systems/n2-express-mineral-purifier http://www.zodiac.co.za/product/351/nature2-express-swimming-pool-sanitiser
Paints and surface coatings	Bioni Hygienic	"Silver Nanoparticles in wall paint prevent the formation of mould inside buildings and the growth of algae on outside walls".	http://www.nanovations.com.au/Press%20Release/Paint%20technology%20from%20Nanovations.pdf
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 concern for me is that the widespread use of nanosilver in consumer products like socks, children's toys [and] keyboards has the potential to promote resistance within bacteria – so the powerful usage in the medical setting will be ruined."

Dr. Diana Bowman, Senior Research Fellow,
Melbourne School of Population Health at The University of Melbourne

"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

"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

"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

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