THE NANO STATE

Hotel rooms, subway cars, offices, airplanes, cruise ships: to most people, the air they breathe inside these places seems benign, if sometimes stuffy and stale. But viewed through the lens of public health, these shared environments sometimes teem with airborne pathogens.

Controlling infectious disease remains one of the most vexing problems in the field, and some of the toughest, most resilient bugs are the ones that survive in air. Among these are the viruses that cause influenza (with their constant mutations, a moving target for vaccines) and the mycobacterium behind tuberculosis (an increasingly drug-resistant agent that kills some 1.3 million people worldwide each year).

Shaw Nielsen

Can tiny engineered particles help protect us from infectious disease?

WATER NANODROPLETS PREVENT DISEASE?

Now imagine this: a fine mist of tiny engineered water nanodroplets—each 2,000 times smaller than the width of a human hair—that acts as an invisible shield against these germs.

At Harvard School of Public Health, associate professor of aerosol physics Philip Demokritou, who directs the Center for Nanotechnology and Nanotoxicology (www.hsph.harvard.edu/nano), and his research team have discovered an "engineered water nanostructure" (EWNS) that may offer a safe, cost-effective way to kill airborne pathogens. The two most common methods currently in use to remove pathogens from air—ultraviolet irradiation and high-efficiency particulate air (HEPA) filtration—are expensive and technologically complicated. Other chemical disinfection techniques, such as chlorine or bleach sprays, can be toxic and are almost impossible to deploy in public spaces.

"These engineered water nanostructures are simple to generate. You simply need water and electricity. You can create a shield of EWNS by generating them where you sit. It can be the interior of an airplane in front of your seat, or in your car," says Demokritou. "It has the potential to change the way we control airborne infectious disease."

"Sometimes," he adds, "thinking big requires thinking small."

SMALL BEHAVES DIFFERENTLY THAN BIG

For the past decade, scientists and the media have been hyping "nano"—the study of matter that is less than 100 nanometers in one dimension—as a transformative technology. Now researchers and industry have the ability to engineer and characterize these extremely small particles, and nanotechnology has become a major economic force in the 21st century.

These invisible structures behave differently than their larger counterparts, often strikingly so. Iron oxide loses its magnetism, gold turns red, and silver kills bacteria as particle size decreases. "We can come up with new

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advanced materials and technologies with specific properties," says Demokritou. "Nanotechnology has the potential to help address global problems from energy consumption and environmental remediation to diagnosis and treatment of disease."

RISKS OF GOING SMALL

Some of these new nanomaterials, if harnessed and used safely, may benefit society. But because the particles are so tiny—far smaller than a human cell—they may also penetrate biological barriers and trigger severe adverse health effects. For instance, many consumer products, from socks to toothbrushes, are coated with silver nanoparticles. Though these particles kill bacteria, they may also be toxic to human cells.

The properties of silver are well documented, but there are thousands of other nanomaterials—many already available in consumer products from snowboards and sunscreens to electronics and building materials—for which the risks and benefits are not fully known. For Demokritou, the question is how to help nanotechnology reach its full potential while still preserving public safety.

ONE-STOP SHOPPING

At the "NanoCenter," as it is called, Demokritou and his research group synthesize and study nano-bio interactions to build a fundamental understanding of why some are more toxic than others. They also hope to develop cheap, high-throughput screening methods to help industry more efficiently test the properties of new materials and discard the most dangerous ones. The NanoCenter tackles these problems with interdisciplinary teams of biologists, materials scientists, engineers, and physicists.

"The goal of the NanoCenter is one-stop shopping," says Joseph Brain, the Cecil K. and Philip Drinker Professor of Environmental Physiology at HSPH. "Center investigators can manufacture particles of different compositions, shapes, and sizes, fully characterize them, study how they attach to cells or disperse in the air, test them on animal models, do exposure assessment for humans and life-cycle analysis, and finally focus on risk assessment and risk communication. Our aim is an integrated, holistic approach."

Demokritou's group works closely with industrial partners such as BASF and Panasonic, which provide funding and pose real-world problems. This close relationship with industry is critical for ensuring the safety of nanotechnology. "We need to bring all stakeholders together: industry, researchers, regulators, and the public, in order to address the societal implications of nanotechnology," says Demokritou. Participating in early-stage industrial R&D allows his team to assess the possible uses and toxicological implications of new nanomaterials before they hit the market.

WATER ELECTROSPRAY PERSISTS FOR HOURS

Demokritou's discovery of a water nanostructure that kills common pathogens was published in the January 2014 issue of the *Journal of Environmental Science: Nano*, and was selected by the Royal Society of Chemistry as one of the most innovative research studies in 2013. It emerged from a well-known technique used in Demokritou's lab, called electrospray. By using a high-voltage electric current, it transforms any liquid—such as bleach—into airborne particles, allowing scientists to study its dispersion pattern and persistence. But Demokritou had never tried it with water alone and had never tried to reduce electrosprayed particles to the nanoscale sizes.

George Pyrgiotakis, a postdoctoral fellow in Demokritou's group who oversaw the experiments, used electrospray to create tiny droplets of water approximately 25 nanometers in diameter (about 10 times wider than a strand of human DNA). He was surprised to find that the tiny water particles persisted in the air for hours instead of evaporating immediately as expected. "It took us a year just to understand why," says Demokritou with a laugh. They discovered that each tiny droplet carries a negative electric charge, which increases the droplet's surface tension and thus slows evaporation.

They also learned that their tiny water droplets contained molecules called reactive oxygen species, or ROS, generated during the electrospray. These molecules can damage cell membranes and human DNA, sometimes leading to injury or even cancer.

Photograph by Kent Dayton / HSPH

The scientists wondered if the highly mobile EWNS could acts as nanobombs, delivering their ROS payload to airborne bacteria such as TB, rupturing their cell membranes and destroying them.

To test this idea, Pyrgiotakis sprayed the EWNS into a chamber containing a common airborne test bacterium called *Serratia*. Thirty minutes after shutting off the sprays, the bacteria were undetectable: the EWNS had destroyed them all.

Philip Demokritou, associate professor of aerosol physics and director of the Center for Nanotechnology and Nanotoxicology

KILLS BUGS, SPARES LUNGS

While the EWNS can't kill tough spores and aqueous biofilms and has not been tested on viruses, it has proven effective against the bacterium *Staphylococcus aureus*—a frequent (and sometimes fatal) cause of skin infection and respiratory disease—and against a mycobacterium similar to the one that causes tuberculosis. The EWNS technology also holds promise for killing foodborne pathogens, such as *E. coli* and *Salmonella*. Demokritou's group recently received a grant from the National Institute of Food and Agriculture, part of the U.S. Department of Agriculture, to investigate this application.

Most important, the same EWNS that damages and kills bacteria doesn't appear to harm the lungs of mice that breathed the mist for four hours. There was no evidence of lung injury or inflammation, and the animals' breathing patterns did not change when the EWNS was turned on and off. Indeed, the mice were unaware of the EWNS in the air. The scientists are not entirely sure why the lungs remain unscathed and say further research is needed.

"If you had to design an ideal agent that would kill bacteria and viruses, but leave no toxic residual material, this would be it," says Brain. "Now the key is making the technology more effective by increasing its lethality for diverse pathogens and scaling it up from small chambers to spaces typically occupied by humans or stored foods."

SAVING LIVES AND THE ENVIRONMENT

Disinfecting a hospital room or a truckload of apples with an EWNS mist might also consume far less energy and resources than any current system. Put simply, this promising environmental nanotechnology, while still at a conceptual stage, has the potential to be an efficient and chemical-free tool in the battle against pathogens.

According to Brain, "Nano's biggest public health contribution over the next 50 years may be decreased energy consumption because of better nano-enabled insulation, paints, and tunable windows and surfaces that would either reflect or absorb heat, depending on the weather. Transportation vehicles such as cars, trains, and planes would be lighter and stronger with composite materials containing nanoparticles and nanofibers. In turn, these technologies would reduce air pollution and CO2 emissions."

Ultimately, nanotechnology's most dramatic impact in public health may stem not just from doing something like disinfection better or cheaper, but from making our lives greener.

Barbara Moran is an award-winning science journalist and author, based in Boston. She received the 2011 National Association of Science Writers Science-in-Society Award.

For more on the NanoCenter's recent work, go to http://hsph.me/nano