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Feature: Chemistry,Nutrition

Nanoparticles in foods raise safety questions

These microadditives enhance color, flavor and freshness. But what do they do in the body?

By Susan Gaidos 1:28pm, October 16, 2015

NOSHING ON NANO Nanoparticles can make foods like jawbreaker candies brighter and creamier and keep them fresh longer. But researchers are still in the dark about what the tiny additives do once inside our bodies.

Magazine issue: Vol. 188, No. 9, October 31, 2015, p. 18

It seemed like a small thing when Paul Westerhoff's 8-year-old son appeared, with his tongue and lips coated bright white. The boy had just polished off a giant Gobstopper, a confectionery made of sugary, melt-in-the-mouth layers. Curious about the white coating, Westerhoff, an environmental engineer, pored over the jawbreaker's contents and discovered just how incredibly small the matter was.

Among the Gobstopper's ingredients were submicroscopic particles of titanium dioxide, a substance commonly added to plastics, paint, cosmetics and sunscreen. At the time, Westerhoff's lab group at Arizona State University was actively tracking the fate of such particles in municipal wastewater systems across the nation.

Titanium dioxide is also a food additive approved by the U.S. Food and Drug Administration. Ground to teensy particles measuring just tens of billionths of a meter in size — much smaller than a cell or most viruses — titanium dioxide nanoparticles are frequently added to foods to whiten or brighten color.

Weeks after his son's candy-coated encounter, Westerhoff went to the supermarket, pulled more than 100 products off the shelves and analyzed their contents. His findings, published in 2012 in *Environmental Science & Technology*, show that many processed foods contain titanium dioxide, much of it in the form of nanoparticles. Candies, cookies, powdered doughnuts and icing were among the products with the highest levels. Titanium dioxide is also found in cheese, cereal and Greek yogurt.

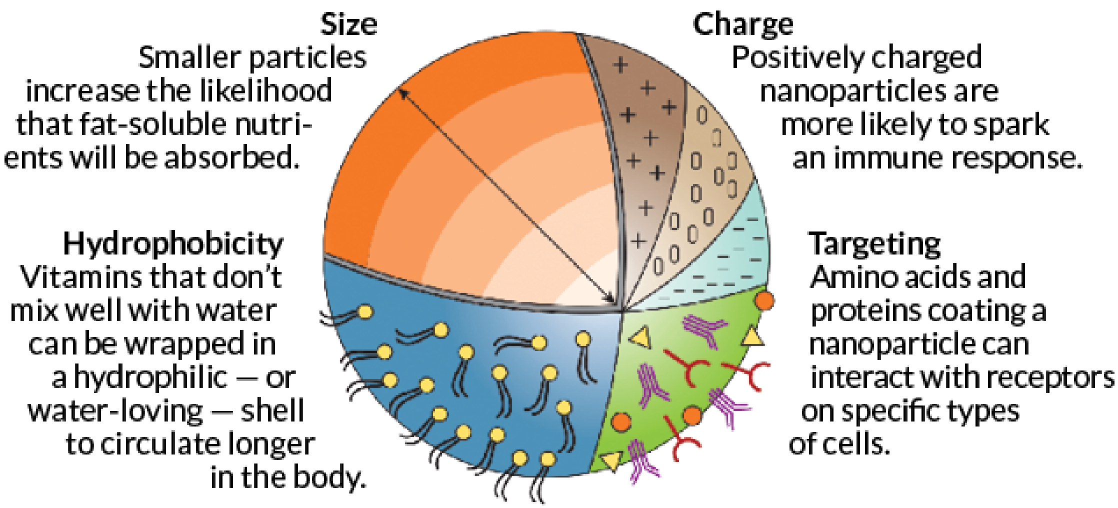
"I began to question why we care about things in the environment — at a few micrograms per liter in water

— if we’re freely ingesting these materials,” Westerhoff says.

Titanium dioxide isn’t the only nanoingredient added to food. Various other materials, reduced to the nanoscale, are sprinkled into food or packaging to enhance color, flavor and freshness. A dash of nano will smooth or thicken liquids or extend the shelf life of some products. Scientists have designed nano-sized capsules to slip beneficial nutrients, such as omega-3 fish oil, into juice or mayonnaise, without the fishy taste.

Story continues after diagram

Shaping behavior



By changing a nanoparticle’s size and surface characteristics, scientists can affect how the particle behaves in the body.

*Source: T. Borel and C.M. Sabliov/*Annu. Rev. Food Sci. Technol. *2014*

Food scientists aren’t stopping there. They are downsizing the structure of a wide array of ingredients with bold plans to help tackle obesity, malnutrition and other health issues (see “Nanocreativity,” below).

But as scientists cook up ways to create heart-healthy mayo and fat-fighting ice cream, some are also considering the potential risks that might accompany the would-be benefits. Because of their small size, ingested nanoparticles may interact with cells or behave differently than their bulkier counter-parts. So far, less-than-perfect laboratory studies offer contradictory results.

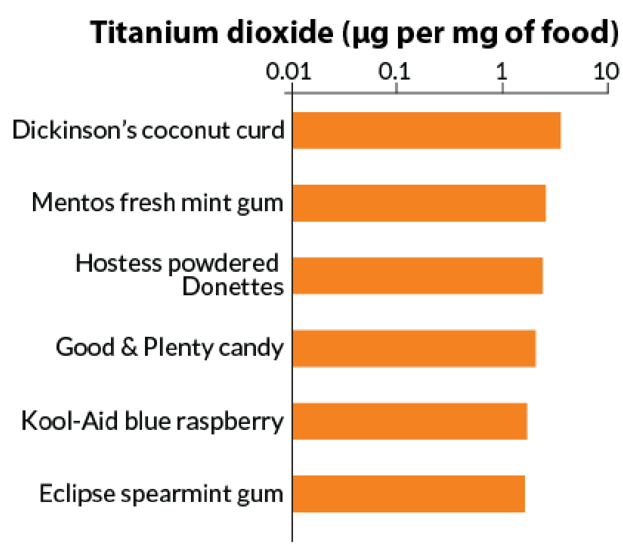
Researchers, including those developing nanofoods, say more information is needed on the ingredients’ potential impacts. Current studies, limited to mice or lab dishes, often analyze megadoses of particles far beyond what any normal diet would include. Scientists need a better handle on what happens when people nosh on nanolaced foods daily, taking in small doses at a time, says Ohio State University pathologist James Waldman. He and others are devising tests to find out.

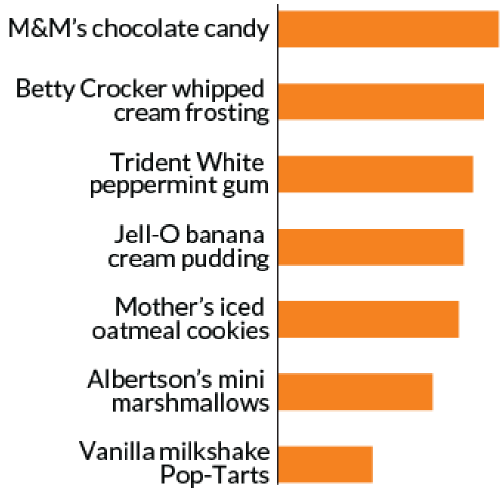
A pinch of nano

Over the last two decades, nano-sized components — smaller than 100 nanometers — have found their way into a wide range of products: clothing, electronics and cosmetics as well as food. But people have been exposed to, and have inevitably ingested, nanoparticles for much longer, says Andrew Maynard, director of the Arizona State University Risk Innovation Lab in Tempe. Since prehistoric times, people have been consuming nanoparticles found in natural foods such as milk (casein micelles, for example, are nano-sized particles that help calves readily digest their mother's milk). Nanoparticles also creep into the food supply from environmental sources. Burning wood, oil and coal; wildfires; volcanic activity; and crashing of ocean waves release ultrasmall particles of metal, carbon or silica into the atmosphere and into the food chain.

Whiter whites

Titanium dioxide is found in many foods. Tests show that on average more than one-third of the titanium dioxide in foods is in the form of nano-sized particles.





Source: A. Weir et al/Env. Sci. Tech. *2012*

Even with this long history of nanoparticle exposure, Maynard says, it's highly unlikely that people had been eating the kinds of particles added to foods today. The distinction is important, he says. "Our bodies have always been exposed to nanoparticles, but they're now being exposed to different types. We just need to make sure that our bodies can deal with the ones we're putting in food."

What makes particles different today is not only their size, but also their specificity. The amino acids and proteins that coat a nanoparticle determine its shape and surface properties, which can enhance or reduce the particle's propensity to bind to certain molecules. By fine-tuning surface features, scientists can control where or how quickly nanoparticles release their contents.

So far, only a few nanoingredients are added directly to foods or packaging: Titanium dioxide, silicon dioxide and zinc oxide are the most common. Larger versions of these ingredients have been used in food and medicines for decades and are considered "generally recognized as safe" by the FDA, which requires that any substance added to food be evaluated for safety.

Unexpected interactions

Scientists have developed numerous ways to test the safety of substances that go into food, but most of the tests were designed decades ago, before ingredients began to go nano. Titanium dioxide, for example, was evaluated in the late 1960s, using particles larger than 100 nanometers. Human cells were exposed to the substance to test for toxic effects and to work out how much of it can be safely consumed.

But those safety tests may not apply to some nano-substances. Size and surface features can improve or impair a nanoparticle's ability to enter cells. Some nanoparticles — including those considered safe by the FDA — interact with cells in odd or unexpected ways, according to several recent studies.

One study, published in April in the journal *Small*, examined the effects of silicon dioxide, titanium dioxide and zinc oxide on cells taken from the human intestinal lining. At high doses — higher than most people would ordinarily consume — all three nanoparticle types damaged DNA, proteins and lipids in the cells. Zinc oxide proved to be the most toxic. Lower levels of exposure to nanozinc oxide impaired certain proteins, such as those that help cells repair DNA damage; higher levels of the substance led to cell death.

Though it's not yet clear if nanoparticles of these types would have toxic effects in the human gut, Gretchen Mahler of Binghamton University in New York says the findings show the difficulty of classifying a particular type of nanoparticle as toxic or safe. Many studies, she says, expose cells to very high levels of nanoparticles, focusing on the effects of a few large exposures or looking for signs of extreme cellular stress or cell death. She questions whether those safety tests are appropriate for nanomaterials.

Mahler's lab group aims to pin down nanoparticles' more subtle effects on the intestine using amounts that a person might consume in a single meal or day. Rather than just examining whether the cells exposed to nanoparticles are alive or dead, she evaluates whether they function the same way as unexposed cells.

In a series of experiments, Mahler set out to see what happens in the gut after a steady stream of small

In a series of experiments, Mahler set out to see what happens in the gut after a steady stream of small doses, the kind you'd get if you were eating nanoparticle-enriched foods daily. Working with scientists at Cornell University and the U.S. Department of Agriculture, she developed a three-dimensional model of the intestinal tract, composed of the various cells that line the human gut. The scientists tracked the effects of polystyrene nanoparticles on the cells and on the intestinal linings of live chickens. Though polystyrene, a polymer, is not used in food products, Mahler says the particles were ideal for testing because they can fluoresce, making them easy to track once swallowed.

The results, published in 2012 in *Nature Nanotechnology*, showed that small doses of the polystyrene nanoparticles created changes in the fingerlike projections that cover the surfaces of the intestine-lining cells. These tiny structures, called villi, are important for absorbing nutrients. After initial ingestion of nanoparticles, iron absorption dropped by almost 50 percent. But in chickens fed over a period of two weeks, iron absorption rose about 200 percent. Over time, the villi became larger, allowing more iron to enter the bloodstream.

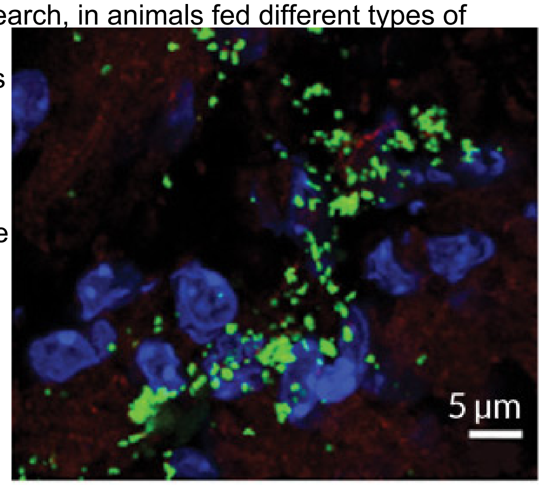
Mahler's lab used the same approach to study how nanoparticles of titanium dioxide and silicon dioxide influence nutrient absorption in human cells in the lab. Preliminary results from the studies, presented in March at the Society of Toxicology annual meeting in San Diego, indicate that titanium dioxide nanoparticles in the gut change the way iron is absorbed, and silicon dioxide nanoparticles alter zinc absorption. Mahler's group is working to piece together the mechanism by which these nanoparticles disrupt absorption in the small intestine.

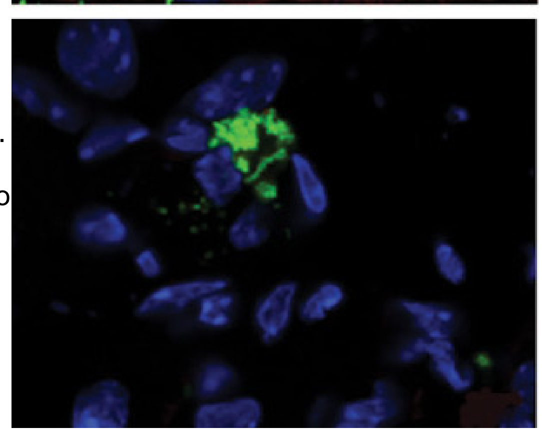
Down the hatch

Most studies of nanoparticles in food focus on the gastrointestinal tract — the mouth, esophagus, stomach and intestines. Waldman's group at Ohio State is tracking the fate of nanoparticles once they're swallowed to see if they travel beyond the gut. In February, the researchers showed that nanoparticles force-fed to mice can reach the liver, kidneys, lungs, brain and spleen. Details were published in the *International Journal of Nanomedicine*.

"Particles are getting into the bloodstream, and once they're there, they can go to any other organ," Waldman says.

The findings were not entirely a surprise, he says. In earlier research, in animals fed different types of nanoparticles, the particles were later detected in organs. But previous studies relied only on crude methods, removing organs and digesting them in acid to look for the tiny particles.

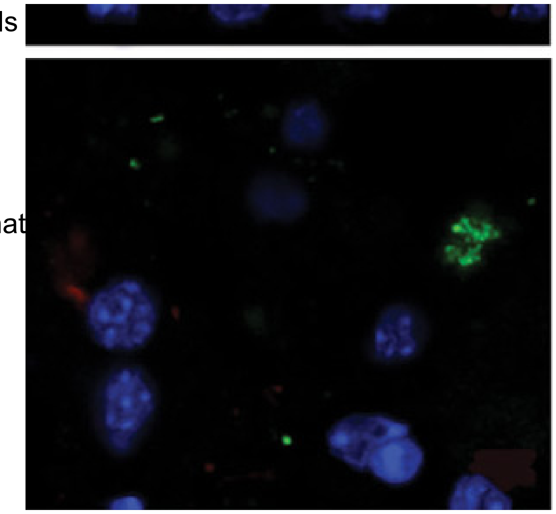




To see where nanoparticles accumulate in live animals, Waldman's group created a nanoparticle filled with quantum dots that fluoresce (*SN: 7/11/15, p. 22*). Working with Ohio State chemist Prabir Dutta, Waldman's group designed particles with outer shells nearly identical to a food-grade nanosilicon dioxide. Because the surface of the particle is what interacts with a cell, the scientists buried the fluorescent molecules inside the silica shell. By doing so, they could ensure that it was silicon dioxide — not the fluorescent tag — interacting with the cell.

The method allowed the scientists to see where the material goes once it enters the body and then count the number of particles actually absorbed. Waldman says that knowing the path that tiny nanoparticles take is essential for settling questions about their potential risk and impact on human health. Scientists need to know, for example, if a particle will be absorbed into the bloodstream and where it will travel. They also need to know if it will stay or be cleared.

Waldman's group plans to incorporate the fluorescent nanoparticles into the mice's chow so they consume them regularly in their food. Every few weeks, the scientists will run tests to see where the particles accumulate and assess the animals' tissues for inflammatory responses and nanoparticleassociated injury. The study will include newly pregnant animals to determine if the particles from food reach cells in the developing fetus.



Fluorescent nanoparticles (green) force-fed to mice found their way beyond the stomach (top) to the kidneys (center) and brain (bottom).
A. Zane et al/int. J. Nanomed. 2015

Chew on this

The FDA has not erected new hoops for food manufacturers that use nanoparticles. Requests to use a food ingredient at the nanometer scale are subject to the same safety requirements applied to other food additives, according to FDA press officer Megan McSeveney. Manufacturers must demonstrate that the substance is safe under the conditions of its intended use.

In June 2014, the agency issued guidelines that go only as far as advising manufacturers to consult with the government before launching nanotechnology products.

So food scientists who are developing futuristic applications are scrambling to assess the safety of their downsized substances. At the University of Massachusetts Amherst, food scientist David Julian McClements is creating nanoparticles using natural ingredients, such as casein micelles from milk or plant proteins, to encapsulate everything from vitamins and antioxidants to omega-3 fatty acids and probiotics.

Once they create a new particle, McClements and colleagues run a gamut of tests to see how the particle reacts in cells in the lab and in mice. Because the nanoparticles he studies are made from ingredients normally found in the human diet, the particles tend to break down during digestion in ways similar to foods. Such particles are expected to be safer than particles made of nonbiodegradable materials, such as titanium dioxide, McClements says. Still, such tests are needed before bringing new foods to the market.

Waldman and Mahler say that to realistically reflect what is happening with people, scientists need to conduct long-term studies, in both animals and people. By feeding animals low doses of a particle over several months' time, researchers should be able to spot potential problems.

“I would study the animal's overall health. If something specific is found, then you can zero in on that particular effect, that organ, that system,” Waldman says.

Ultimately, epidemiological studies — designed to track peoples' intake of nanoparticle-laced foods over extended periods of time — would be most informative, the scientists say. The ideal would be to track large groups of people who consume many foods containing nanoparticles and those who eat fewer nanoparticles, monitoring their health over months or years.

Waldman says studies should include individuals with intestinal diseases and pregnant women — groups that could be more vulnerable to any potential effects. People who have inflammatory bowel disease — in which the intestinal wall is “leaky” — may be at higher risk of nanoparticles getting into circulation and reaching other tissues, he says.

Meanwhile, scientists agree that, based on studies to date, the nanofoods found on supermarket shelves are probably safe to eat — when consumed at “typical” quantities. A few nanolaced cookies probably won't do harm.

Waldman says he doesn't avoid eating foods containing nanoparticles. Westerhoff, whose son devoured the Gobstopper, agrees. Food nanotechnology actually makes food better, he says, “giving chocolate a smooth, creamy texture or preventing dry ingredients from clumping.”

Still, skeptical consumers, who cannot always find nanoparticles listed on ingredient labels, want to be assured that the additives are safe. While nanotechnology offers new ways of transforming the features of food, creating safer, more nutritious fare, McClements says, scientists must find ways to demonstrate the safety of new types of nanoparticles before they are brought to market. “As with any new technology, you have to be cautious about how you use it and understand what's going on.”

Nanocreativity

Cristina Sabliov, a bioengineer at Louisiana State University, says food manufacturers are experimenting with loading tiny particles with nanonutrients and fine-tuning the surface of the particles to customize where and how the contents are released in the body. At the University of Massachusetts Amherst, food scientist David Julian McClements is building nanocrystals of proteins found in milk or derived from plants that can be loaded with beneficial components tailored to meet different needs. Among the items now in development:

Vitamins that hit the spot. Sabliov's lab is developing microscopic delivery systems for vitamins. For example, she is wrapping vitamin E within tiny spheres designed to travel unimpeded through the stomach's acidic environment before breaking down in the small intestine. Adding certain enzymes to a particle's surface allows it to adhere to cells in the intestinal wall for better absorption.

Food with less salt and sugar. Capsules of nanoparticles that dissolve in the mouth, latching on to the tongue's taste receptors to deliver bursts of flavor, may mean foods with less salt or sugar can still be tasty.

Nutraceutical delivery. To improve uptake of two nutrients that are hard for the body to absorb, lycopene and carotene, McClements is suspending them in liquid nanodroplets to deliver digestible doses in beverages, desserts and yogurts.

Suppress the appetite. To keep hunger pangs at bay and encourage people to eat less, diet foods are being fortified with nanoparticles that break down slowly, or that deliver peptides — such as pancreatic polypeptide or peptide YY — that signal fullness.

Age-specific foods. To deal with reduced stomach acid levels in the elderly, food products are fortified with vitamin-filled particles that break apart quickly in the presence of lower-than-normal levels of acid.

Beneficial bacteria. Food scientists are inserting teensy portions of probiotics into particles crafted to remain intact until they reach the colon. — *Susan Gaidos*

This article appears in the October 31, 2015, Science News *with the headline, "Noshing on nano: The tiny particles in what we eat raise big questions."*

Editor's Note: The story was updated on October 20, 2015 to add a label to the Whiter whites bar chart.

Citations

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