Biochemist, physicist team to see antibacterial TCS deform mitochondria

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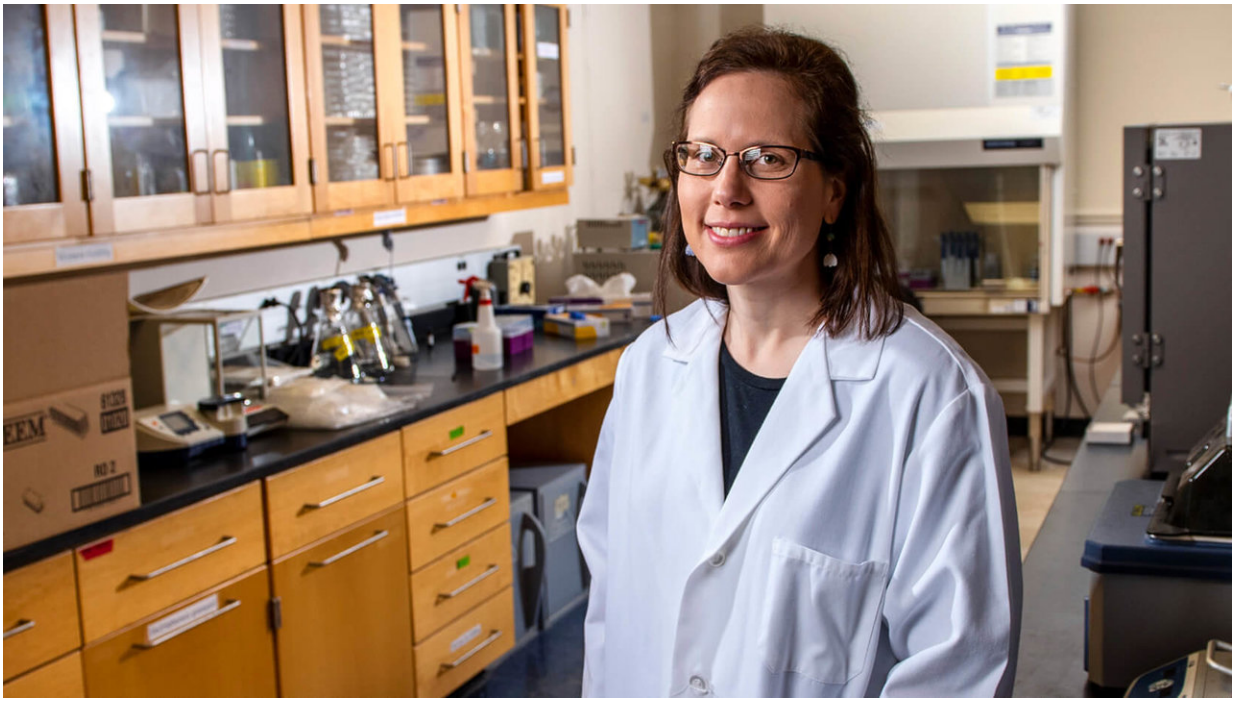

Credit: University of Maine

Grocery shopping can be an illuminating chore for a toxicologist.

Julie Gosse, a University of Maine associate professor of molecular and biomedical sciences, has scanned the supermarket aisles for products that contain triclosan (TCS), a synthetic antibacterial agent.

Since the '90s, TCS has been in a slew of consumer products, including facial cleansers, toothpaste, mouthwash and hand sanitizers.

For years, Gosse has studied TCS, which for decades also has been used as a hospital scrub to reduce risk of infection.

She became interested in examining triclosan when listening to a talk by Environmental Protection Agency scientist Susan Richardson and noting that the molecular structure of TCS resembles the molecular structure of dioxins, which are toxic environmental pollutants.

In 2016, the Food and Drug Administration banned triclosan from consumer bar soaps, liquid soaps and body washes. At that time, the FDA challenged manufacturers to either prove TCS was more effective at killing germs than plain soap, or to remove it from their soap product within a year.

The antimicrobial agent, which is readily absorbed into the skin and the lining of the mouth, has recently been found to have detrimental effects on human fertility, development, thyroid function and immunology, and has been associated with increased occurrence of asthma.

Then, about six months ago, the FDA also announced a ban on products such as hand washes and antiseptic rubs containing TCS that are used in medical settings.

There's no such ban on Colgate Total, the popular toothpaste that contains TCS. That's because it's been found to be more effective at treating gingivitis than toothpaste without it.

Gingivitis is an important health concern as it can lead to tooth loss. And research has indicated the bacteria that causes periodontitis can enter a person's bloodstream and harm the heart and lungs.

Gosse understands why people with gingivitis would use Colgate Total; she just wants millions of people without gingivitis who also use the product to be aware of possible risks.

"Our job is to do the best science we can do and make people aware," she says. "As scientists, we communicate our findings, and the public or companies or government decides what they should do."

Triclosan also remains in certain "antibacterial" products not under the FDA's control—such as cutting boards and baby products.

In various studies, Gosse and colleagues have made multiple discoveries about TCS. In conducting their research, they've used TCS dosages that correspond to doses people are exposed to when brushing their teeth or showering with products that contain the antimicrobial.

One discovery is that TCS is a mitochondrial uncoupler. That is, it's toxic to mitochondria, which are the energy powerhouses of cells. When mitochondria are deformed or shut down, they can't make the energy that cells need to perform functions—including immune defense.

One study outside of UMaine found increased TCS levels in mothers of babies with birth defects. Another study, also outside of UMaine, indicated mitochondrial dysfunction was linked to cognitive decline in monkeys.

Gosse determined TCS is 30 to 60 times more toxic than 2,4-dinitrophenol, another uncoupler once used in diet drugs (and to make explosives) that was banned in the late 1930s because it resulted in death or severe side effects.

In UMaine's most recent study, the team sought to determine the mechanisms underlying TCS disruption of mitochondrial function and

mast cell signaling.

To do so, Gosse and her doctoral student Lisa Weatherly teamed with professor of physics Sam Hess and his doctoral student Andrew Nelson.

Hess invented a fluorescence photoactivation localization microscopy (FPALM) technique that allows researchers to witness triclosan's deformation of live cells' mitochondria, in real time.

Mitochondria are generally an elongated oval shape. TCS either deforms mitochondria from an oval to a doughnut shape or breaks up the energy powerhouses, within minutes.

Gosse has pored through conference proceedings and publications and believes the UMaine team is the first to use super-resolution microscopy work in the field of toxicology.

Following up on the microscope findings, Gosse and her team determined the biochemical mechanisms that underlie triclosan's fission of mitochondria—including generation of damaging reactive oxygen species.

TCS, says Gosse, also inhibits cellular cytoskeletons, which are microscopic networks of protein filaments and tubules in the cytoplasm of living cells. Cytoskeletons help the cell move, transport cargo, and carry out many other tasks essential for health.

When TCS inhibits cytoskeletons, it inhibits mast cell function. Mast cells are part of the immune and nervous systems that, when stimulated, release chemicals that play many roles in the body, including antimicrobial defense, cancer and even emotional regulation.

Mast cells are in most human tissues, including the lining of the mouth

and in skin—both of which absorb TCS. So, when mast cells are inhibited, problems may arise.

The Gosse lab also found that, of several cell types tested, primary human skin cells were the cells most harmed by TCS.

The UMaine team's most recent findings were published in April in the article "Antimicrobial agent triclosan disrupts mitochondrial structure, revealed by super-resolution microscopy, and inhibits mast cell signaling via calcium modulation" in *Toxicology and Applied Pharmacology*.

In addition to Gosse, Hess, Weatherly and Nelson, UMaine researchers participating in the study included graduate students Juyoung Shim and Andrew Hart and undergraduates Erik Gerson and Abigail Riitano; as well as Timothy Ryan and Jaime de Juan-Sanz of Weill Cornell Medicine; and Roger Sher of Stony Brook University.

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Thanks to research conducted by Gosse and other scientists, consequences of exposure to triclosan are becoming better understood and known.

And thanks to Hess' FPALM technique, the field of toxicology has a powerful new tool for understanding chemical effects on human health.

Triclosan, though, is one of about 80,000 synthetic chemicals that people are regularly exposed to, says Gosse. And many of their long-term

effects have not been studied.

More information: Lisa M. Weatherly et al. Antimicrobial agent triclosan disrupts mitochondrial structure, revealed by super-resolution microscopy, and inhibits mast cell signaling via calcium modulation, *Toxicology and Applied Pharmacology* (2018). DOI: 10.1016/j.taap.2018.04.005

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