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Phone: +1 646 783 7100 | Fax: +1 646 783 7161 | customerservice@law360.com

What Manufacturers Should Know About Triclosan Findings

By **Doug Pfeifer, Richard Morgan and Brent Kerger**
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Doug Pfeifer


Richard Morgan


Brent Kerger

In late May of 2018, a group of American and Chinese researchers headed by scientists from the University of Massachusetts Amherst published a study in Science Transitional Medicine suggesting that triclosan, a common antibacterial agent, can promote colonic inflammation and colon cancer in mice when ingested at what the authors deemed normal human exposure levels from using certain consumer products such as toothpaste.[1]

Over this past summer, the mainstream media as well as numerous health-related internet websites jumped on the study, with bold headlines stating that triclosan may harm the gut and fuel cancer — but did so in many cases without citing the limitations of the study.

Sensational headlines often grab the attention of the bar as well as that of manufacturers. But what does the study really say — and is it ready for the courtroom?

What Is Triclosan?

Triclosan is a prevalent antibacterial and antifungal agent in consumer products such as clothing, furniture, cosmetics, medical devices, deodorant, kitchenware and a variety of other products including toothpaste and mouthwash. Due to its widespread use and moderate persistence, triclosan has been cited as a common wastewater contaminant.

In a 2003-2004 study, the U.S. Centers for Disease Control and Prevention found triclosan in the urine of 75 percent of the study participants, reflecting the common occurrence of background exposures in the general population. In September 2016, the U.S. Food and Drug Administration banned the use of triclosan in over-the-counter consumer antiseptic washes, including antibacterial soaps, hand washes and antibacterial body washes, because manufacturers did not demonstrate that triclosan is both safe for long-term daily use and more effective than plain soap and water.[2]

The FDA did not ban triclosan in toothpaste, as there is scientific evidence that it aids in reducing plaque and gingivitis.[3]

What Does the Study Say?

The 2018 study by Haixia Yang and colleagues summarized a complex series of related studies that examined effects of triclosan administration on gut bacteria, colitis and colon cancer in mice. The mice used in the study were fed triclosan in an amount intended to cause blood plasma concentrations of triclosan similar to those of humans who used triclosan containing toothpaste as part of a Swedish study.

The authors reported that significant low-grade colonic inflammation and associated colitis pathology was observed in mice fed 80 ppm triclosan in feed for 3 weeks, but not at 10 ppm. A chemical-induced mouse colitis model was used to show that similar triclosan feeding worsened the colitis pathology at 80 or 10 ppm in feed, but not at 5 ppm.

Triclosan at 80 ppm in feed was also reported to significantly increase colon cancer in the chemical-induced mouse colitis model with addition of a known colon carcinogen (azoxymethane), but 10 ppm did not induce a significant response. The authors also observed significant changes in the distribution of gut microflora and increased intestinal permeability with triclosan treatment at 80 ppm, and that inflammation-triggering receptors in mice (an important one for ulcerative colitis is known as Toll-like receptor 4 or TLR4) were activated in vitro by blood plasma from mice treated with 80 ppm triclosan.

They also reported that germ-free mice (lacking normal gut microflora) and mice genetically modified to remove TLR4-triggered inflammation exhibited significantly less colitis pathology from 80 ppm triclosan in feed compared to wild type mice in the chemical-induced mouse colitis model.

The authors concluded that triclosan could cause adverse effects on colonic inflammation and colon cancer in mice through modulation of the gut microbiota and TLR4 signaling. Although the authors did acknowledge there were “challenges” in translating their mouse study findings to humans, given the uncertain relevance of the testing protocols, they did posit relatively strong statements indicating potential colitis and colon cancer risks to humans following “brief exposures” to triclosan “at relatively low doses.”

Their context for the doses they used being comparable to current consumer exposures (orally) was based on a human volunteer study by Swedish researchers that reported no effects of triclosan on liver enzyme activity or thyroid hormones following toothpaste-related exposures at plasma concentrations up to 296 ng/g.[4] Perhaps most importantly, Yang and colleagues showed in several experiments with mice that the pathological effects of triclosan on the colon are not observed at lower dietary doses more plausibly encountered with use of consumer products containing this antimicrobial agent.

The positive responses with triclosan in mouse colitis and colitis-colon cancer models at high doses may have no toxicological importance in humans. As reviewed by Belgian researchers, 85 percent of bacteria found in the mouse gut microbiota are not present in humans, and each of the mouse models for colitis and colon cancer has important limitations in understanding or predicting human disease risks.

For example, mice have at least 10-fold greater gastrointestinal surface area relative to body size when compared to humans — inferring enhanced potential for colitis, as illustrated by description of some 60 different mouse colitis models in available literature.[5] In addition, given the limited and intermittent nature of human ingestion exposures to triclosan (e.g., from toothpaste and mouthwash) and the absence of critical responses at lower doses of 5 to 10 ppm that better represent such human exposures

to the colon, the conclusions of Yang and colleagues may be somewhat overstated. Thus, additional research in human populations is needed to help gauge the toxicological implications of their mouse model findings.

What Does This Mean for Manufacturers?

While the study is sure to generate interest, we suspect it is unlikely to find its way into the courtroom in its present state. As described above, the study raises more questions than it answers, and may not directly correlate to humans.

Researchers recognize that although mice are commonly used in studies, they are in many cases poor models of how humans will actually respond in certain situations.[6] In fact, one toxicologist suggested that tossing a coin may give better results than using mice to predict effects on humans.[7]

Further, the Amherst study has limited application. The amount of triclosan ingested by the mice was intended to cause blood plasma concentrations of triclosan similar to those of humans who used triclosan containing toothpaste, and was not intended to mimic triclosan exposure via other means. Currently there is only one toothpaste in the U.S. market that contains triclosan.

These limitations should not go unnoticed by any court presented with the study. Though exceptions always exist, federal courts have historically recognized, and continue to recognize, the unreliability of extrapolating animal studies to humans without validation from other sources, including human epidemiologic studies.[8] Presently, that validation does not appear to exist for the Amherst study; however, the interest generated by the authors' strongly-stated conclusions is likely to prompt further investigation into the relationship, if any, between triclosan and gut health.

Therefore, it is recommended that manufacturers of products containing triclosan continue to monitor emerging studies, especially human-based studies, that may more directly apply to triclosan-containing products on the market today and their relationship to gut health.

Douglas L. Pfeifer and Richard G. Morgan are partners at Bowman and Brooke LLP. Brent Kerger, PhD., DBAT, is a principal scientist at Exponent Inc.

[1] Haixia Yang et al., A Common Antimicrobial Additive Increases Colonic Inflammation and Colitis-Associated Colon Tumorigenesis in Mice, 10 Sci. Transl. Med. eaan4116 (May 2018)

[2] Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use, 81 Fed. Reg. 61106 (Sept. 6, 2016).

[3] U.S. Food & Drug Administration, 5 Things to Know About Triclosan (Dec. 19, 2017), https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm205999.htm.

[4] Mats Allmyr et al., Human Exposure to Triclosan Via Toothpaste Does Not Change CYP3A4 Activity of Plasma Concentrations of Thyroid Hormones, 105 Basic Clin. & Pharmacol. & Toxicol, 339-344 (2009).

[5] Thi Loan Anh Nguyen et al., How informative is the mouse for human gut microbiota research? 8(1) Dis Models Mech 1-16 (2015).

[6] Junhee Seok, et al., Genomic Responses in Mouse Models Poorly Mimic Human Inflammatory Diseases, 110 Proc. Natl. Acad. Sci. U.S.A. 3507-12 (2013).

[7] “Mice predict the effect on humans with about 43 percent efficiency, so sometimes it would seem that tossing a coin would give better results.” Dr. Thomas Hartung, Director of the Center for Alternatives to Animal Testing at Johns Hopkins University in Baltimore. Animal Testing, Scripps Howard News Service Special Report, Spring 2011.

[8] See, e.g., In re Zoloft Products Liability Litigation, 26 F. Supp.3d 466 (E.D. Penn. 2014) (“courts caution against direct extrapolation from cellular and animal studies to humans, because where sound epidemiological data do not exist, or the epidemiological research produces results inconsistent with the animal research, ‘the rate of error is likely to be quite high’”) (citing Raynor v. Merrill Pharm. Inc., 104 F.3d 1371, 1375 (D.C. Cir. 1997)).