Promotional Consideration: A Potential Mechanistic Link between Neonicotinoid Insecticides and Hormone-Dependent Breast Cancer

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Neonicotinoid insecticides have famously come under fire for harming honey bees.¹ In a study of human cell lines published in *Environmental Health Perspectives*, researchers showed that two neonicotinoids, thiacloprid and imidacloprid, may also activate excess estrogen production in breast tissue by altering promoter activity.² If confirmed, this would make thiacloprid and imidacloprid emerging candidates for the growing list of endocrine-disrupting chemicals (EDCs).³

In hormone receptor–positive breast cancer, which accounts for more than 80% of cases,⁴ increased production of estrogen in the tumor microenvironment helps spur the growth of cancer cells. A key regulator of this process is production of the enzyme aromatase, which may be controlled by four different promoters in the *CYP19* gene.^{5,6} The activity of the different *CYP19* promoters differs between breast cancer cells and normal breast tissue; the most common promoter, I.4, is less likely to be active in cancer cells, while the other three promoters are more likely to be active.⁷

In the new study, the investigators showed that the Hs578t breast cancer cell line is able to use all four promoters. Without

insecticide exposure, the cells were more likely to express aromatase via the I.4 promoter. But exposure to either thiacloprid or imidacloprid induced a pattern of promoter activity seen in breast cancer cells and increased the catalytic activity of aromatase.

“This provides *in vitro* evidence that neonicotinoids can be endocrine disruptors and that aromatase may be one of their targets,” says first author Élyse Caron-Beaudoin, a recent PhD graduate who is now at the University of Montréal. “Importantly, the promoter switch happens at concentrations that are highly relevant to humans.” Comparable concentrations have been detected in North American water⁷ and soil⁸ samples as well as in the urine of farmers⁹ and women¹⁰ in Japan.

Aromatase, which converts androgens to estrogens, is a key enzyme in breast cancer, especially for postmenopausal women. Commonly prescribed drugs for reducing the risk of progression or recurrence of breast cancer include aromatase inhibitors.¹¹ That was one reason why Caron-Beaudoin and senior author Thomas Sanderson, an associate professor of toxicology at the National Institute of Scientific Research in Laval, Québec, studied the effect of neonicotinoids on aromatase expression.

Neonicotinoid insecticides are widely used around the world. New *in vitro* evidence indicates the potential for neonicotinoids to play a role in hormone-dependent diseases. But far more research is needed to determine whether human health risks actually exist. Image: © venusvi/Shutterstock.

According to Martin van den Berg, the discovery of a chemical that induces a cancer-related promoter switch in an *in vitro* system is remarkable. “This is a significant accomplishment, especially since neonicotinoids are among the most widely used pesticides in the world,” says van den Berg, a professor of toxicology at the University of Utrecht, the Netherlands, who was not involved in the study. “We do not know much about their toxicity in humans because they were developed to kill insects. But the new findings warrant more detailed risk assessment studies in human populations.” Such studies could be of particular relevance for regularly exposed people, such as farm workers and pesticide applicators.

For Andrea Gore, a professor of pharmacology and toxicology at the University of Texas at Austin, the research strategy has two noteworthy features. “One is its focus on a hormone-converting enzyme, rather than the hormone receptor systems pursued by traditional EDC studies,” says Gore, who also was not involved in the study. “The other is that it relates exposures to the most relevant functional outcomes—not just gene expression, but the actual catalytic activity of the enzyme, which is the key physiological end point for understanding the effects of environmental chemicals.”

In fact, Sanderson believes that the cell line used in this study, Hs578t, is a promising new screening tool for other environmental contaminants. “Hs578t has not been extensively studied in the past, but it is a great model for aromatase expression, because we now know that all four breast tissue-specific *CYP19* promoters are active in this cell line,” he says. “This means we can evaluate other conditions that may inhibit or induce the promoter switch.”

Sanderson is now developing a coculture model of Hs578t estrogen-producing cells and breast epithelial cells that express the estrogen receptor. With this model, he can study neonicotinoids in an environment more similar to actual breast cancer tissue. He can also test whether signaling pathways involved in new blood vessel growth regulate aromatase in concert with the *CYP19* promoters, as suggested by the present study.

“The coculture may also suggest new ways of blocking the pathways that cause the overproduction of estrogen,” Sanderson says. “Since the use of multiple tissue-specific *CYP19* promoters is unique to humans, I believe this *in vitro* assay has greater *in vivo* relevance than rodent models.”

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