High risk of Parkinson's disease for people exposed to pesticides near workplace

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In April 2009, researchers at UCLA announced they had discovered a link between Parkinson's disease and two chemicals commonly sprayed on crops to fight pests.

That epidemiological study didn't examine farmers who constantly work with pesticides but people who simply lived near where farm fields were sprayed with the fungicide maneb and the herbicide paraquat. It found that the risk for Parkinson's disease for these people increased by 75 percent.

Now a follow-up study adds two new twists. Once again the researchers returned to California's fertile Central Valley, and for the first time have implicated a third pesticide, ziram, in the pathology of Parkinson's disease. Second, instead of looking just at whether people lived near fields that were sprayed, they looked at where people worked, including teachers, firefighters and clerks who worked near, but not in, the fields.

They found that the combined exposure to ziram, maneb and paraquat near any workplace increased the risk of Parkinson's disease (PD) threefold, while combined exposure to ziram and paraquat alone was associated with an 80 percent increase in risk. The results appear in the current online edition of the *European Journal of Epidemiology*.

"Our estimates of risk for ambient exposure in the workplaces were actually greater than for exposure at residences," said Dr. Beate Ritz, senior author and a professor of epidemiology at the UCLA School of Public Health. "And, of course, people who both live and work near these fields experience the greatest PD risk. These workplace results give us independent confirmation of our earlier work that focused only on residences, and of the damage these chemicals are doing."

In addition, Ritz noted, this is the first study that provides strong evidence in humans that the combination of the three chemicals confers a greater risk of Parkinson's than exposure to the individual chemicals alone. Because these pesticides affect different mechanisms leading to cell death, they may act together to increase the risk of developing the disorder: Those exposed to all three experienced the greatest increase in risk.

"Our results suggest that pesticides affecting different cellular mechanisms that contribute to dopaminergic neuron death may act together to increase the risk of PD considerably," said Ritz, who holds a joint appointment in the UCLA Department of Neurology.

Scientists knew that in animal models and cell cultures, such pesticides trigger a neurodegenerative process that leads to Parkinson's, a degenerative disorder of the central nervous system that often impairs motor skills, speech and other functions and for which there is no cure. The disease has been reported to occur at high rates among farmers and in rural populations, contributing to the hypothesis that agricultural pesticides may be partially responsible.

In the past, data on human exposure had been unavailable, largely because it had been too hard to measure an individual's environmental exposure to any specific pesticide.

"This stuff drifts," Ritz said. "It's borne by the wind and can wind up on plants and animals, float into open doorways or kitchen windows - up to several hundred meters from the fields."

So several years ago, Ritz and her colleagues developed a geographic information system - based tool that estimates human exposure to pesticides applied to agricultural crops, according to the distance from fields on which pesticides are sprayed. This GIS tool combined land-use maps and pesticide-use reporting data from the state of

California. Each pesticide-use record includes the name of the pesticide's active ingredient, the amount applied, the crop, the acreage of the field, the application method and the date of application.

From 1998 to 2007, the researchers enrolled 362 people with Parkinson's and 341 controls living in the Central Valley, then obtained historical occupational and residential addresses from all the study participants. Employing their geographic information system model, they estimated ambient exposures to the pesticides ziram, maneb and paraquat, both at work and home, from 1974 to 1999.

The results reaffirmed what their previous research had suggested, that the data, "suggests that the critical window of exposure to toxicants may have occurred years before the onset of motor symptoms, when a diagnosis of Parkinson's is made."

Knowing that the fungicide ziram is commonly used in agriculture and suspecting its relationship to Parkinson's, Ritz turned to her colleague Jeff Bronstein, a UCLA professor of neurology and co-author of the study, for confirmation. His lab performed a genetic screen using genetically modified cells to identify pesticides that inhibit the breakdown of important proteins such as alpha-synuclein. Ziram was one of the best inhibitors they identified; they found, in fact, that synuclein accumulated in dopamine neurons, selectively killing them. When it was given systemically to rodents, it reproduced many of the features of Parkinson's disease.

"So the present study clearly demonstrates that exposure to ziram in humans is associated with a significant increased risk of developing PD," Bronstein said.

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