Exposure to pesticides increases the risk for Parkinson's disease (PD) by as much as 80%, according to a new meta-analysis, although the heterogeneity could not be assessed in some included studies.

The analysis shows that exposure to the weed killer paraquat or to the fungicides maneb or mancozeb was particularly toxic, yielding about a 2-fold increase in the risk for PD, and that the risks of farming and rural living are also significant.

"Exposure to pesticides and solvents may be a modifier of the progression of Parkinson's disease as well as a risk factor for the development of the disease, so clinicians should not only encourage patients to avoid further exposure to these compounds but also make them aware that treatments could be less effective than expected," said author Emanuele Cereda, MD, PhD, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

The findings reinforce the importance of protective equipment and compliance with recommended prevention practices, particularly in high-risk workplace environments, said Dr. Cereda.

The analysis is published in the May 28 issue of Neurology.

Any Pesticide

The authors selected 104 articles for qualitative assessment. They included 89 in the meta-analysis, providing data on 6 prospective investigations and 83 case-control comparisons.

From the case-control studies, the analysis showed that PD was associated with exposure to any type of pesticide, herbicide, insecticide, and solvent, with the risk ranging from 33% to 80%.

In 51 case-control studies, the overall odds ratio (OR) for exposure to pesticides in PD was 1.78 (95% confidence interval [CI], 1.56 - 2.04; \( P = .433 \)). However, in 33 studies in which the Newcastle-Ottawa Scale score was less than 7, the OR was 1.88.

In 16 studies of solvents, the overall OR for PD was 1.35 (95% CI, 1.09 - 1.67; \( P = .025 \)). With respect to individual solvents, Dr. Cereda believes that the most toxic compounds for dopaminergic pathways or neurons are toluene and trichloroethylene.

There was a 2-fold increase in risk for PD with exposure to paraquat (overall OR, 2.19; 95% CI, 1.48 - 3.26; \( P = .003 \)) and maneb/mancozeb (OR, 1.49; 95% CI, 0.85 - 2.63), whereas there was no association with exposure to the insecticide dichlorodiphenyltrichloroethane (DDT) (OR, 1.03).

As well, the researchers found that PD was associated with proxy conditions of exposure to organic pollutants. For example, overall ORs were 1.30 for farming (\( P = .171 \)), for 1.34 for well-water drinking (\( P = .006 \)), and 1.32 for rural living (\( P = .424 \)). In some studies, farming increased the PD risk by more than 40%.

There was no association with fungicides, rodenticides, organochlorines, or organophosphates.
High-quality studies often resulted in reduction of the risk for PD. In particular, exposure to insecticides, farming, and well-water drinking was no longer associated with PD. Conversely, high quality resulted in an increase in risk for PD with exposure to solvents.

In a sensitivity analysis on high-quality studies that included 200 or more cases, heterogeneity remained greater than 40% only for insecticides (70.4%), organochlorines (61.3%), organophosphates (77.9%), and farming (57.9%).

**Dose-Dependent**

Risk seemed to increase with length of exposure. There was also evidence of a dose-dependent effect, but a meta-analysis was not possible for this effect because of differences in the definition and quantification of exposure (e.g., days per year or dose per year, thresholds for cumulative lifetime exposure), said the authors.

Although many of the agents studied are no longer used in the United States and Europe, some are still found in developing parts of the world. Dr. Cereda also pointed out that PD may not develop until many years after exposure.

Only a few studies investigated the role of genetic susceptibility, but there's a growing belief that a gene-environmental interaction exists, said Dr. Cereda. He added that some people seem more susceptible to the toxic action of these compounds.

Asked for perspective on these findings, Rajesh Pahwa, MD, professor of neurology, director, Parkinson's Disease and Movement Disorder Center, University of Kansas Medical Center, Kansas City, and member of the American Academy of Neurology, told *Medscape Medical News* that he agrees that genes probably play a role. Underlying genetic predisposition may explain why only 1 or 2 people exposed to exactly the same toxin develop PD, he said.

However, Dr. Pahwa noted that this analysis can't evaluate such a predisposition because environmental studies often don't consider it. "It would be ideal to track environmental exposures along with genetic testing to evaluate these issues," he said.

Although the analysis provided updated information on the relationship between exposures to various environmental toxins and the risk for PD, it highlights some still unresolved public safety issues, said Dr. Cereda.

**Exposure Route**

"We were not able to clarify what is the most important route of absorption for these toxicants. For example, we don't know if exposure is more detrimental if it is by way of inhalation or through a transcutaneous route."

Knowing, for example, whether mixing pesticides directly with the hands is more dangerous that spraying it could have implications for prevention practices, he said.

It's possible that since the same people may use several compounds, different routes of exposure may act synergistically in increasing risk, he said.

Complying with current recommended prevention practices, such as wearing proper masks and gloves, is "very important," but it's unclear whether such practices are being followed, said Dr. Cereda.
Further high-quality, prospective case-control studies are needed to substantiate a cause and effect relationship, said Dr. Cereda. He would also like to see investigations into the exposure risks of other types of parkinsonisms.

While the study is important, Dr. Pahwa feels it doesn’t add any new information. The meta-analysis, he said, “basically confirmed” that rural living and exposure to herbicides, pesticides, and solvents are risk factors for PD.

Anyone with a family history of PD should be concerned about the possible risks posed by such exposures, stressed Dr. Pahwa.

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