

Understanding Pesticide Toxicity

NIEHS-funded research on genetic factors that affect individual sensitivity to pesticide exposure paves the way for policy changes.

Exposure to a group of pesticides called organophosphates can contribute to neurodevelopmental problems, among other health challenges.³² Since 1989, the National Institute of Environmental Health Sciences (NIEHS) has supported research into the role of a gene called PON1, which helps protect people from the harmful effects of organophosphate exposure.

Organophosphates disrupt communication between nerve cells. The PON1 protein plays a protective role in humans by detoxifying certain organophosphates before they can damage the nervous system.

Some people are more sensitive to organophosphates than other people. Over time, investigators have learned that sensitivity depends on how much PON1 protein a person produces, and how effective the protein is at breaking down organophosphates.¹⁰⁻¹¹

In 2018, a team partly funded by NIEHS made recommendations to decision makers to minimize people's exposure to the pesticide chlorpyrifos.³² Three years later, the U.S. Environmental Protection Agency (EPA) determined chlorpyrifos was not safe for use on food sold in the country.³³

"Our work on PON1 helped inform the EPA decision," said longtime NIEHS grantee Clement Furlong, Ph.D., who, with collaborator Lucio Costa, Ph.D., has studied PON1 for decades.



Agricultural workers in California. (Photo courtesy of Kim Harley)

"The quantity and effectiveness of the PON1 protein determine your resistance to certain pesticides."

Now

Clement Furlong, Ph.D.
University of Washington

Marking Milestones



Understanding Sensitivity

Researchers found that PON1 protein concentrations in the blood and protein activity — how effective the protein is at breaking down organophosphates — both influence a person's sensitivity to certain organophosphates.¹⁰⁻¹¹



Identifying Vulnerable Groups

Studies suggested that fetuses and infants are more susceptible than adults to the toxic effects of organophosphate exposure.¹³⁻¹⁶

Sharing Results

Investigators with CHAMACOS have given more than 1,000 presentations, and educated more than 30,000 partners and community members, about their research on pesticides and other chemicals.⁹



Reducing Exposures

Researchers proposed an action plan to reduce organophosphate pesticide exposure for consideration by governments, public health and medical institutions and organizations, and agricultural entities.³²



Informing Policy

In 2021, the EPA banned use of chlorpyrifos on food sold in the United States.³³

Then and Now

Then

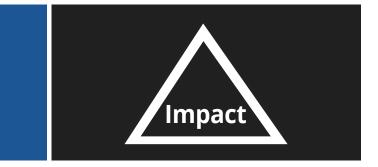
- Investigators initially thought PON1 provided protection against the pesticide parathion.⁸
- Researchers described common genetic variations in PON1 that affect how protective the gene is against organophosphate toxicity.⁴
- Studies indicated that fetuses and infants are more sensitive than adults to organophosphate exposure.¹³⁻¹⁶
- Researchers found associations between PON1 and human birth outcomes and neurodevelopmental effects.²¹⁻²⁷

- Research showed that PON1 is not protective against parathion. Rather, it targets toxic breakdown products of the pesticides chlorpyrifos and diazinon.⁸
- Investigators reported that PON1 protein quantity and protein activity influence a person's sensitivity to the chemicals.^{5,10-11}
- Research suggested that maternal PON1 protein quantity and activity might affect fetal sensitivity to organophosphates.³¹
- The EPA banned the use of chlorpyrifos on food sold in the United States.³³

PON1 and Pesticides

Policv Application and Synthesis Implementation and Adjustment **Fundamental** and Questions Practice 1990 1999-2000 2004-2014 Reported that PON1 genotype and Showed that human PON1 variants Found that administering the PON1 protein to rats protected against exposure protein quantity may better predict introduced into mice influenced their to chlorpyrifos oxon, the toxic breakdown organophosphate sensitivity than sensitivity to organophosphate toxicity; genotype alone.¹⁰⁻¹¹ identified associations between PON1 product of the pesticide chlorpyrifos.¹ and human birth outcomes and neurodevelopmental effects.²⁰⁻²⁷ 2003 1991 Purified human PON1 protein for Demonstrated the validity of a 2008 the first time; cloned human PON1 gene functional genomic assay in detecting Suggested that human PON1 protein for further study.²⁻³ PON1 mutations.¹² expressed in bacteria could be used to treat exposure to diazoxon, a metabolic byproduct of diazinon.²⁸ 1993 2003-2006 Observed that mice lacking PON1 were Indicated that fetuses and newborns susceptible to organophosphate toxicity and 2008 are more sensitive to organophosphate atherosclerosis, or plaque buildup in arteries; exposure than adults; suggested that found that PON1 protection depends on the Developed laboratory protocols for PON1 levels plateau between 6 and type of organophosphate exposure.⁶⁻⁸ determining people's PON1 blood 15 months of age, with high variability concentrations and activity levels without between individuals.13-16 the use of toxic organophosphates.²⁹ 1999 2004-2012 CHAMACOS was established at the University 2009 of California, Berkeley, to investigate the Found that chlorpyrifos exposure Observed that low levels of a less active form effects of pesticides and other environmental interfered with brain development exposures among children living in an of the PON1 protein were associated with the in rats and humans.¹⁷⁻¹⁹ agricultural region in California.⁹ inhibition of butyrylcholinesterase, a protein used to monitor organophosphate exposure.³⁰ _____







Using mice, found that maternal PON1 protein quantity and activity influenced neonatal sensitivity to chlorpyrifos exposure.³¹



Recommended policy reforms on organophosphate use. ³²



Informed by NIEHS-funded studies, among others, the EPA banned use of chlorpyrifos on food sold in the United States.^{33*}

*No NIEHS funding was used to advocate the EPA for this policy change.

NIEHS supported research for all of the milestones highlighted above.

Addressing Exposures in a Farming Community

A long-term project based at the University of California, Berkeley, has investigated the risk that organophosphate exposure poses to certain populations. Established in 1999 and funded partly by NIEHS, the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) follows more than 800 children in a farmworker community in the Salinas Valley, with the aim of characterizing chemical exposures and associated health effects.⁹

This project has also investigated the role of PON1. In one study, CHAMACOS researchers found that infants with lower levels of less active PON1 protein were born earlier and had smaller head measurements than infants with higher levels of more active PON1 protein.²⁵ In related work, investigators found an association between PON1 levels and activity and children's cognitive performance and, to a lesser extent, measures of muscle coordination.^{23,27}



Participants in the CHAMACOS Study. (Photo courtesy of the CHAMACOS Study)



Members of the CHAMACOS Youth Council — a group of high school students from Salinas, California, that works with the CHAMACOS team — collaborated with artist José Ortiz to create a mural illustrating how they can protect themselves from pesticide exposure. (Photo courtesy of Hijos del Sol Productions and the CHAMACOS Study)

Research Challenges and Solutions

Challenge: Researchers needed to sequence PON1 to study its role.

Solution: They used genetic material from rabbits to ultimately isolate the human PON1 gene. Rabbit PON1 and human PON1 showed striking similarities, suggesting that the protein may serve the same metabolic role across species.³

Challenge: Investigators wanted to examine the PON1 protein in a living organism.

Solution: They deleted the PON1 gene in mice, replacing it with human PON1 DNA. After exposing the mice to different organophosphates, they found that PON1 played an important role in breaking down toxic metabolic byproducts of the pesticides diazinon and chlorpyrifos.⁸

Challenge: Few human studies had investigated connections between the PON1 protein and other proteins affected by organophosphate exposure.

Solution: Working with agricultural pesticide handlers, researchers found that low PON1 quantity and activity were linked with interference of a protein called butyrylcholinesterase, which is used to monitor organophosphate exposure.³⁰



A farmworker in a Salinas Valley strawberry field. (Photo courtesy of the CHAMACOS study)

For references, supplementary information, and more on the impact of NIEHS research, please visit <u>https://niehs.nih.gov/research/programs/translational/examples</u>.