Question 5. What scientific information or additional information supports your submittal?

References. Please note that the reference numbers listed below match the corresponding citations used throughout our responses to Question 4.

Dietary Exposure and Biomonitoring

1. **Chensheng Lu, Kathryn Toepel, Rene Irish, Richard A. Fenske, Dana B. Barr, Roberto Bravo; Organic Diets Significantly Lower Children's Dietary Exposure to Organophosphorus Pesticides. *Environ. Health Perspect.* 1 February 2006; 114 (2): 260–263. DOI:10.1289/ehp.8418**

   https://pubs.acs.org/evhpaz/article/114/2/260/5248420/Organic-Diets-Significantly-Lower-Children-s

   Description: This is a peer-reviewed 15-day study of 23 elementary-age children that used urinary biomonitoring to compare conventional and mostly organic diets. During five consecutive organic-diet days, metabolites of the organophosphorus pesticides malathion and chlorpyrifos fell immediately to nondetectable levels, returning after conventional foods resumed. Other metabolites also declined. The longitudinal dietary intervention indicated that diet was children's primary exposure source and that organic food provided immediate protection.

2. **Curl CL, Fenske RA, Elgethun K. Organophosphorus pesticide exposure of urban and suburban preschool children with organic and conventional diets. Environ Health Perspect. 2003 Mar;111(3):377-82. DOI: 10.1289/ehp.5754.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC1241395/

   Description: Peer-review study where researchers assessed dietary organophosphorus pesticide exposure in Seattle preschool children using food diaries and 24-hour urine samples. Children eating conventional diets had median dimethyl pesticide-metabolite levels about six times higher than those eating organic diets. Estimated exposures suggested organic fruits, vegetables, and juice could reduce children's OP pesticide exposure from above EPA guidelines to negligible-risk levels, offering parents a practical exposure-reduction strategy.

3. **Lu C, Barr DB, Pearson MA, Waller LA. Dietary intake and its contribution to longitudinal organophosphorus pesticide exposure in urban/suburban children. Environ Health Perspect. 2008 Apr;116(4):537-42. doi: 10.1289/ehp.10912. PMID: 18414640; PMCID: PMC2290988.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC2290988/

Description: The Children's Pesticide Exposure Study followed 23 Seattle-area children ages 3–11 for one year, collecting urine samples twice daily across four seasons. During five-day periods when conventional fruits and vegetables were replaced with organic options, urinary metabolites of malathion and chlorpyrifos fell to nondetectable or near-nondetectable levels. Seasonal variation also tracked fresh-produce consumption, indicating that dietary intake is young children's primary source of organophosphorus pesticide exposure.

California birth-cohort and child neurodevelopment studies

4. **Bouchard, M.F., Chevrier, J., Harley, K.G., Kogut, K., Vedar, M., Calderon, N., Trujillo, C., Johnson, C., Bradman, A., Barr, D.B., & Eskenazi, B. (2011). "Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year-Old Children."** ***Environmental Health Perspectives*****, 119(8), 1189–1195. DOI: 10.1289/ehp.1003185.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC3237357/

   Description: CHAMACOS longitudinal birth-cohort study of predominantly Mexican-American families in California's Salinas Valley. Higher maternal urinary OP metabolite concentrations during pregnancy were associated with lower scores across several cognitive domains at age seven. Children in the highest quintile of prenatal exposure averaged approximately 7 points lower in full-scale IQ than children in the lowest quintile.

5. **Marks, A.R., Harley, K., Bradman, A., Kogut, K., Barr, D.B., Johnson, C., Calderon, N., & Eskenazi, B. (2010). "Organophosphate Pesticide Exposure and Attention in Young Mexican-American Children: The CHAMACOS Study."** ***Environmental Health Perspectives*****, 118(12), 1768–1774. DOI: 10.1289/ehp.1002056.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC3002198/

   Description: CHAMACOS study examining attention at ages 3.5 and 5 years. Higher prenatal urinary OP metabolite concentrations were associated with more attention problems and ADHD-related scores, particularly at age five; associations were generally stronger in boys.

6. **Sagiv, S.K., Harris, M.H., Gunier, R.B., Kogut, K.R., Harley, K.G., Deardorff, J., Bradman, A., Holland, N., & Eskenazi, B. (2018). "Prenatal Organophosphate Pesticide Exposure and Traits Related to Autism Spectrum Disorders in a Population Living in Proximity to Agriculture."** ***Environmental Health Perspectives*****, 126(4), 047012. DOI: 10.1289/EHP2580.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC6071837/

Description: CHAMACOS study examining whether prenatal OP exposure was associated with traits related to autism spectrum disorder, rather than clinical autism diagnoses. Maternal urinary OP metabolites and residential proximity to agricultural OP use were evaluated against parent-, teacher-, and child-based measures through age 14. The findings provided some evidence of associations between prenatal OP exposure and ASD-related traits, but results varied by exposure metric, outcome measure, age, and sex and should not be summarized as showing that OP exposure "causes autism."

7. **Gunier, R.B., Bradman, A., Harley, K.G., Kogut, K., & Eskenazi, B. (2017). "Prenatal Residential Proximity to Agricultural Pesticide Use and IQ in 7-Year-Old Children."** ***Environmental Health Perspectives*****, 125(5), 057002. DOI: 10.1289/EHP504.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC5644974/

   Description: CHAMACOS study using California DPR Pesticide Use Reporting data to estimate agricultural pesticide use near mothers' residences during pregnancy. Greater nearby use of OPs, toxicity-weighted for acetylcholinesterase inhibition, was associated with lower cognition at age seven. The OP association remained after adjustment for maternal urinary OP metabolites and other neurotoxic pesticide classes, although high correlations among pesticides made it difficult to identify individual chemicals responsible for the associations.

Independent U.S. birth cohorts

8. **Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D.B., & Whyatt, R. (2011). "Seven-Year Neurodevelopmental Scores and Prenatal Exposure to Chlorpyrifos, a Common Agricultural Pesticide."** ***Environmental Health Perspectives*****, 119(8), 1196–1201. DOI: 10.1289/ehp.1003160.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC3237355/

   Description: Columbia University longitudinal birth cohort in New York City. Prenatal chlorpyrifos exposure was measured in umbilical-cord blood. Each standard-deviation increase in chlorpyrifos was associated with declines of approximately 1.4% in full-scale IQ and 2.8% in working memory at age seven.

9. **Rauh, V.A., Perera, F.P., Horton, M.K., Whyatt, R.M., Bansal, R., Hao, X., Liu, J., Barr, D.B., Slotkin, T.A., & Peterson, B.S. (2012). "Brain Anomalies in Children Exposed Prenatally to a Common Organophosphate Pesticide."** ***Proceedings of the National Academy of Sciences*****, 109(20), 7871–7876. DOI: 10.1073/pnas.1203396109.**

   https://pmc.ncbi.nlm.nih.gov/articles/PMC3356641/

Description: MRI study of 40 children from the Columbia cohort comparing 20 with higher and 20 with lower prenatal chlorpyrifos exposure. Higher exposure was associated with measurable differences in cerebral surface morphology and cortical thickness. Because the study was small, it is best presented as supporting neuroimaging evidence, not as a stand-alone definitive demonstration of structural brain injury.

10. **Engel, S.M., Wetmur, J., Chen, J., Zhu, C., Barr, D.B., Canfield, R.L., & Wolff, M.S. (2011). "Prenatal Exposure to Organophosphates, Paraoxonase 1, and Cognitive Development in Childhood."** ***Environmental Health Perspectives*****, 119(8), 1182–1188. DOI: 10.1289/ehp.1003183.**

    https://pmc.ncbi.nlm.nih.gov/articles/PMC3237356/

    Description: Mount Sinai birth cohort. Higher prenatal total OP metabolite concentrations were associated with poorer mental development at 12 months among Black and Hispanic children. In children ages 6–9, higher prenatal OP metabolites were associated with poorer perceptual reasoning among children whose mothers had a PON1 genotype associated with slower detoxification of chlorpyrifos oxon. The study therefore provides evidence both of neurodevelopmental effects and of differences in susceptibility related to OP metabolism.

Systematic reviews and major evidence syntheses

11. **González-Alzaga, B., et al. (2019). "Effects of Prenatal and Postnatal Exposure to Organophosphate Pesticides on Child Neurodevelopment in Different Age Groups: A Systematic Review."** ***Environmental Research*****, 176, 108546.**

    https://pubmed.ncbi.nlm.nih.gov/31041704/

    Description: Systematic review of 50 studies; 45 reported an association between OP exposure and at least one neurodevelopmental outcome. The authors concluded that the available evidence more strongly supports prenatal than postnatal exposure as a sensitive window, while also noting heterogeneity and methodological limitations across studies.

12. **Muñoz-Quezada, M.T., et al. (2013). "Neurodevelopmental Effects in Children Associated with Exposure to Organophosphate Pesticides: A Systematic Review."** ***NeuroToxicology*****, 39, 158–168. DOI: 10.1016/j.neuro.2013.09.003.**

    https://pmc.ncbi.nlm.nih.gov/articles/PMC3899350/

    Description: Systematic review of 27 studies. Twenty-six reported some adverse neurobehavioral association, with outcomes involving cognition, attention/behavior, motor function, and other neurodevelopmental domains. The review found substantial consistency across the longitudinal prenatal-exposure studies while also recognizing differences in exposure assessment and study design.

13. **National Academies of Sciences, Engineering, and Medicine. (2018). *Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War.* National Academies Press. DOI: 10.17226/25162.**

https://www.nationalacademies.org/read/25162/chapter/7

Description: Independent review of the epidemiologic literature, including CHAMACOS, Columbia, Mount Sinai, HOME, and international studies. The committee concluded that there was "sufficient evidence of an association between prenatal exposure to OPs and neurodevelopmental effects." It found the evidence inadequate or insufficient for other prenatal developmental outcomes.

14. **Alqudaimi, M., et al. (2026). "The Impact of Prenatal Organophosphate Exposure on Children's Neurodevelopment: A Quantitative Analysis with Regional Comparison." *International Journal of Environmental Health Research*. DOI: 10.1080/09603123.2026.2676785.**

https://pubmed.ncbi.nlm.nih.gov/42163786/

Description: Meta-analysis of 46 publications involving 25,975 participants examining prenatal OP exposure and child neurodevelopment. The study found statistically significant associations between prenatal OP exposure and adverse neurodevelopmental outcomes, including poorer cognitive outcomes, while also examining geographic differences in results.

California exposure and environmental-justice evidence

15. **Rotkin-Ellman, M., Carpenter, C., Richardson, M.J., English, P.B., Gunier, R.B., & Harley, K.G. (2025). "Temporal Trends of Agricultural Organophosphate Pesticide Use in California and Proximity to Pregnant People in 2021." *BMC Public Health*, 25, 3121. DOI: 10.1186/s12889-025-23939-y.**

https://pmc.ncbi.nlm.nih.gov/articles/PMC12481947/

Description: California-wide study linking 2021 birth-certificate residential addresses with DPR pesticide-use data. 29,386 pregnant people—7.5% of California births—lived within 1 km of agricultural OP use during pregnancy. The number of different OPs applied within 1 km ranged from one to six. Exposure prevalence was particularly high in the Central Coast and among Hispanic/Latine and younger pregnant people.

16. **Suarez-Lopez, J.R., Gould, C.F., Vashishtha, D., et al. (2026). "Acetylcholinesterase Activity from Childhood to Young Adulthood." *Journal of Exposure Science & Environmental Epidemiology*, 36, 818–826. DOI: 10.1038/s41370-026-00866-7.**

https://doi.org/10.1038/s41370-026-00866-7

Description: Longitudinal study of 746 participants ages 4–26 in an agricultural region of Ecuador, based on 3,119 AChE measurements over 16 years. Its primary purpose was to establish age- and sex-specific reference values for AChE activity. Greater floriculture acreage within 300 meters of participants' homes was associated with lower AChE activity, suggesting potential exposure to cholinesterase-inhibiting pesticides. Because both OPs and carbamates inhibit AChE, it should not be described as specific evidence of OP exposure alone.

Adult neurological outcomes & Susceptibility

17. **Wang, A., Cockburn, M., Ly, T.T., Bronstein, J.M., & Ritz, B. (2014). "The Association Between Ambient Exposure to Organophosphates and Parkinson's Disease Risk."** ***Occupational and Environmental Medicine*****, 71(4), 275–281. DOI: 10.1136/oemed-2013-101394.**

    https://pubmed.ncbi.nlm.nih.gov/24436061/

    Description: Population-based case-control study of 357 incident Parkinson's disease cases and 752 controls in California's Central Valley. GIS-based pesticide-use records were used to estimate ambient exposure to 36 OP pesticides from 1974–1999. Ambient exposure to the OPs evaluated was associated with increased Parkinson's disease risk, and the researchers observed an exposure-response pattern as the number of OPs to which participants were exposed increased.

18. **Manthripragada, A.D., Costello, S., Cockburn, M.G., Bronstein, J.M., & Ritz, B. (2010). "Paraoxonase 1, Agricultural Organophosphate Exposure, and Parkinson Disease."** ***Epidemiology*****, 21(1), 87–94. DOI: 10.1097/EDE.0b013e3181c15ec6.**

    https://pubmed.ncbi.nlm.nih.gov/19907334/

    Description: Population-based case-control study of 351 incident Parkinson's disease cases and 363 controls in three rural California counties. Among people carrying the PON1-55 MM genotype, which influences metabolism of some OPs, estimated residential exposure to diazinon or chlorpyrifos was associated with more than twice the Parkinson's disease risk compared with unexposed people without that susceptibility genotype; no corresponding increased risk was observed for parathion.

19. **Costa, L. G., Giordano, G., Cole, T. B., Marsillach, J., & Furlong, C. E. (2013). Paraoxonase 1 (PON1) as a genetic determinant of susceptibility to organophosphate toxicity.** ***Toxicology, 307*****, 115–122.**

    https://pubmed.ncbi.nlm.nih.gov/22884923/

Description*:* This review explains that PON1 variants—especially Q192R and regulatory variants affecting enzyme expression—can change PON1 activity and susceptibility to certain OP insecticides. It appropriately characterizes the human evidence as emerging rather than definitive.

Regulatory and policy context

20. **European Commission. (2026). *EU Pesticides Database.* Directorate-General for Health and Food Safety.**

    https://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/start/screen/active-substances

    Description: Official European Commission database showing current and historical EU approval status for pesticide active substances. It can document whether individual OP active ingredients are approved, not approved, expired, or withdrawn in the EU. It is regulatory-comparator evidence, not evidence of a health effect. Twelve of the 13 organophosphate active ingredients still reported used in California in 2023 are not approved for use as plant-protection active substances in the European Union. Several—including chlorpyrifos, dimethoate, ethoprophos, and phosmet—were previously approved but subsequently failed to obtain renewal. Malathion is the only one of the 13 that remains EU-approved, and its renewal assessment is still underway.