2401 Occupational Pesticide Exposure and Parental Report of Attention Deficit Hyperactivity Disorder in Adolescent Pesticide Applicators in Egypt

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Exposure to environmental chemicals, including organophosphorus pesticides, has been associated with attention disorders such as attention deficit hyperactivity disorder (ADHD). Previous studies have identified associations between ADHD and prenatal exposures; additionally one cross-sectional study reported an association between organophosphate metabolite levels and a diagnosis of ADHD among school-age children. However, the impact of occupational pesticide exposure and ADHD in adolescents has not been examined. Adolescent pesticide applicators and non-applicators, 12-18 years old, participated in a 10-month longitudinal study examining health effects from pesticide exposure before, during and after the application season. Parents from a subset of the cohort (N=64) completed the ADHD Rating Scale. Repeated urine and blood samples were collected at various time points during the 10-months to assess biomarkers of exposure and effect. Cumulative urinary TCPy over the study period was used to classify participants into low (< median) and high (≥ median) exposure groups. Participants in the high exposure group had significantly more symptoms of ADHD than participants in the low exposure group. The prevalence odds ratio of having symptoms greater than the cut off in the high exposure group was 2.8 (95% CI = 0.5-14.7) times the odds in the low exposure group. More participants with symptoms above the cut-off score reported applying pesticides at home and had greater cumulative TCPy levels, than participants with symptoms below the cut-off score. However, there were no differences between the groups on years worked as a pesticide applicator for the Ministry of Agriculture. Although limited by a small sample size, this study provides preliminary evidence of an association between occupational pesticide exposure and ADHD symptoms, however, additional research is warranted.

2402 Organophosphorous Pesticide Exposure and Neurobehavioral Performance Among Adolescents in Egypt: A Ten-Month Prospective Study

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Chlorpyrifos, an organophosphorus pesticide, is widely used for agricultural operations. The goal of the current study was to examine the impact of chlorpyrifos exposure on biomarkers of exposure and neurobehavioral performance in adolescents before, during and after the application season. At each test session, participants (N=89) completed a neurobehavioral test battery and urine was collected for analysis of the chlorpyrifos metabolite 3,5,6-trichloro-2 pyridinol (TCPy) (biomarker of exposure). Cumulative urinary TCPy over the study period was used to classify participants into low (< median) and high (≥ median) exposure groups. Urinary TCPy increased during the application season with recovery following the end of application. Participants in the high exposure group had significantly elevated metabolite levels throughout the 10-month study period. Deficits in motor skills and slower reaction times, along with deficits in executive function and short-term memory were found between the high and low exposure groups. Changes in neurobehavioral performance across the application season indicate a pattern of impaired performance in the high exposure group compared to the low exposure group. Deficits increased during the application season and remained for months after application ended. This study is the first to examine the impact of changes in pesticide exposure and neurobehavioral performance before, during and after the application season. The findings indicate that neurobehavioral deficits increase during the application season, as exposure also increases, and remain after the application ends, even when the biomarkers of exposure are reduced. This is particularly important when considering the developmental changes that occur during adolescence.

2403 Multi-endpoint Analysis of Organophosphate Developmental Neurotoxicity in a Freshwater Planarian

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Organophosphates (OPs) are among the most commonly used pesticides in the US and act by irreversibly inhibiting acetylcholinesterase (AChE), leading to cholinergic overstimulation due to increased synaptic levels of acetylcholine, paralysis and death. Their environmental abundance, although below acutely toxic levels to humans, has been suggested to be at least partially responsible for the observed increase in childhood neurodevelopmental disorders. However, it is unknown through which mechanisms chronic, low-dose prenatal and infant OP exposure causes neurotoxicity in the developing brain. In this study, we analyzed the toxicological profiles of five common OPs (chlorpyrifos, dichlorvos, diazinon, malathion and parathion) using a multi-endpoint planarian screening platform. The freshwater planarian, Dugesia japonica, is an excellent *in vivo* model for developmental neurotoxicology studies because its remarkable regenerative capabilities allows development to be induced at will by amputation. Moreover, because of their short development time (12 days) and similar size, regenerating and adult animals can be tested simultaneously using the same assays to identify development-specific toxicity. Importantly, despite its simplicity, features of the planarian brain are conserved in the mammalian brain on the molecular and structural levels making mechanistic analysis of neurotoxicity in this animal directly relevant to human health. With this platform, we characterized effects on lethality, regeneration and a range of stimulated and unstimulated behaviors. We found that the different OPs varied widely in toxic dose, affected endpoints and developmental sensitivity. Lastly, through biochemical analysis of AChE activity in OP-treated animals, we found that, depending on the OP, prolonged inhibition of AChE was not necessary for or necessarily indicative of toxic effects. This indicates that toxicity may be induced by alternative mechanisms, necessitating further in depth mechanistic studies.

2404 Kinetic Analysis of the Interactions Between the Organophosphorus Pesticide Metabolite Phorate Oxon and Oximes with Acetylcholinesterase

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Phorate is an agricultural pesticide that is currently used in the US. Like many other organophosphorus (OP) pesticides, the primary mechanism of the acute toxicity of phorate is acetylcholinesterase (AChE) inhibition mediated by its bioactivated oxon metabolite. Reactivation of inhibited AChE with oximes is a critical aspect of the therapeutic strategy for acute OP intoxication and little is known about the oxime-assisted reactivation of AChE inhibited by phorate oxon (PHO). Thus, phorate represents a widely used pesticide that is highly toxic to mammals with little published data regarding its toxic effects or response to therapy. To help fill this knowledge gap, we evaluated the kinetics of inhibition, reactivation, and aging with PHO, recombinant AChE derived from three species (rat, guinea pig and human), and five oximes: 2-PAM Cl, HI-6 DMS, obidoxime Cl2, MMB4-DMS, and HLö7 DMS. The inhibition rate constants (ki) for PHO were calculated for AChE derived from each species and found to be low (i.e., 4.8 x 103 to 1.4 x 104 M-1 min-1) compared to many other OPs. Obidoxime Cl2 was the most effective reactivator tested and guinea pig AChE was more resistant to reactivation in general than rat or human AChE. Furthermore, the aging rate of PHO-inhibited AChE was very slow (limited aging was observed out to 48 hours) for all three species. The results of this study support the following conclusions: (1) Obidoxime Cl2 was a more effective reactivator than the other oximes tested. (2) The oxime currently approved for use in the US, 2-PAM Cl, showed limited effectiveness in reactivating PHO-inhibited AChE, which suggests that it may have limited usefulness in the clinical management of acute PHO intoxication. (3) The therapeutic window for oxime administration following exposure to phorate (or PHO) is not limited by aging.

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