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# COMMENTARY

# New Evidence of Effects of Organophosphate Pesticides on Neurodevelopment in Children

**Commentary on the article by Kofman *et al.* on page 88**

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Inner-city minority and rural populations are at high risk for exposure to environmental contaminants, including rarely studied pesticides. Organophosphate (OP) pesticides have been widely used on fruits and vegetables and in treatment of homes, although residential use is banned. They can act as developmental neurotoxicants when administered during gestation or postnatally, as has been demonstrated in experimental animal studies (1).

However, few human studies have been conducted to date examining the impact of acute or chronic exposure to OP pesticides on neurodevelopment of young children. Moreover, as Kofman *et al.* note (2), despite the critical role of acetylcholinesterase (AChE) in cortical function and development, little is known about the long-term consequences of the disruption of the cholinergic system in young children. Animal models are valuable in risk assessment for determining neurotoxicity using experimental designs that control most effectively for potential confounding factors and for examining neurostructural and neurochemical substrates that may mediate neurotoxicological effects. By contrast, human studies are able to determine and characterize the cognitive and behavioral endpoints that may be altered in children or the doses at which adverse effects become evident. To evaluate these issues, it is critical to find human cohorts exposed at sufficiently high doses for the effects to be observed and studied.

The study published in today's issue of Pediatric Research by Kofman *et al.* (2) provided a unique opportunity to examine the long-term impact of OP on a small group of otherwise healthy Bedouin children who were accidentally exposed to these pesticides and hospitalized before the age of 3 y and to compare their performance to that of children exposed to another toxicant at the same age. In this well-designed study Kofman *et al.* compared OP-exposed children with a comparison group of children exposed to kerosene and a control group matched to each of the exposure groups by age and gender. The children were administered a battery of assessments which were selected as potentially sensitive outcome measures on the basis of previous research. The tests were administered by native Arabic-speaking graduate students with degrees in psychology and experience working in the educational system with Bedouin children. Despite the small sample size, the authors were able to demonstrate specific effects of OP and kerosene in two domains, verbal learning and motor inhibition, while showing that delayed and recall memory were not affected. In addition, the OP exposure deficit on the motor inhibitory control test was specific to OP and not seen in the kerosene-exposed children. Inclusion of the kerosene comparison group was elegant since it provided evidence that certain effects were specific to the OP exposure and not a result of toxic exposure *per se*. In addition, in their study and in other research on environmental toxicants or of substance-exposed children, it is not always possible for the examiners to be blind with regard to exposure. Inclusion of the kerosene group in this study permitted the examiners to be partially blind regarding which exposure they were dealing with when testing the children.

Although the authors of this study made some predictions regarding the cognitive domains likely to be affected by OP exposure based on animal and human studies relating to the cholinergic system, in any first human study of an environmental exposure to a suspected neurotoxicant, it is important to consider a broad range of neurobehavioral endpoints that might be impacted, not just those observed in previous studies. For example, when we initiated our research on the effects of prenatal exposure to polychlorinated biphenyls (PCBs) in the early 1980s, little was known about the neurotoxicity of that

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**Abbreviations: AChE,** acetylcholinesterase; **OP,** organophosphate; **PCBs,** polychlorinated biphenyls

ubiquitous environmental contaminant that had been used from the mid-1930s until 1975 as heat transfer chemicals and lubricants in electrical transformers and capacitors (3). Therefore, we felt it was important to determine whether effects could be detected using the most sensitive measures available at the time. Given the public health concern, we felt that every effort should be taken not to miss effects that may actually be related to the exposure (4). In a public health context, in addition to the risk of spuriously attributing an observed effect to neurotoxic exposure (Type I error), failure to detect a real effect (Type II error) is also of particular concern. Despite caveats by researchers that no inference can be made from a null finding, the need to evaluate the risks associated with a potentially toxic exposure will inevitably lead negative findings to be interpreted to mean that the exposure is safe. A failure to detect real risks associated with an exposure may prevent necessary public health warnings and precautions from being implemented. Therefore, studies like the one presented in the Kofman *et al.* paper and other research on human neurobehavioral teratology and toxicology presenting first findings on a potential neurotoxic exposure need to be concerned about Type II considerations.

Kofman *et al.* report the significance level of some of their findings after making a Bonferroni correction for multiple comparisons. But there is reason to believe that this approach may be overly conservative. The Bonferroni correction was devised to deal with the concern that, if a large number of outcomes are examined, a certain proportion (5%, $p < 0.05$ significance level) will be significant by chance. The Bonferroni approach requires that the $p$-level used to determine whether an effect is significant be reduced by the number of outcomes assessed, so that, if 10 endpoints are examined, effects would not be considered significant unless $p < 0.005$. The problem with this approach is that important effects could be missed since only very large effects would be considered statistically significant. For this reason, it is usually preferable to use the traditional $p = 0.05$ significance level and to acknowledge that any effects not previously observed in the literature need to be replicated. Thus, in our initial PCB research in Michigan, in which we found subtle adverse effects on infant visual recognition memory, we recognized that replication would be needed (3). These effects have since been replicated in three independent studies in Taiwan (5), upstate New York (6), and among the Inuit in Arctic Quebec (Jacobson SW *et al.*, International Conference on Circumpolar Health, September 2004, Nuuk, Greenland), and PCB-related IQ and achievement deficits were later detected in these children at 11 y in the long-term follow-up of our Michigan cohort (7). Thus, detection of subtle effects in infants and children like those reported by Kofman et al. can provide early indicators of more serious cognitive deficits that may emerge later in development.

Another problem with the Bonferroni approach is that it encourages researchers to limit the number of outcomes assessed in a given study. However, in a study, such as the one presented by Kofman *et al.*, once the investment has been made to assemble and assess an often difficult-to-access exposed cohort, researchers should not hesitate to examine other domains not previously considered as possible endpoints for this exposure. Effects seen on such endpoints would need to be acknowledged as being more tentative and in particular need of replication before they are broadly accepted. On the other hand, effects not specifically predicted that are consistent across multiple measures (neuropsychological, neuroimaging, self-report, parental report, etc.) have substantial credibility even before replication by contrast to a single effect in a domain whose other measures are largely unaffected. Ultimately, our confidence in the validity of a finding depends on how it relates to findings in other studies, whether these studies are conducted before or after the association is initially found (8). The motor and memory findings reported by Kofman *et al.* greatly strengthen and go beyond the previous parental reports of impulsivity in exposed children.

Kofman *et al.* provide an excellent first human study on the long-term effects of OP pesticides on children. The investigators used sensitive state-of-the-art tests, appropriate native-speaking examiners, conducted work on a new exposure under very challenging circumstances and a difficult-to-access population, and have presented findings that expand on previous animal findings and have important public health implications. As Kofman *et al.* indicate, future research in this area is needed to confirm these findings and to explore whether they reflect delayed development or permanent impairment. An additional strength of this study is its use of accidental exposures in which the doses were high enough to detect neurotoxic effects on development. In assembling the cohort for our Michigan PCB study, it was necessary to screen over 8,000 Western Michigan families to locate 242 recently-delivered mothers who had consumed relatively large quantities of PCB-contaminated Lake Michigan fish (3,7). By examining school-aged children who were accidentally exposed and hospitalized in infancy, Kofman *et al.* were able to use an unfortunate occurrence to advance our understanding of the long-term impact of this exposure without first surveying a large population. Given that such accidents are rare, it is important for investigators to conduct studies like the one by Kofman and her colleagues and to make use of these unique opportunities when they arise.

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