Invited commentary: persistent organic pollutants and childhood learning and behavioural disorders

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Association of learning disabilities and attention-deficit disorder with concurrent levels of persistent organic pollutants

In this issue of *Journal of Epidemiology & Community Health*, Lee *et al*[1] (***see page 591***) demonstrate an association of both learning disabilities (LD) and attention-deficit disorder (ADD) with concurrent serum levels of persistent organic pollutants (POPs) among 12–15-year-old participants in the National Health and Nutrition Examination Survey (NHANES 1999–2000). For example, among children with detectable versus non-detectable levels of heptachlorodibenzo-*p*-dioxin (HPCDD), the adjusted prevalence odds ratios (95% CI) for LD and ADD were 2.08 (1.17 to 3.68) and 3.41 (1.08 to 10.8), respectively. This is perhaps the first published study to describe a potential POP-associated increased risk of LD or ADD. Previous studies have primarily assessed continuous cognitive or behavioural measures among generally healthy populations. LD and ADD are clinical end points that have obvious public health impacts in terms of childhood (and adult) morbidity as well as educational, medical and social costs of supporting individuals with these diagnoses.[2] If confirmed, Lee *et al*'s findings could make a substantial contribution to the identification of potentially remediable risk factors for these increasingly common disorders.[3 4]

However, the strength of the associations observed in Lee *et al*'s study are surprising. Previous epidemiological findings generally support a modest association of early-life exposure to some POPs (eg, polychlorinated biphenyls (PCBs)) with poorer attention,[5 6] impulse control,[7 8] memory and learning skills,[6 9 10] and school achievement.[11] Furthermore, the Lee *et al* analysis had a small sample size (278 NHANES children had available exposure and outcome data) including only 44 cases of LD and 26 cases of ADD; used dichotomised exposure measures (levels were categorised as detectable vs non-detectable); measured exposure concurrently (whereas in most previous epidemiological analyses early-life exposures to POPs have been most predictive of later developmental or behavioural ability)[12]; and relied on self-reported diagnoses of LD and ADD, outcome measures that potentially involve considerable, presumably non-differential measurement error. All these circumstances should mitigate against the statistically significant, relatively large effect estimates that they report.

This apparent paradox suggests either that the observed association reflects a substantial underlying relationship or that chance or study design limitations are at issue. The possible study design issues highlight a key challenge in the assessment of environmental risk factors for adverse neurocognitive development in childhood—that is, the relative merits of assessing clinically defined abnormalities versus continuous, largely normative outcomes. In general, the latter approach has been more common, perhaps because of the availability of well-validated continuous outcome measures and their advantages in power and sensitivity. Furthermore, although assessment of clinically defined, discrete outcomes has undeniable public health relevance, it is important not to underestimate the implications for population health of the neurobehavioural deficits often noted in association with exposures to environmental toxicants where continuous outcomes are used.[13] We know that small changes in the mean value of health indicators such as serum cholesterol level, blood pressure or body mass index can signal substantial changes in the prevalence of clinically evident disease within a population.[14] Similarly, the mean changes noted in continuously distributed measures of neurobehaviour, although of uncertain significance with regard to an individual's well-being, can, depending on the shape of the dose–effect relationship, indicate increases in disease occurrence in the population, such as those identified by Lee *et al*.[15]

The study of clinically defined abnormalities of child development is difficult for a number of reasons. Case definitions of learning or behavioural disorders that are appropriate for epidemiological analysis are difficult to establish[16]; the necessary clinical assessment process tends to be variable, complex and resource intensive. Diagnoses such as LD and ADD are, by definition, syndromal and therefore lack confirmatory laboratory testing. For example, in Lee *et al*'s study, it is impossible to establish that diagnostic criteria were applied similarly across individuals. Although these disorders are increasingly common, they are relatively rare in the epidemiological sense. Among school-aged children, approximately 5% attending public schools have an LD[3] and 3–12% have ADD.[17 18] A standard case–control study of these outcomes would be limited by cross-sectional exposure assessment, a potential source of exposure misclassification particularly for POPs, where early-life exposures have typically been the most adverse. There is also the theoretical possibility of reverse causality—that is, current exposure could be influenced by a child's behaviour—although this is less likely for POPs than for other neurotoxicants for which behavioural disorders can be related to exposure risk, such as lead.[19] Lee *et al*'s analysis addressed reversed causality via possible disease-related changes in diet or body mass index, but found no differences between children with and without an LD or ADD, suggesting that these factors did not confound the exposure measure. In addition, serum POP measures are expensive. By using NHANES, a large population-based sample for whom exposure and outcome data were readily available, Lee *et al* at least theoretically avoided some of these limitations. However, large serum volume requirements and the high analytical costs of POPs, in particular, still precluded direct exposure measures for a large population of children in NHANES.

The particular POPs implicated as risk factors in this analysis—HPCDD, OCDD and HPCDF—are typically present at very low (parts per trillion) serum concentrations. Serum levels of these analytes in the general population are at least several orders of magnitude lower than levels of common PCB congeners, for example. The study assessed POPs for which at least 20% of children had serum levels greater than the limit of detection. The NHANES 1999–2000 analytical methods had good sensitivity for detecting dioxins, furans and coplanar PCBs, but the limits of detection for more prevalent POPs, such as PCB congeners 138, 153 and 180, were high.[20] Thus, these more common exposures were not available for study.

In addition, HPCDD, OCDD and HPCDF are associated with dioxin-like activity. Although experimental models support a potential role for dioxins in learning and behavioural disorders,[21] epidemiological studies on the developmental toxicities of these compounds are limited, in part, because they are typically present at such low levels.[12] For PCBs, it has been postulated that the non-dioxin-like congeners may be more deleterious to neurocognitive functions than those with dioxin-like properties.[22 23] Lee *et al*'s findings support the possibility that aryl hydrocarbon receptor-mediated mechanisms are more potent determinants of cognitive and behavioural development than has been previously recognised. However, in the absence of measures of non-dioxin-like PCBs, moderate correlations among dioxin- and non-dioxin-like PCBs, dioxins and furans preclude mechanistic inferences.[12 24]

Perhaps the most important issue for this study is that the validity of self-reported diagnoses of LD or ADD is unclear. Unexpected findings such as the relatively low male predominance of ADD (58%), the high prevalence of LD (16%) and the absence of any relationship of either study outcome with blood lead levels among a larger sample of 2246 children suggest potential limitations in the data. A male:female ratio of up to 4:1 has been described for ADD[17]; the much lower sex distribution found by Lee *et al* suggests potential selection bias and/or limitations in self-reported diagnosis. Similarly, a significant relationship of lead with ADD has been described in another NHANES (1999–2002) analysis, although the case definition included the use of medication.[25] Lack of corroboration with the 1999–2000 subset of data is surprising; further exploration of this apparent discrepancy would be of interest.

Additional limitations need to be considered before any steadfast conclusions are drawn. With complex, multifactorial outcomes such as LD and ADD, there is the potential for substantial confounding; however, somewhat limited covariates were available for the analysis. For example, there are regional differences in the diagnosis of LD and ADD, and exposure to POPs in the US population. Reportedly, the NHANES design cannot accommodate stratification by region.[20]

Despite the many strengths of the NHANES data, including the availability of exposure biomarkers and clinically relevant abnormalities as outcome measures, the study's conclusions are constrained by a small number of disease cases, the self-reported case definition, cross-sectional exposure assessment, a limited set of detectable POPs and binary exposure data. Still, these provocative findings underscore the need for efficient, valid and sensitive methodologies for studying the potential role of xenobiotics in disorders of child development. Most importantly, these findings support the need for further studies on environmental risk factors for LD and ADD with better outcomes and covariate specifications and, as the authors acknowledge, better assessment of exposures including a prospective design. Tempered by its design limitations, this study is an exciting first step in elucidating the potential role of prevalent POPs in the aetiology of increasingly common and costly developmental disorders of childhood.

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