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*J Pediatr*. Author manuscript; available in PMC 2009 February 1.

Published in final edited form as:
*J Pediatr*. 2008 February ; 152(2): 155–157.

# Neurotoxicology: What can context teach us?

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Neurodevelopment and cognitive function are among the most important outcomes of interest in public health, particularly with the rise of developed countries dominated by knowledge-based economies. In developing countries and poor communities in the United States, the simultaneous presence of several adverse childhood exposures can alter both development and organization of the central nervous system.[1]

Perhaps the most common factors that predispose children to adverse neurodevelopmental outcomes are malnutrition, environmental toxicants, and sociocultural conditions which act as psychosocial stressors. Because these factors tend to cluster in the poorest populations, studies typically statistically adjust for the potential confounding effects of joint exposure, in order to eliminate confounding bias in the estimate the main effect. This paradigm has been the standard in neuroepidemiologic research for many years and has done much to discover neurotoxicants and to better establish the basic principles and methodology of neurotoxicology research. However, all paradigms deserve periodic re-evaluation and the idea that we must consider multiple toxic exposures primarily as confounders may not be the optimal method for understanding how environment molds the developing brain.

In this issue of *The Journal*, Solon et al demonstrate a 2–3% decrease in cognitive test scores for a 1 ug/dL increase in blood lead.[2] This is a remarkable finding as the dose response between blood lead levels and child neurodevelopment, whether measured by a Bayley Scale Mental Developmental Index or by IQ is generally less than a 1% decrease in neurodevelopment test score for a 1 ug/dL increase in blood lead levels. As the authors point out, the majority of the previous studies were conducted in more developed countries. The findings in this study may therefore be more representative of the effects of lead in developing countries in which the social, toxicologic, and nutritional factors influencing neurodevelopment differ from those of developed countries. But if we adjust for these factors, why would the main effect of lead be so different in these countries? The initial response might be to suggest that the results of Solon et al are because of unmeasured confounding (i.e. unmeasured genetic, nutritional, or social factors) which both track with increased risk of lead poisoning and are independently neurotoxic as well. The differences in the effect estimate of Solon et al vs those of prior studies are because of residual confounding and the true dose response of lead with neurodevelopmental outcomes is similar to that in developed countries. If these confounders had been measured more precisely, so the argument goes, we would have found exactly that. Indeed, most studies of lead poisoning adjust for the effects of socioeconomic factors, nutrition (e.g. iron deficiency), and to a lesser, extent genetics. For years now, our goal has been to narrow in on the main effect of a neurotoxicant, whether the research is population based or animal research. Animal studies are typically tightly controlled experiments in which the only factor which differs between groups is the dose of the neurotoxicant. Although epidemiologic

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studies may measure concurrent states of social and other physical/chemical risk factors, the potential for synergistic joint effects of such factors when combined with lead poisoning are seldom considered. Instead, each is treated as an independent risk factor for neurodevelopmental toxicity and its variance and covariance are adjusted for statistically. Although observational in nature, this is still fundamentally a reductionist approach, like the experimental study. However, what do we lose by reducing a toxicant to its main effect? Should we expect main effects to be relatively constant in size across populations? Main effects are more likely to be relative across populations, that is, they are dependent on context. Life does not occur in a cage, people are inherently different and societies are inherently different. Toxicants therefore may plausibly act differently in different people (host susceptibility) or even different societies. Even though it is certainly plausible that nutrition, genetics, or social environment are truly confounders of chemical toxicant effects, it is equally biologically plausible that they may be modifiers of chemical toxicant effects, an assumption which requires a different statistical approach than modeling effects as confounders. Not doing so is a missed opportunity, and perhaps by studying the interactions of social, nutritional, and genetic factors with neurotoxicants chemicals we can better understand how to prevent and even treat chemical toxicants.

I do not mean to imply that no work has been done to address context as a factor in neurotoxicogy. To illustrate the role of context in chemical toxicity, one need only look to animal research on enriched environments. Enriched environment itself alters neurodevelopment, but the effect may not end there. Recent animal studies have demonstrated that the toxicity of lead in rats is modified by socially enriched environments. For example, Schneider et al 2001[3] demonstrated that animals raised in social isolation were more sensitive to the neurotoxic effects of lead than animals raised in an enriched environment. Perhaps even more striking, Guilarte et al,[4] demonstrated that among rats, an enriched environment provided *following* lead exposure was associated with reversal of lead induced learning impairment, increased gene expression of hippocampal NMDA receptors, and increased induction of brain derived neurotrophic factor mRNA. The former study suggests that social factors modify the toxicity of lead, and the later study suggest that social environment may be an effective *treatment* following lead exposure. This is a promising and immensely important finding. Although chelation has not been associated with improved developmental outcomes following lead exposure, this line of work suggests that social and perhaps behavioral interventions might be an effective treatment for lead poisoned children.

Even though observational research studies in humans are not optimal for determining treatment effect, they can nonetheless point us toward potential treatments. In epidemiology, studying the joint effects of two risk factors on an outcome is termed “effect modification.” One factor modifies the effect of the other. Addressing effect modification, addresses the effect of context in studies of neurotoxicity and provides insight as to the underlying biology of that toxicity. In Solon et al, serum folate modified the association between lead and cognitive outcomes. This finding has two potential meanings. One is that the nutritional context in which lead poisoning occurs in the Philippines may differ from that in more developed countries and may help explain the steeper dose response curve between blood lead levels and cognitive outcomes in the Philippines. The second is that folate supplementation might be an effective treatment or preventative intervention for children at high risk for lead poisoning. Although the relationship between lead and folate is not well understood, and further research is needed to determine the underlying biology of this interaction, by studying folate as an effect modifier of lead, rather than as a confounder of lead poisoning, we begin to open new biological pathways of study and most importantly- potential interventions. Had Solon et al merely modeled serum folate as a confounder of lead poisoning, the authors would have missed this opening. Effect modification (and the more familiar concept of “biological synergism”) means that joint exposure is multiplicatively more (or less) toxic than effects that occur when the

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modifying factor is absent. Studies of effect modification are difficult to conduct as they require larger sample sizes and more measurements, increasing costs. But such costs come with exceptional potential benefits. Clearly, more work needs to be done on the role of folate in lead poisoning, and there are potential mechanisms, such as changes in DNA methylation, a process involving folate metabolism[5] and a process known to be influenced by metals.[6,7] Whether this finding leads to future treatments for lead poisoning is speculative at this stage, but what is clear is that more toxicologic research needs to consider the possibility that joint exposures act synergistically and not independently. Doing so will lead to better understand of how our environment shapes our health and what interventions will either prevent or treat toxic exposures.

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