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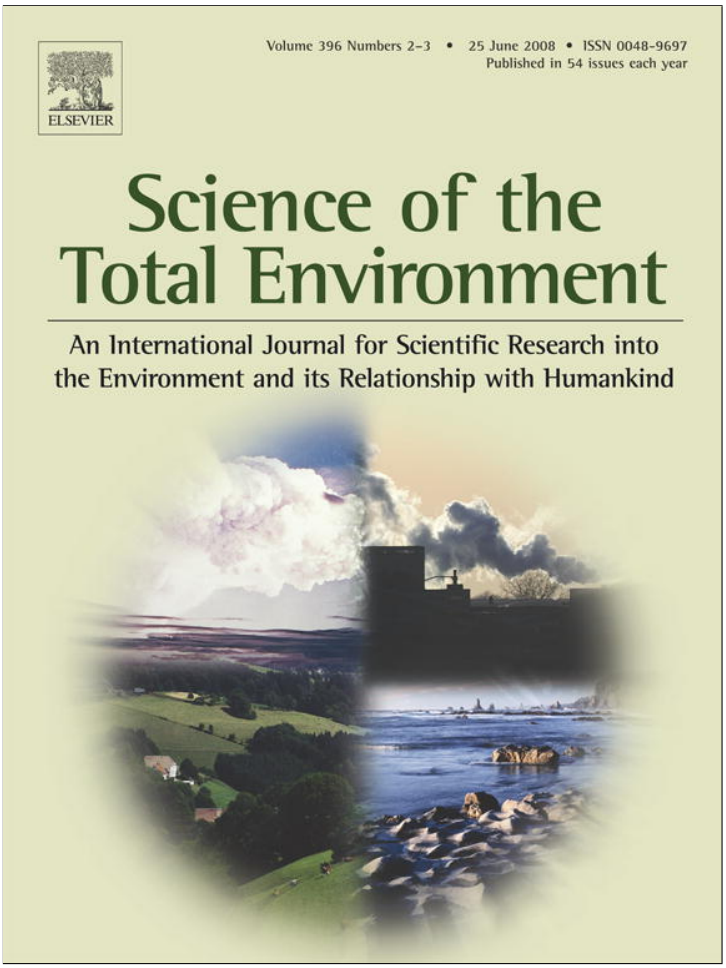

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Discussion

The conundrum of unmeasured confounding: Comment on: "Can some of the detrimental neurodevelopmental effects attributed to lead be due to pesticides? by Brian Gulson"

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ABSTRACT

The problem described by Dr. Brian Gulson – confounding by unmeasured exposures to pesticides – is only the most recent in a series of potential confounders cited to explain the observed effect of lead on children's intellectual abilities or behavioral problems. Despite the persistent problem of unmeasured confounders, there are several lines of evidence implicating lead as a toxicant at blood lead levels <10 μg/dL. First, in striking contrast with pesticides, there is considerable evidence from numerous studies linking low-level lead exposure with cognitive deficits and behavioral problems, even after controlling for a variety of potential confounders. Second, the consistency of evidence from diverse cohorts and distinct, if not always directly measured potential confounders — enhances our confidence that the lead effect observed at blood lead levels <10 μg/dL is not attributable to unmeasured confounders. Third, in our reanalysis of the Rochester Lead Study, the inclusion of parent-reported mouthing behaviors and breastfeeding status did not attenuate the effect of lead exposure on children's intellectual function. Finally, although we can never entirely dismiss unmeasured confounding in observational studies, we can rely on experimental studies of lead-exposed animals to confirm that lead is a toxicant. Thus, while we must remain vigilant for unmeasured or poorly measured confounders, it is crucial to balance the endless search for confounders with the evidence of toxicity and the need to take action to protect public health. The alternative, to perpetually permit children to be exposed to lead and other emerging toxicants, is both absurd and unacceptable.

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In their quest to control or conquer disability, disease and death, epidemiologists strive to isolate the unique contribution of a specific risk factor. But it isn't easy. Indeed, it isn't unusual for an epidemiologist to spend his or her entire career trying to identify and quantify the contribution of a risk factor, or exposure variable, for a disease. Beyond the practical problem of obtaining funds to conduct their research, investigators must deal with a variety of confounders that can bias the estimated effect of an exposure variable.

Confounding, the erroneous attribution of an effect to an exposure variable, results from a failure to account for risk factors that are associated with both the exposure variable and the outcome. The effect of confounding on the exposure variable can either be positive or negative — that is, the effect of the confounder, if it is ignored, is to increase or decrease the effect of the exposure variable. Many reviewers, however, focus on positive confounding when the estimated exposure effect is positive. To qualify as a confounder, a risk factor must not be on the causal pathway between the exposure variable and the outcome. Investigators can design observational studies to minimize confounding by precisely measuring all of the potential confounders and accurately characterizing their association with the exposure variable, but it is difficult to eliminate it (Lawlor et al., 2004; Bellinger, 2007).

Unmeasured confounding can be a particularly troublesome problem in observational epidemiology. There are usually reasons that confounders aren't measured. Unmeasured confounders may represent exposures that occurred in the distant past or there may not be validated instruments or biomarkers to measure them. It is difficult and expensive, for example, to precisely measure prenatal exposures for a disease that arises in adolescence. Nobody would fault epidemiologists for failing to adjust for pesticide exposures in published studies of lead-exposed children; it has only recently become feasible to routinely measure biomarkers of pesticide exposure in epidemiologic studies. Finally, even after a new study is published showing that the effects of an environmental toxicant persists after incorporating a risk factor that was previously suspected of acting as an unmeasured confounder, there is always another unmeasured confounder lurking in the imagination of an industry consultant or on the freshly printed pages of a peer-reviewed publication.

The problem described by Dr. Brian Gulson – confounding by unmeasured exposure to pesticides – is only the most recent in a series of potential unmeasured confounders cited to explain the observed effect of lead on children's intellectual abilities or behavioral problems (Gulson, 2008). Other investigators have written about potential confounding from unmeasured or poorly measured variables, such as poor parenting, maternal depression, iron status, tobacco exposure, poverty and pica (Pocock et al., 1994; CDC, 2005; Ernhart, 2006).

On the surface, Dr. Gulson is right to be concerned about pesticide exposure acting as a potential confounder of lead toxicity. Pesticides have been shown to be associated with diminished cognition and behavioral problems in children, if only in a few studies (Fenster et al., 2007; Rauh et al., 2006; Eskenazi et al., 2007). It shouldn't be surprising if we find that some pesticides are associated with cognitive deficits; pesticides were designed to be neurotoxic. Finally, children who have higher blood lead concentrations often have higher exposures to other environmental toxicants than children with lower blood lead concentrations (Mannino et al., 2003).

While the data are sparse, the most commonly used and widely studied pesticides, organophosphorous insecticides, have not been shown to be correlated with blood lead levels in maternal (prenatal) samples. Although blood lead concentrations were only available for a subset of children ($n=89$) in the study by Rauh et al. (2006), there was no significant correlation between maternal blood lead levels and serum chlorpyrifos levels ($r=0.08$, $p=0.49$). Similarly, in a preliminary analysis of our unpublished Health Outcomes and Measures of the Environment (HOME) Study ($n=187$), we found no statistically significant correlation of maternal blood lead concentrations with organophosphorous (OP) insecticide exposure measured using two creatinine-adjusted metabolites of OP insecticides, dimethylphosphate ($r=-0.03$, $p=0.67$) and diethylphosphate ($r=0.07$, $p=0.31$) in maternal urine. These data diminish, but do not dismiss concerns about pesticides acting as unmeasured confounders for the observed effects of environmental lead toxicity.

Despite some uncertainties – and the persistent problem of unmeasured confounders – there are several lines of evidence implicating lead as a toxicant at blood lead levels <10 μg/dL. First, in striking contrast with pesticides, there is considerable evidence from numerous studies linking low-level lead exposure with cognitive deficits and behavioral problems, even after controlling for a variety of potential confounders (Needleman et al., 1979, 1990, 1996; Bellinger et al., 1992; Baghurst et al., 1992; Burns et al., 1999; Wasserman et al., 1997; Dietrich et al., 2001; Canfield et al., 2003; Lanphear et al., 2005a; Braun et al., 2006). Second, the consistency of evidence from diverse cohorts – and distinct, if not always directly measured potential confounders – enhances our confidence that the lead effect observed at blood lead levels <10 μg/dL is not attributable to unmeasured confounders (Lanphear et al., 2000; Canfield et al., 2003; Wasserman et al., 2003; Lanphear et al., 2005a; Tellez-Rojo et al., 2006; Kordas et al., 2006; Schnaas et al., 2006; Hu et al., 2006; Surkan et al., 2007).

Despite the consistent evidence, there are a plethora of other variables – mouthing behaviors, breastfeeding, maternal depression, iron status and imprecisely measured exposure to prenatal tobacco smoke, to name only a few – that may be acting as unmeasured or poorly measured confounders in epidemiologic studies of lead toxicity. Tobacco exposure and iron status are the two most obvious potential confounders for lead toxicity. Investigators have reported that iron deficiency and tobacco smoke exposure are both associated with a higher blood lead concentration and cognitive deficits (Mannino et al., 2003; Wright et al., 1999; Fried et al., 2003; Yolton et al., 2005). Although iron deficiency is arguably on the causal pathway for lead absorption (Wright et al., 1999), and there is considerable room to improve the measurement of iron status and tobacco exposure in studies of low-level lead exposure in children, the effects of lead exposure have persisted in several studies after adjustment for iron status and tobacco exposure (Dietrich et al., 1993; Lanphear et al., 2000; Wasserman et al., 1997, 2003; Canfield et al., 2003; Lanphear et al., 2005a). Thus, it is unlikely that the lead effect is confounded by tobacco exposure or iron deficiency.

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In their review of the adverse effects at blood lead concentrations <10 μg/dL, the Centers for Disease Control Advisory Committee for Childhood Lead Poisoning Prevention singled out mouthing behaviors as a particularly important unmeasured confounder (CDC, 2005). Mouthing behaviors, which are a normal part of child development, are a risk factor for having an elevated blood lead concentration (Clark et al., 1991; Lanphear et al., 2002, Malcoe et al., 2002), but they have not been shown to be associated with intellectual abilities. More importantly, mouthing behaviors (e.g., ingestion of lead-contaminated house dust, soil or paint chips) sit precisely on the causal pathway between lead exposure and children's blood lead concentration. Thus, it would be inappropriate to consider mouthing behaviors as a confounder.

On the other hand, mouthing behaviors may be vulnerable to reverse causation. That is, children who have lower intellectual ability may exhibit more frequent or persistent mouthing behaviors, ingest more lead and subsequently have higher blood lead concentrations.

Using data from our previously published study (Canfield et al., 2003), we evaluated whether children ($n=172$) who exhibited mouthing behaviors had lower intellectual ability. Mouthing behaviors, collected when the children were 6, 12, 18 and 24 months of age, were based on parent report of their child putting soil, dirt or paint chips in their mouths (Lanphear et al., 2002). IQ was measured using the Stanford–Binet at 3 and 5 years of age (Canfield et al., 2003). The mean IQ for the 96 (56%) children who were ever reported to put soil or dirt in their mouths during the first two years of life was not significantly different than those who reportedly did not put soil or dirt in their mouths (90.1 versus 89.3, $p=0.58$). Similarly, the mean IQ for the 31 (18%) children who were ever reported to put paint chips in their mouths during the first two years of life was not different than those who reportedly did not put paint chips in their mouths (89.4 versus 90.0, $p=0.75$).

Although mouthing behaviors are on the causal pathway of lead exposure and intellectual deficits, and thus cannot be a true confounder, we tested whether the inclusion of mouthing behaviors and breastfeeding in our multivariable analysis attenuated or extinguished the estimated effect of lead exposure on children's intellectual ability (Canfield et al., 2003). In our reanalysis of the Rochester Lead Study, the inclusion of parent-reported mouthing behaviors and breastfeeding status (ever/never) did not attenuate the effect of lead exposure on children's intellectual function (Table 1). Thus, the lead effect was not confounded by either mouthing behaviors or breastfeeding status. Still, the skeptical epidemiologist might reasonably argue that no study has tested whether maternal depression or pesticide exposures are acting as unmeasured confounders and that there are always more potential unmeasured confounders lying in-wait.

Although we can never entirely dismiss unmeasured confounding in observational studies, we can rely on experimental studies of lead-exposed animals to confirm whether a metal or a chemical is a toxicant. The profile of behavioral changes seen in lead-exposed children is paralleled by observations from animal studies. In a recent study, we reported that children from the Rochester cohort exhibited specific deficits in tests that evaluated reaction time, memory, learning and reversal learning, and planning/executive function (Canfield et al., 2004). Similar impairments in learning and reversal learning or memory have been reported in rodents and non-human primates (Cory-Slechta, 1995; Cory-Slechta, 2003; Rice, 1993). Experimental trials also show that such behavioral changes appear to reflect perseverative behavior, increased distractibility and impulsivity (Brockel et al., 1998; Rice, 1993). The effects observed in experimental models occur at levels of exposure similar to those experienced by contemporary children. Discrimination reversal deficits in monkeys were found with developmental exposures resulting in peak blood lead levels of 15 to 25 μg/dL and steady state levels of 11 to 13 μg/dL (Rice, 1993). Increased impulsivity in rodent models was observed at blood lead levels of 9 to 11 μg/dL (Brockel et al., 1998; Rice 1993). Finally, in vitro studies have shown that disruptive effects of lead on intracellular processes and neurite growth occur at picomolar concentrations (Bressler et al., 1999; Schneider et al., 2003).

In our quest to isolate the unique contribution of a risk factor, we shouldn't forget that the inclusion of competing risk factors and exposure misclassification may inappropriately diminish lead's effect. It has, for example, become conventional for studies of environmental toxicants to include the HOME Inventory, a measure that reflects the quality and quantity of emotional and cognitive stimulation in the home environment, as well as an objective measure of housing condition. Because housing condition is a surrogate for lead exposure, its inclusion

Table 1 – Adjusted changes in children's IQ for each 1 μg/dL increase in concurrent and lifetime average blood lead concentration*

	Original adjusted results β + SE	*p* value	Adjusted for breastfeeding and mouthing behaviors β + SE	*p* value
Total sample ($n=172$)				
Lifetime average	−0.46 ± 0.15	0.004	−0.48 ± 0.16	0.003
Concurrent	−0.46 ± 0.14	0.002	−0.49 ± 0.15	0.001
Peak blood lead <10 μg/dL ($n=101$)				
Lifetime average	−1.37 ± 0.60	0.026	−1.45 ± 0.61	0.021
Concurrent	−1.58 ± 0.46	0.001	−1.61 ± 0.47	0.001

* The first model, taken from Canfield, et al. (2003) was adjusted for maternal IQ, maternal education, prenatal tobacco exposure, household income, race, HOME Inventory, child's sex, birth weight, preterm birth and iron status. The second model, which was adjusted for all of these variables as well as breastfeeding and parent reported mouthing behaviors (soil and paint chip ingestion) during the first two years of life, was a new analysis of data from Canfield, et al. (2003).

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may attenuate or diminish the effect estimate for blood lead concentration (Bellinger, 2004). Imperfect measures of lead exposure that result in exposure misclassification can also diminish the estimated effect of lead exposure on neurodevelopmental effects (Bellinger, 2007). Indeed, two studies using innovative biomarkers of lead exposure – bone lead and plasma lead – indicate that observational studies using whole blood lead concentration may have underestimated lead's effect on cognitive abilities or behavioral problems (Wasserman et al., 2003; Hu et al., 2006).

1. Conclusions

While we must remain vigilant for unmeasured or poorly measured confounders, it is crucial to balance the endless search for confounders with the evidence of toxicity and the need to take action to protect public health. The conundrum of unmeasured confounding described by Dr. Gulson thus raises another quandary; if we can never entirely eliminate the potential for unmeasured confounders from observational studies, is it possible to know enough to take action or promulgate a new standard for lead and other environmental toxicants? This quandary makes it imperative to establish a formal classification scheme to guide scientists and policy-makers in making inferences about the causal association of exposures to environmental chemicals and metals with neurobehavioral endpoints. This classification scheme, analogous with those used by the International Agency for Research on Cancer (IARC) and the National Academies of Science (IARC, 1987; IOM, 2000), should be used to categorize evidence as sufficient for a causal relationship, sufficient for an association, limited or suggestive for an association, inadequate or insufficient for an association, and limited or no evidence for an association. The primary value of this categorization is that it would allow us to acknowledge the limitations of observational epidemiology without prohibiting us from taking action to protect public health. The alternative, to perpetually permit children to be exposed to lead and other emerging toxicants, is both absurd and unacceptable.

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