Comments on "Recent Developments in Low-Level Lead Exposure and Intellectual Impairment in Children"

We commend Koller et al. (2004) for their thoughtful and detailed review of recent research on childhood lead exposure and intellectual development, and we take this opportunity to clarify and respond to several of their questions regarding our study of children with blood lead concentrations < 10 μg/dL) (Canfield et al. 2003).

The children in our cohort were recruited between 24 and 30 months of age, and all had participated in a prior randomized dust control trial (Lanphear et al. 1999). In that trial, dust and blood lead concentrations were assessed at 6, 12, 18, and 24 months of age as part of an evaluation of whether dust control measures reduced children's blood lead concentrations. Koller et al. (2004) raised several questions related to whether children's participation in the prior study affected the results we reported (Canfield et al. 2003). Specifically, their concerns related to confounding, where an imbalance in the distribution of intervention/control participants across levels of blood lead and IQ could bias the association between blood lead concentrations and IQ.

Our statistical model was developed *a priori* and included covariates that were established predictors of children's intelligence (Canfield et al. 2003). Because home visitation by a dust control team (intervention) seemed unlikely to increase children's IQ and because children who participated in the intervention actually had slightly lower IQ scores at 3 and 5 years of age compared with controls, intervention status was not considered a plausible confounder. To demonstrate that participation in the dust control trial did not introduce any bias of consequence and to illustrate our basis for excluding intervention status from our published models, in this letter we summarize results for a semiparametric spline model, which is identical to the one we reported previously (Canfield et al. 2003) except for the inclusion of intervention status as a potential confounding factor. The estimated decline in IQ as blood lead concentration increases from 1 to 10 μg/dL is 6.8 points when controlling for intervention status. This estimate is not meaningfully different from the 7.4-point decline we reported previously (Canfield et al. 2003). Furthermore, the shape of the dose–response function is preserved, with a steeper slope at lower blood lead concentrations. Estimates of the predicted decline in IQ from parametric models with linear and quadratic terms for blood lead also differ by < 10% from the reported results (Canfield et al. 2003) when intervention status is included in the model.

Additionally, Koller et al. (2004) suggested that the Stanford-Binet IV Test of Intelligence (SBIV) may not have provided the most accurate estimate of IQ for our cohort because of the relative weighting of verbal and nonverbal skills that are assessed and because of problems with the standard method of dealing with zero-scored subtests. Koller et al. (2004) suggested that the Wechsler Primary and Preschool Scales of Intelligence (WPPSI) would have yielded a more reliable and valid measure of intelligence. We first note that despite many attractive features of the WPPSI (and especially of the WPPSI-Revised, which we considered using), the SBIV has features that we believe made it a superior test for our particular cohort. Most importantly, the SBIV can be administered to 2-year-olds, whereas the youngest age for the WPPSI-R is 3 years. Because our sample was predominantly composed of families with lower parental education and income, we preferred the test with the lower floor.

With respect to how zero-scored subtests are handled, we indeed followed the standard scoring procedure for the SBIV, which states that a zero score "should not be included in the determination of the related Area Score or of the Composite Score" (Delaney and Hopkins 1987). Because this scoring method was used in the standardization of the instrument, a different approach would yield scores with unknown psychometric properties and thereby compromise interpretation of the results.

Nevertheless, any particular scoring method has its weaknesses, and we agree that it would be useful to know whether our results change markedly by incorporating information about zero scores. We therefore added as a time-varying covariate in our mixed models the number of subtests on which each child scored zero. In the semiparametric spline model, the estimated decline in IQ as blood lead concentration increased from 1 to 10 μg/dL was 6.3 points. Estimates from parametric models with linear and quadratic terms for blood lead differed by < 5% from the results we reported previously (Canfield et al. 2003). Thus, the incorporation of information about zero-scored subtests did not change our results markedly.

Potential sources of confounding and misclassification need to be carefully considered in the design and analysis phase of any study, observational or otherwise, and in the interpretation of results. The detailed attention given to these issues by Koller et al. (2004) has allowed us the opportunity to provide additional information about our methods and results and thereby address these methodologic issues.

Bruce P. Lanphear has acted as an expert witness for several plaintiffs in lead cases, but he has not received financial remuneration; instead, any payment has been donated directly to the Cincinnati Children's Hospital Medical Center. The other authors declare they have no competing financial interests.

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Low-Level Lead Exposure and Intellectual Impairment in Children: Koller et al. Respond

We are grateful to Jusko et al. for addressing two concerns raised in our review (Koller et al. 2004) relating to confounding and their use of the Stanford-Binet test in their original report (Canfield et al. 2003). They provide valuable additional analysis of their data, which further support their original findings.

Of relevance to the area of confounding is a recent publication by Mink et al. (2004)

in which the effects of different combinations of confounders on multivariate analyses of neurobehavior and neurotoxic exposure were studied. Taking maternal intelligence, home environment, and socioeconomic status as the three most important confounders in this field, Mink et al. urged caution in associating small differences in IQ score in the range of 3–10 points with the effects of environmental exposure; they also made a strong case for *a priori* consideration and planning for all potential confounders in epidemiological studies. As Jusko et al. explain, this is indeed the method they used in their original analyses (Canfield et al. 2003).

We feel that the weight of evidence across a number of studies has come down in support of an effect of low-level lead exposure on children's intellectual and neurobehavioral function; as stressed by Bellinger (2004), this evidence is supported by studies on experimental animals in which confounding is largely irrelevant.

The authors declare they have no competing financial interests.

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TCDD and Puberty in Girls

We would like to comment on the article by Warner et al. (2004), in which the authors reported no significant associations between age at menarche and exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), an extremely potent antiestrogenic xenobiotic. The exposure of girls to TCDD at Seveso, Italy, resulted in very high serum TCDD levels (> 100 pg/g lipid), 10–100 times levels usually seen today. Warner et al. noted that the literature is mixed regarding the agonist/antagonist effects in humans of persistent exposures of this type. First, polybrominated biphenyl exposures have been associated with earlier menarche in girls, whereas experimental models show delayed puberty, a discordance that may be due to timing of exposure (Blanck et al. 2000). Second, as Warner et al. (2004) noted, the experimental data show that TCDD and other estrogen antagonists delay vaginal opening (VO) and disrupt cyclicity in rodents treated prenatally (Gray et al. 1997; Levy et al. 1995). However, hormonal activity depends on both timing and level of dose, such that phytoestrogens, for example, may be estrogenic—hastening VO—at high doses given after birth (Lamartiniere et al. 1995; Whitten et al. 1995).

Epidemiologic data regarding hormonally dependent female cancer are equivocal, such that there have been suggestions of a protective (i.e., antiestrogenic) effect of TCDD for breast and uterine cancer in TCDD-exposed women from Seveso (Bertazzi et al. 2001), whereas a carcinogenic effect has been observed in cohorts exposed for longer times (Manz et al. 1991; Warner et al. 2002). The findings of Warner et al. (2004), albeit not statistically significant, suggest earlier menarche with higher TCDD level among women who were younger than 8 years of age at the time of exposure [hazard ratio, 1.08 for 10-fold increase in TCDD levels; 95% confidence interval (CI), 0.89–1.30) but not among all women regardless of age. The study population appears to have the usual patterns of risk for menarche as indicated by associations that occur in the expected directions [e.g., for Seveso zone, body mass index (BMI), physical activity, alcohol intake]. Also, TCDD levels were higher among younger girls (median, 205 ppt) than in all girls (median, 140 ppt), an effect that may reflect lower BMI among younger girls and dilution of body burden by greater body size in older girls, but also a significantly higher target-organ dose.

Warner et al. (2004) examined associations in premenarcheal girls who were a younger subset (0–8 years of age) during the exposure window in 1976. This age stratum should capture any strong underlying associations among girls exposed early in life. However, it is known that pubertal transition occurs around 5–7 years of age and that age at menarche is strongly correlated with age at first signs of development (de Ridder et al. 1992; Nicolson and Hanley 1953). Therefore, hormonal exposures before 5 years of age might alter the milestones of female development, including menarche, either more potently or in a different direction than peripubertal exposures. Therefore, the youngest girls in this population (Warner et al. 2004) may have been more susceptible to hormonal effects of environmental toxicants. Recognizing the limitation of small numbers available for further age stratification, it would be interesting to know whether risk of earlier (or later) puberty was raised among girls exposed at earlier ages, such as 0–4 years.

The authors declare they have no competing financial interests.

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TCDD and Puberty: Warner and Eskenazi Respond

As Wolff et al. note, in data from the Seveso Women's Health Study (SWHS) we found no change in age of onset of menarche associated with TCDD exposure in all women in the cohort or in women exposed before 8 years of age (Warner et al. 2004). However, Wolff et al. comment that hormonal exposures before 5 years of age might be the more relevant time period, given that the pubertal transition occurs around 5–7 years of age. Recognizing that our data may be limited by small numbers, Wolff et al. are interested in knowing whether risk of earlier (or later) puberty was seen among girls who were exposed before 5 years of age.

Of the 282 women in the SWHS cohort who were premenarcheal at the time of the explosion on 10 July 1976, 84 women were < 5 years of age. The mean age of menarche reported for the 84 women was 12.6 ± 1.5 years, and the median lipid-adjusted serum TCDD level was 233 ppt (range, 3.6–56,000 ppt). In Cox proportional hazards models, when $\log_{10}$TCDD was entered as the exposure variable, the hazard ratio associated with a 10-fold increase in TCDD was 1.2 [95% confidence interval, 0.98–1.6; p for trend = 0.07]. That is, the risk of early menarche was increased with the presence of a 10-fold increase in serum TCDD level (e.g., from 10 to 100 ppt), but not significantly. The data were too sparse in the lower exposure groups to perform categorical analyses. The observed increase was limited to the subset of women who were < 5 years of age at exposure, as the effect was diminished when we considered including older ages (< 6 years, < 7 years).

In summary, the sample size is too small to state with certainty, but it seems that the women who received higher exposure and were < 5 years of age at the time of the explosion may have been at somewhat increased risk for earlier menarche. As we stated in our article (Warner et al. 2004), the women in this study experienced significant TCDD exposure during the postnatal but prepubertal developmental period. Given that animal evidence suggests *in utero* exposure can affect onset of puberty, continued follow-up of the offspring of the SWHS cohort is important.

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Comment on "Breast Milk: An Optimal Food"

In their editorial "Breast Milk: An Optimal Food," Pronczuk et al. (2004) stated that "in most cases, mothers can and should be reassured that breast milk is by far the best food to give to their babies," despite the evidence that "a myriad of potential chemical contaminants … can be detected in breast milk," mainly because *a*) levels of environmental contaminants, as determined by subsequent surveys, continue to decrease; *b*) exposure through

Errata

Because the study "Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat" (Johnson et al. 2003) was a long-term and continuous study, the authors compiled the data from controls of several treatment groups. The control "sets" were statistically analyzed comparing the data to each other before being combined. The authors opine that the control values were statistically consistent across and throughout all the treatment groups. Using the control data in a cumulative manner increased the generalizability of the data, which purports to demonstrate the background rate and variability around rate estimates. The larger sample size somewhat increased statistical power without the inappropriate use of further valuable animal resources.

Table 1 presents the date ranges of experimental treatment and the coinciding control treatments. Each treatment exposure had a corresponding control group. Also, because of the more detailed information on competing financial interests now included in *EHP*'s Instructions to Authors, the authors now report that S.J. Goldberg served as an expert witness for a plaintiff in a judicial hearing in 1997. As previously stated in a prior letter to the editor (Johnson et al. 2004), at all times throughout this research, the authors were free to design, conduct, interpret, and publish the research without compromise by any controlling sponsor as a condition of review or publication.

Table 1. Control versus TCE treatment groups and dates of exposure.

Control		TCE		
Fetuses/mothers[a]	Dates	Dose	Fetuses/mothers	Dates
135/15	14 Jun 1989–10 Oct 1992	1,100 ppm	105/9	29 Jun 1989–12 Mar 1990
155/13	11 Dec 1992–20 Oct 1993[a]	1.5 ppm	181/13	29 Dec 1989–26 Dec 1990
62/6	15 Apr 1994–23 May 1994[a]			
120/10	6 Jul 1994–7 Jul 1995	2.5 ppb	144/12	6 Jun 1995–13 Jun 1995
134/11	18 Jul 1995–6 Oct 1995	250 ppb	110/9	5 Jul 1995–21 Jul 1995

[a]The total number of control rat fetuses/mothers was 606/55. [b]Other studies that coincided with these control groups were carried out during December 1989–June 1995 [e.g., metabolites that were reported in other articles (Johnson et al. 1998a, 1998b).

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In "Environmental Health Disparities: A Framework Integrating Psychosocial and Environmental Concepts" by Gee et al. [Environ Health Perspect 112:1645–1653 (2004)], the title of Figure 1 should be "Stress–exposure disease framework for environmental health disparities."

breast milk may be less important than exposure *in utero*; and *c*) there is little evidence that exposure through breast milk is associated with damage.

We believe that there is probably a fourth good reason in support of their recommendation. There is in fact some evidence that breast-feeding may counteract some of the negative effects of exposure to environmental contaminants *in utero*.

For example, Boersma and Lanting (2000) showed that at 6 years of age cognitive development is affected by prenatal exposure to polychlorinated biphenyls (PCBs) and dioxins. Breast-fed children, however, when compared to formula-fed children, had an advantage in terms of quality of movements, fluency, and cognitive development tests at 18 and 42 months of age and at 6 years of age, despite a higher PCB exposure from breast milk.

Ribas-Fito et al. (2003), studying a birth cohort of 92 mother–infant pairs highly exposed to organochlorine compounds, found that prenatal exposure was associated with a delay in mental and psychomotor development at 13 months of age and that long-term breast-feeding counterbalanced this damage because it was associated with better performance on both the mental and motor scales compared to short-term or no breast-feeding.

Vreugdenhil et al. (2004) found that children who were breast-fed for at least 16 weeks did not show the delays in development of the central nervous system that are present in children breast-fed for 6–16 weeks or formula-fed, despite a similar prenatal exposure to PCBs.

This evidence is not conclusive (scientific evidence rarely is), but we believe that it should not be omitted in an article on environmental contaminants and breast-feeding.

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Editor's note: In accordance with journal policy, Pronczuk et al. were asked whether they wanted to respond to this letter, but they chose not to do so.