It is unclear whether the SDA long-term morbidity results (*10*) are coherent with mortality results. Among individuals who were symptom-free at the start of the study, there was an association between increased symptoms and PM. These risk estimates were 40-fold greater than those estimated for smoking. There were no analyses presented for those individuals who had symptoms at the start of the study, but became symptom-free at the end of the study. This analysis is just as important as the analysis of incidence of new symptoms. If both showed an association with PM, the results would not be internally coherent (*1*).

I presented evidence showing why reduced lung function could be a confounder in these studies and that it meets the criteria for confounding. First, reduced lung function must be a risk factor for increased mortality (*1*). Second, reduced lung function must be correlated with between-city variations in $PM_{2.5}$, although the relationship shown in Figure 3 (*1*) could only be tested with the ecologically based exposure measures used in that study. Third, reduced lung function should not be on the same causal pathway as $PM_{2.5}$ for mortality; the point of the example shown in Figure 4 (*1*) was to suggest that important differences occur in the distribution of risk factors between cities, with lung function being one of many possible risk factors. I do not believe that adjustment for a few individual-level risk factors has adequately addressed the complex overall potential for confounding in these studies. We all realize that we can never make all groups completely comparable, but between-city differences in $PM_{2.5}$ concentrations are so small and relative risks so low that these studies are particularly susceptible to even slightly confounded results.

I believe this paper (*1*) and the questions raised by Künzli and Tager are in line with the scientific process of verification and refutation. They have led to further discussion that will hopefully lead to additional testing. However, it is disappointing that Künzli and Tager chose to question the integrity of the author's motivation based on affiliation. Judgment on whether or not my critique clouds the complex issues around $PM_{2.5}$ and mortality should be determined not by my affiliation but solely on the scientific merits of the argument.

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Methylmercury Neurotoxicity Independent of PCB Exposure

A prospective study of methylmercury neurotoxicity in a Faroese birth cohort (*1*) has been scrutinized at a workshop recently summarized in *EHP* (*2*). The meeting was convened by the NIEHS on behalf of the White House Office of Science and Technology Policy. One of the main issues considered by the expert panels was whether concomitant prenatal exposure to polychlorinated biphenyls (PCBs) affected the neurobehavioral response variables assessed at 7 years of age. In a previously published paper (*1*), we showed that adjustment for the cord PCB concentration barely changed the regression coefficients for the cord-blood mercury concentration as a predictor of neurobehavioral deficits. In response to questions raised at the workshop, we have now conducted some additional analyses to explore this issue

On the basis of the 436 cord PCB analyses completed (*1*), children with complete data were divided into tertile PCB exposure groups. The main source of increased PCB exposure in the Faroe Islands is whale blubber, but almost half of Faroese mothers are known not to eat this food item (*3*). The lowest tertile is therefore thought to correspond to a control group with a background exposure to PCB. Based on psychometric properties, one outcome variable was selected to reflect each of five different domains of brain function, i.e., motor function, attention, visuospatial function, language, and memory (*1*). A regression equation with a uniform series of confounder variables (*1*) was then fitted to the data for each of the three subgroups.

Table 1 shows the regression coefficients for the logarithmic transformation of the cord-blood mercury concentration, i.e., the change in the outcome variable associated with a 10-fold increase in methylmercury exposure. The hypothesis of no difference between the regression coefficients was then tested, and in all cases resulted in an acceptance of the hypothesis, with p-values of 0.16–0.94. Accordingly, the effect of mercury exposure can be explained by three parallel lines. The hypothesis of no PCB effect resulted in p-values between 0.07 and 0.73, thus suggesting no difference in the intercept between the three lines. Thus, given the acceptance of both null hypotheses, the effect of mercury exposure on each of the five neurobehavioral outcome variables can be explained by a single line. All mercury regression coefficients for the control group suggest a deficit at increasing concentrations similar to the one for the overall material (*1*). Also, when compared to the two other tertile groups, the mercury effect in the control group was the greatest for three of five outcome variables

However, some information may be lost, as the PCB exposure variable in this analysis was reduced to tertile classes only. Thus, the possible effect modification by PCB exposure was investigated in regression analyses, which in addition to the confounders, also included the mercury and PCB exposure variables as well as a product term between the two exposure biomarkers. The p-value for no effect modification was between 0.21

Table 1. Confounder-adjusted regression coefficients for effects of the logarithmic transformation of the cord-blood mercury concentration on neurobehavioral test performance in 7-year-old Faroese children separated according to the tertiles (low, middle, and high) of their cord-PCB concentration

Outcome	Lowest	Middle	Highest	All (CI)
NES-2 Finger tapping, preferred hand	-2.21	-1.41	-1.68	-1.60 (-3.38–0.18)
NES-2 Continued Performance Test, reaction time	44.14	34.11	31.65	40.03 (18.64–61.42)
Bender Visual Motor Gestalt Test, errors on copying	0.84	-0.12	3.86	1.25 (-0.29–2.80)
Boston Naming Test	-1.04	-1.04	-1.71	-1.93 (-3.39– -0.47)
California Verbal Learning Test, long delay recall	-1.26	-0.31	-0.38	-0.95 (-1.84– -0.07)

CI, 95% confidence interval.

and 0.75, thus suggesting that no interaction occurred. As previously reported (*1*), an independent effect of PCB exposure was suggested for the Boston Naming Test, although it affected the mercury regression coefficient only slightly

All of the above calculations were based on the wet-weight PCB concentrations, which showed a better correlation (r = 0.41, after logarithmic transformation) with the cord-blood mercury concentration than did the lipid-based PCB concentration (r = 0.31). The potential confounding and interaction effect were thereby maximized. No significant relationship with the outcome variables was found when using the lipid-based cord concentration as the PCB exposure biomarker. However, both PCB and methylmercury exposure biomarkers are likely to be imprecise indicators of the causative neurotoxicant concentrations, thereby possibly resulting in attenuated regression coefficients. Nonetheless, among the exposure biomarkers examined, the cord-blood mercury concentration remains the best predictor for neurobehavioral dysfunction in this population (*1*). The expanded analyses do not suggest that the mercury effect can be explained by concomitant PCB exposure or that PCB exposure results in an increased mercury-associated effect.

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