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Calculation of Mercury's Effects on Neurodevelopment

http://dx.doi.org/10.1289/ehp.1206033

Bellinger (2012) recently estimated the loss of cognitive function in terms of Full-Scale intelligence quotient (IQ) in children exposed to certain environmental chemicals. To ascertain prenatal exposures of methylmercury (MeHg) in children, he used exposure data on mercury (Hg) concentrations in hair of U.S. women of childbearing age (16–49 years) from NHANES (National Health and Nutrition Examination Survey) 1999–2000 (McDowell et al. 2004). Bellinger applied a regression coefficient of –0.18 IQ points per microgram per gram increase in maternal hair as calculated by Axelrad et al. (2007). However, the results of Axelrad et al. (2007) relied on incomplete data from a prospective study in the Faroe Islands and on nonadjusted results from the Seychelles study, later found to be confounded by nutrients from seafood (Strain et al. 2008). Bellinger (2012) then applied the regression coefficient to hair Hg levels > 1.11 μg/g (90th percentile), because this level corresponds to the reference dose of MeHg established many years ago. Assuming a concentration of 1.73 μg/g (95th percentile) as the midpoint (rather than the average, which is higher) for the hair Hg levels of the 10% of U.S. women with a level > 1.11 μg/g, he estimated a total IQ loss of 284,580 points. We believe that Bellinger's general approach is sound but that the dose–response information is outdated, a caveat that Bellinger noted, although it was not reflected in the summary table. We therefore wish to complement these calculations using updated dose–response data.

Prospective data justify a lower threshold Hg level of 0.58 μg/g hair corresponding to 50% of the reference dose (Grandjean and Budtz-Jørgensen 2007). In addition, a 1-μg/g increase in hair Hg concentration is more likely associated with an average adverse impact of 0.465 IQ points, as discussed by Pichery et al. (2012). Assuming a log-normal exposure distribution, a 75th percentile hair Hg concentration of 0.42 μg/g, and a 90th percentile of 1.11 μg/g as reported by McDowell et al. (2004), we estimate that 18.5% of women exceed a threshold of 0.58 μg/g hair Hg and that the average concentration for 0.58–1.11 μg/g is approximately 0.8 μg/g. For the sake of comparing these values with Bellinger's calculations (Bellinger 2012), we used a median concentration of 1.73 μg/g as the average hair Hg level of the 10% of U.S. women with a level > 1.11 μg/g. On the basis of these assumptions, we calculated a total IQ loss for the U.S. population of children 0–5 years of age (n = 25.5 million) to be 1,590,000 IQ points, or 264,000 IQ points per year.

We recently used similar calculations to estimate the annual costs of Hg pollution in France (Pichery et al. 2012), a country one-fifth the size of the United States. At slightly higher exposure levels, the annual loss in IQ points was estimated to be 157,000. Greater losses were obtained using a log-scale effect (Pichery et al. 2012). With an estimated value of each IQ point of $18,000 in terms of lifetime earnings, the current loss of IQ points associated with MeHg exposure represents a very substantial value to society.

The authors declare they have no actual or potential competing financial interests.

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Calculation of Mercury's Effects on Neurodevelopment: Bellinger Responds

http://dx.doi.org/10.1289/ehp.1206033R

In my paper (Bellinger 2012), I noted among the limitations that the calculations are only as valid as the data on which they are based. My hope was that those with a special interest in a particular risk factor would be stimulated to provide stronger data on either the exposure distribution or the dose–response relationship so that the calculations could be refined. I am therefore grateful to Grandjean et al. for providing an updated estimate of the dose–response relationship for prenatal methylmercury, the use of which suggests that the total Full-Scale IQ loss among U.S. children is considerably larger than my initial estimate. All of the estimates listed in Table 2 of my paper (Bellinger 2012) should be considered provisional and should be updated when more precise data become available.

The author has served as an expert witness in civil litigation involving exposures of children to lead and metallic mercury and has received travel funding and honoraria to present lectures on environmental heath of children.

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Estimating Risk of Circulatory Disease from Exposure to Low-Level Ionizing Radiation

http://dx.doi.org/10.1289/ehp.1206046

The comprehensive meta-analysis of Little et al. (2012) summarized possible circulatory disease risks related to medium and low doses of whole-body radiation exposure in humans. The authors looked at excess relative risk (ERR) estimates from 10 different epidemiological studies. Using two statistical measures to calculate pooled ERR, they determined aggregate measures of ERR for four detrimental health outcomes and they reported mostly significant values for the ERR per unit dose in their Table 2.

Nine of the 10 studies Little et al. (2012) considered included moderate cumulative doses > 0.4 Sv (see their Table 1), and they observed that risk trends in most cohorts were driven by a relatively small number of

highly exposed individuals. The authors then fitted a linear ERR model to the data of the meta-analysis and derived mortality risks at low-level radiation by extrapolation.

Linear extrapolation is used in radiation protection if cohort strata pertaining to low doses and dose rates have low statistical power. There are, however, indications for nonlinear protective effects of low doses delivered at low dose rates for end points related to atherosclerosis in mice (Mitchel et al. 2011). Moreover, the recent review of Rödel et al. (2012) showed that low-dose ionizing radiation modulates inflammatory immune reactions mostly with discontinuous or biphasic dose dependencies. These recent findings suggest that nonlinear dose responses might also play a role in the determination of the radiation risk for circulatory diseases.

In this context we note that in the 10 studies analyzed by Little et al. (2012), risk estimates were mainly calculated with linear no-threshold (LNT) models (in fact, 7 of the 10 studies applied only the LNT model). Motivated by recent radiobiological findings, we fitted a large number of dose responses, in addition to the LNT model, to the data of the Life Span Study (LSS) cohort of Japanese atomic-bomb survivors, which is among the cohorts considered by Little et al. (2012). We realized that several models fitted the data about equally well (Schöllnberger et al. 2012). Instead of picking a single model of choice for risk assessment (here, the LNT model), we allowed for model uncertainty via multimodel inference. By reducing the bias from model selection, we obtained larger uncertainty intervals for risk estimates. The "model-averaged" dose response predicted markedly lower risks than the LNT model for cerebrovascular disease (CVD) and for cardiovascular diseases excluding CVD. For example, for CVD an ERR model with a step at 0.6 Sv strongly influenced the average with a weight of 0.55 compared with the LNT model with a much lower weight of 0.26 (see Table 1 of Schöllnberger et al. 2012). We did, however, not find any evidence for a protective effect but only for the contribution of pathways that have a threshold.

Our results might have implications for issues of public health in the assessment of risk–benefit ratios for radiodiagnosis or radiotherapy. Thus, we encourage the use of multimodel inference techniques in the analysis of other cohorts. From our experience with the LSS cohort, we would expect lower risk estimates in the lower dose range with a more comprehensive characterization of uncertainties and improved support of the epidemiological data.

The authors declare they have no actual or potential competing financial interests.

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Estimating Risk of Circulatory Disease: Little et al. Respond

http://dx.doi.org/10.1289/ehp.1206046R

We welcome Schöllnberger and Kaiser's comments on our review (Little et al. 2012). The biology of radiation-associated atherosclerosis has been extensively reviewed (Advisory Group on Ionising Radiation 2010; Little et al. 2010). As we stated in our paper, there are "biological data suggesting that many inflammatory end points potentially relevant to circulatory disease may be differentially regulated below and above about 0.5 Gy," which is why we studied low-to-moderate exposures (Little et al. 2012). Mitchel et al. (2011) and Rödel et al. (2012) support a possible biphasic dose response, as do many other data (Advisory Group on Ionising Radiation 2010; Little et al. 2010).

Schöllnberger et al. used multimodel inference (Burnham and Anderson 1998) to assess circulatory disease risk in their analysis of the Life Span Study (LSS) cohort of atomic-bomb survivors who were exposed briefly to radiation (Schöllnberger et al. 2012). We doubt that the effect they observed can be simply generalized to studies of other groups, in particular those chronically exposed. More important, most studies do not have information on potential confounders. We judge that the focus should not be to improve statistical modeling techniques, but to critically address the problems of confounding or other bias and to assess low-dose biological mechanisms.

We also question the validity of the threshold models Schöllnberger et al. (2012) used. No data suggest a threshold for biological markers relevant to circulatory disease (Advisory Group on Ionising Radiation 2010; Little et al. 2010).

Schöllnberger et al. (2012) used older LSS data (Preston et al. 2003) limited to deaths in proximal survivors since 1968; we judge these restrictions to be questionable for circulatory disease end points. In our analyses (Little et al. 2012), we used current LSS data (Shimizu et al. 2010) that show substantially more deaths (12,139 vs. 3,954 for stroke; 14,018 vs. 4,477 for heart diseases), which means the analysis by Schöllnberger et al. (2012) has much less statistical power and that some of their inferences are likely inconsistent with the current data.

In summary, Schöllnberger et al. (2012) used biologically questionable models fitted to a single, older (LSS) data set, disregarding evidence from radiation-induced circulatory disease risks in several populations with low-to-moderate exposures (Little et al. 2012). It is important to know whether low doses or dose rates of radiation are associated with increased morbidity and premature mortality and, if so, by what mechanism. The point of our paper was to address this clinical and public health concern.

The authors declare they have no actual or potential competing financial interests.

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Is Ambient $PM_{2.5}$ Sulfate Harmful?

http://dx.doi.org/10.1289/ehp.1205873

Lepeule et al. (2012) associated reduced $PM_{2.5}$ (particulate matter ≤ 2.5 μm in aerodynamic diameter) with decreased mortality over almost four decades. Because the sulfate/$PM_{2.5}$ ratio dropped among six localities but the $PM_{2.5}$ mortality coefficient did not "substantially" increase, the authors concluded that sulfate must be "about as toxic" as average $PM_{2.5}$. In a two-pollutant world, perhaps.

When a single source emits several $PM_{2.5}$ species, and a specific species is emitted from several sources, chemical-specific associations might not reflect inherent toxicity but rather status as a marker of harmful coemissions (Grahame and Hidy 2007; Mostofsky et al. 2012). Furthermore, because total $PM_{2.5}$ is often associated with adverse health outcomes, association of a constituent representing a large portion of total mass (e.g., sulfate) may occur unrelated to any inherent toxicity (Mostofsky et al. 2012).

Toxicological studies have not indicated adverse health effects from sulfate per se (Schlesinger and Cassee 2003). However, reducing a unit of black carbon (BC) increased life expectancy 4–9 times more than reducing a unit of $PM_{2.5}$ (Janssen et al. 2011). Evidence from both toxicological and human panel studies with accurate subject exposure consistently has linked BC with adverse cardiovascular health outcomes (Grahame and Schlesinger 2010). Metals and other emissions from older steel plants are particularly toxic (Dye et al. 2001).

Substantial reductions in BC and polycyclic aromatic hydrocarbons from diesel engines and coke ovens, various metals from steel plants, and nickel and vanadium from residual oil have occurred over the time frame examined by Lepeule et al. (2012). Sulfur was coemitted by all of these sources. Because less abundant but more toxic $PM_{2.5}$ species were also substantially reduced over this period, changes in the sulfate/$PM_{2.5}$ ratio as applied to mortality might reflect toxicity of coemissions, not of sulfate. Is sulfate inherently toxic or merely a coemission of harmful PM species?

Researchers must use models that include many relevant $PM_{2.5}$ species to successfully parse adverse health effects of each (Grahame and Hidy 2007). BC (and to a lesser extent nickel) remains consistently associated with adverse health outcomes when increasingly sophisticated models—all including 18 $PM_{2.5}$ species—are used; however, sulfate associations become negative and insignificant (Mostofsky et al. 2012).

Further, subject exposure measures must be reasonably accurate; associations found with accurate exposure may not be found when central monitor concentrations are proxies for exposure across a metropolitan area (Suh and Zanobetti 2010).

Human panel studies can examine effects of $PM_{2.5}$ species with more accurate subject exposure. Schwartz et al. (2005) found consistent associations for measures of heart rate variability with BC, but fewer associations for $PM_{2.5}$. In that study, the authors used an algorithm separating BC from $PM_{2.5}$ and found no associations with the $PM_{2.5}$ remainder (termed "secondary $PM_{2.5}$" by the authors), which would include both secondary sulfate and its reaction products.

Any conclusions regarding sulfate toxicity are premature until consistent results from advanced models (Mostofsky et al. 2012), which are able to examine many chemical species and incorporate good exposure measures, are available and are congruent with toxicology.

The authors declare they have no actual or potential competing financial interests.

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Is Ambient $PM_{2.5}$ Sulfate Harmful? Schwartz and Lepeule Respond

http://dx.doi.org/10.1289/ehp.1205873R

Grahame and Schlesinger make two arguments against the conclusions of our paper (Lepeule et al. 2012). Regarding their first point, we argued that if sulfates are nontoxic—and the fraction of particles that are