

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.

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Estimating Risk of Circulatory Disease: Little et al. Respond

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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.

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Is Ambient PM_{2.5} Sulfate Harmful?

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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.

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

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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 non-toxic—and the fraction of particles that are