

Letters to the Editor

Readers are invited to submit letters for publication in this department. Submit them to: The Editor, Journal of Occupational and Environmental Medicine, 605 Worcester Road, Towson, MD 21286-7834. Letters should be sent as hard copy with an accompanying diskette and should be designated "For Publication."

Short-Term Exposure to Urban Dust

To the Editor: The recent study by Riechelmann et al¹ raises important clinical issues. What is the amount of time that their environmental exposure model would need to be in place to cause a permanent, fixed altered mucosa? For example, an environmental exposure for many years would easily extrapolate to chronic increase in sinus conditions. However, a one-time, 1-hour exposure could not plausibly be argued to permanently raise a patient's risk of selected upper respiratory conditions. Finally, if a one-time exposure does raise the risk, for what period of time is that risk elevated?

Mark H. Hyman, MD
Los Angeles, CA

References

1. Riechelmann H, Rettinger G, Lautebach S, et al. Short-term exposure to urban dust alters the mediator release of human nasal mucosa. *J Occup Environ Med.* 2004;46:316–322.

Response

To the Editor: Dr Hyman raises an important question concerning time-extrapolation of data gained in acute exposure investigations. As a rule, sub-acute (14 days < 3 months) exposure studies allow deliberate data extrapolation to subchronic (3 months < 2 years) or chronic (> 2 years) exposure conditions.¹ This is not true for acute exposures lasting few hours. The main reason is that within a few hours, compensatory mechanisms in response to the action of an inhaled agent may not be in effect. Such compensatory mechanisms have been reported for, eg, inhaled ozone.² Data on long term

effects of urban dust in real-world concentrations are available from epidemiologic investigations.³ This study adds some information on possible physiopathologic mechanisms underlying these epidemiologic findings.

However, this study did not actually aim at chronic effects. Short peak concentrations of environmental dusts also may increase the incidence of upper respiratory tract conditions.^{4,5} Such peak concentrations are satisfactorily mimicked by the exposure setting chosen. The observed subtle alterations in nasal cytokine profile per se do not allow one to conclude a raised risk for respiratory conditions, but synoptically with the epidemiologic observations, increased risk for respiratory conditions after environmental dust peak concentrations becomes a plausible concept. Apparently, the onset of the increased incidence of respiratory conditions is 1 to 2 days after the concentration peaks and lasts 1 to 2 days.⁵

References

1. Kalberlah F, Fost U, Schneider K. Time extrapolation and interspecies extrapolation for locally acting substances in case of limited toxicological data. *Ann Occup Hyg.* 2002;46:175–185.
2. Plopper CG, Paige R, Schelegle ES, Uckpitt AB. Time-response profiles: implications for injury, repair, and adaptation to ozone. In: Bates DV, Brain JD, Driscoll KE, et al, eds. *Relationships Between Acute and Chronic Effects of Air Pollution.* Washington: ILSI Press; 2000.
3. Calderon-Garciduenas L, Rodriguez-Alcaraz A, Villarreal-Calderon A, Lyght O, Janszen D, Morgan KT. Nasal epithelium as a sentinel for airborne environmental pollution. *Toxicol Sci.* 1998;46:352–64.
4. van der Zee SC, Hoek G, Boezen MH, Schouten JP, van Wijnen JH, Brunekreef

B. Acute effects of air pollution on respiratory health of 50–70 yr old adults. *Eur Respir J.* 2000;15:700–709.

5. Hajat S, Anderson HR, Atkinson RW, Haines A. Effects of air pollution on general practitioner consultations for upper respiratory diseases in London. *Occup Environ Med.* 2002;59:294–9.

Herbert Riechelmann, MD, PhD
Department of Otolaryngology
University of Ulm, Medical School
Ulm, Germany

DOI: 10.1097/01.jom.0000141777.15678.c1

Arsenic in Drinking Water and Bladder Cancer Mortality in the United States: An Analysis Based on 133 U.S. Counties and 30 Years of Observation (*J Occup Environ Med.* 2004;46:298–306)

To the Editor: Lamm et al.¹ analyzed the association between arsenic exposure through drinking water and bladder cancer mortality in 133 US counties. They concluded that the results provide a direct estimate of arsenic-related cancer risk for the US residents. Although we concede that their analysis has some advantages over a previous study² by conducting their study in the US, we found some serious methodologic flaws and cannot support the assumption that an ecologic study provides an appropriate risk estimate for the association of exposure to arsenic with the development of bladder cancer. Our line of arguments will focus on three points.

First, Lamm et al.¹ correlated the bladder cancer mortality of 133 US counties with arsenic levels in the ground water. Such studies are prominent for a bulk of biases because they are grounded on aggregate measures and not on individual data. Therefore, ecological studies are generally considered prone to an ecological fallacy and thus especially problematic for a quantitative risk assessment.³ Although Lamm et al.¹ are aware of this matter they state that their results provide a direct estimate of the arsenic-related cancer

risk for US residents. We cannot follow this argument. In 1999 the National Research Council⁴ evaluated the risk of arsenic in drinking water. For the risk estimation, they extrapolated data from an ecologic Taiwanese study⁵ but considered “ecological studies most problematic when the groups being analyzed are very heterogeneous. That would be the case, for example, if one were to measure arsenic concentrations for every county in the United States and then try to correlate those concentrations with county-specific cancer rates” (National Research Council report,⁴ p. 269); such an approach was applied by Lamm et al.¹ Many factors may result in a low reliability of the results. Mortality data are less appropriate than incidence data because survival rates are relatively high for bladder cancer and death certificates are of limited quality. Smoking prevalence referring to the most important risk factor for bladder cancer may considerably vary between counties. It can be questioned whether there is an equal contribution of the amount of ground water to the daily fluid intake in all counties due to differences in climate and other circumstances.

Second, Lamm et al¹ used a linear regression model instead of Poisson regression with the county-specific standardized mortality ratios (SMR) as dependent and the median county arsenic concentration as independent variables. This is an incorrect application of straight-line regression because at least three of the five statistical assumptions for such a model are violated. Especially the linearity assumption that SMR is a straight-line function of the arsenic concentration can obviously not be held by inspecting their Figure 1. In addition, the homoscedasticity is violated due to different population sizes of the countries. Therefore, the variance of the country-specific SMRs is not constant but varying according to the Poisson distribution of observed cancer cases and correspondingly of the SMRs as the ratio of observed to

expected cases.⁶ Hence, the assumption of a Gaussian distribution of the country-specific SMRs also is incorrect. It is well known that violating at least one of the linear regression assumptions will lead definitely to invalid results. Instead, Poisson regression should be used with the natural logarithm of the county-specific SMRs as dependent variable.⁶ This has the additional advantage that the noncomparability of the SMRs—although they have the same reference population—is no longer a problem.⁷

Third, Lamm et al¹ provided SMRs with 95% confidence intervals (CI) for different strata of arsenic levels (see Table 1¹). There are exact as well as approximative methods available to calculate the confidence limits of SMRs. Lamm et al¹ do not refer to the method used. By inspection we presume the application of the Fieller approach because it is implemented in the SISA program.⁸ Using their published figures, we calculated exact CIs for the arsenic concentrations 3.0–3.9 $\mu\text{g/L}$ and 4.0–4.9 $\mu\text{g/L}$, respectively, with the PAMCOMP software.⁹ The exact confidence intervals are 0.90 to 0.99 for the arsenic level 3.0–3.9 $\mu\text{g/L}$ and 0.89 to 0.99 for 4.0–4.9 $\mu\text{g/L}$, respectively, assuming that the observed deaths follow a Poisson distribution. In contrast to the published CIs, these CIs are statistically significant. The majority of methods to calculate SMRs, including asymptotic methods, will produce statistically significant results at the 5% level for both strata because of large numbers of observed cases.

In summary, we consider the ecologic nature and the inappropriate statistical analysis as methodologic shortcomings that do not allow one to conclude on the direct respectively “true” bladder cancer risk of arsenic in drinking water. We confirm the National Research Council’s suggestion⁴ for the need of well-conducted epidemiologic studies involving individual exposure assessment and confounder controlling. Frost et al¹⁰

have demonstrated that there is enough power to perform cohort studies to detect a potential bladder cancer risk in the United States. At this point of time, ecologic studies do not add to the question if there is an arsenic-related health risk of bladder cancer from drinking water. Instead, such studies may even provide a biased estimate of the association.

Dirk Taeger, MSc
Beate Pesch, MSc, PhD
Berufsgenossenschaftliches
Forschungsinstitut für
Arbeitsmedizin (BGFA)
University of Bochum
Bochum, Germany

References

1. Lamm SH, Engel A, Kruse AB, et al. Arsenic in drinking water and bladder cancer mortality in the United States: an analysis based on 133 U.S. counties and 30 years of observation. *J Occup Environ Med.* 2004;46:298–306.
2. Wu MM, Kuo TL, Hwang YH, et al. Dose-response relation between arsenic concentration in well water and mortality from cancers and vascular diseases. *Am J Epidemiol.* 1989;130:1123–1132.
3. Rothman KJ, Greenland S. *Modern Epidemiology*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.
4. National Research Council. *Arsenic in Drinking Water. National Research Council, National Academy of Sciences.* Washington, DC: National Academy Press; 1999.
5. Tseng WP, Chu HM, How SW. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst.* 1968;40:453–463.
6. Breslow NE, Lubin JH, Marek P, et al. Multiplicative models and cohort analysis. *J Am Stat Assoc.* 1983;78:1–12.
7. Checkoway H, Pearce N, Kriebel D. *Occupational Epidemiology*, 2nd ed. New York: Oxford University Press; 2004.
8. Uitenbroek DG. SISA-Binomial. 1997. Available at: <http://home.clara.net/sisa>; Internet; accessed August 8, 2004.
9. Taeger D, Sun Y, Keil U, et al. A stand-alone windows applications for computing exact person-years, standardized mortality ratios and confidence intervals in epidemiological studies. *Epidemiology.* 2000;11:607–608.
10. Frost F, Craun G, Brown KG. Detection of excess arsenic-related cancer risks. *Environ Health Perspect.* 2002;110:A12.

Response

To the Editor: Taeger and Pesch raise certain methodologic issues concerning our published analysis of county-specific bladder cancer mortality and groundwater arsenic levels in the United States and our use of an ecologic study to develop a risk estimate for the association between arsenic exposure and bladder cancer. They contrast our ecologic analysis on US data with the ecologic analyses of the NRC (and EPA) on Taiwanese data.

We do agree that individual exposure data (as well as data on potential confounders) are preferable to aggregate data and the lack of specific information on potential confounding variables. However, neither our study nor the Taiwan study has that information. Nonetheless, we believe that these analyses can be useful in putting bounds on the relationship between bladder cancer and arsenic exposure from drinking water.

Taeger and Pesch would have preferred that we had conducted our analysis using a Poisson regression model rather than the linear regression model, indicating that use of the natural logarithm of the SMR (rather than the SMR itself) as the dependent variable would remove the non-comparability of the SMRs as a problem. We have conducted the analysis as they ask and obtain results that are not appreciably different from those we published, ie, no association is found between arsenic

exposure and bladder cancer mortality (whether using the mean or the median as the measure of exposure or performing either weighted or unweighted regression). In our published analyses, we included both models using weighted regression and using a restriction to counties with 10 or more cases to deal with some of the inherent variability and to demonstrate whether our results were method-dependent or data-dependent.

Taeger and Pesch, likewise, would have preferred us to use other methods for calculating the 95% CIs. Their methods result in intervals that are barely different from ours (an interval of 0.90–0.99 for the 3.0–3.9 $\mu\text{g/L}$ strata in our Table 2 compared to our interval of 0.89–1.01 and an interval of 0.89–0.99 for the 4.0–4.9 $\mu\text{g/L}$ stratum in our Table 2 compared to our interval of 0.88–1.02). Taeger and Pesch used methodology that assumes on a theoretical basis that the “real” SMR for these strata is 1.00. We believe that this is not necessary and is unlikely. We had already demonstrated that the estimated SMR for the total group of 133 counties (SMR = 0.94; 95% CI = 0.90–0.98) did not include 1.00. We speculate that this is because the US counties that depended on groundwater for their drinking water supplies during the med-twentieth century were less likely to be large urbanized areas with both greater occupational and cigarette smoking exposures. The important

finding in our analysis is that there is no apparent dose-related arsenic risk factor in the distribution of the bladder cancer SMRs among these 133 counties with median arsenic exposures in the 3–59 $\mu\text{g/L}$ range.

The US data seem to exclude the more extreme extrapolations downwards from data at higher doses from Chile, Argentina, and from Taiwan such as that of the most recent NAS report. They do not exclude the extrapolation used by the Environmental Protection Agency in their risk assessment in the year 2000. Another possibility that some of the present authors (Lamm et al., 2003) consider more likely is that the Taiwan study demonstrates a high arsenic dose-response risk only for the artesian well-dependent villages and not for the villages with shallow wells.

It is hard to prove a negative. Although the risk cannot be demonstrated to be below the one in a million lifetime risk, using conservative extrapolation techniques that are often used by Environmental Protection Agency, the risk at present arsenic levels for most Americans is undetectable and might be considered negligible.

Steven H. Lamm, MD
Arnold Engel, MD
Michael B. Kruse, PhD
Manning Feinleib, MD
Daniel M. Byrd, PhD
Shenghan Lai, MD
Richard Wilson, DPhil

DOI: 10.1097/01.jom.0000141655.00168.0d