[1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene] levels. Serum DDE was assessed only in blood drawn at entry to the cohort, which, for all participants, was subsequent to childbearing and lactation. Serum DDE prior to lactation is not known for these women. Note that serum DDE at study entry was uncorrelated with months of lactation (Pearson correlation coefficient = .096; $P = .15$).

In our study, parity did not confound the relationship between serum DDE level and breast cancer. Our reported regression coefficient for DDE as a continuous variable was .0823 in conditional logistic regression adjusted for first-degree family history of breast cancer, lifetime lactation, and age at first full-term pregnancy. When adjustment for number of full-term pregnancies was added to this model, the regression coefficient for DDE as a continuous variable changed only negligibly, to .0822 ($P = .007$).

NEIL DUBIN
PAOLO G. TONIOLO
ERIC W. LEE
Institute of Environmental Medicine
NYU Medical Center
New York, NY
MARY S. WOLFF
Division of Environmental and Occupational Medicine
Mt. Sinai School of Medicine
New York

Reference

(*1*) Wolff MS, Toniolo PG, Lee EW, et al: Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 85:648–652, 1993

Note

Correspondence to: Mary S. Wolff, Ph.D., Division of Environmental and Occupational Medicine, Mt. Sinai School of Medicine, Box 1057, 1 Gustave L. Levy Place, New York, NY 10029.

Re: Lung Cancer Incidence Among Patients With Beryllium Disease

It has been reported by Steenland and Ward (*1*) that an excess of lung cancer has developed in a series of patients admitted to the Beryllium Case Registry with diagnoses of nonneoplastic disease associated with beryllium. An accompanying editorial by Saracci (*2*) emphasized the importance of that report in confirming a causal relationship between exposure to beryllium and lung cancer in humans. Of particular importance in the Steenland and Ward article was the finding that a disproportionate number of the lung cancers occurred in individuals with a history of the acute forms of beryllium disease. This finding had been noted previously by Ward et al. (*3*).

There were 689 patients in the Steenland and Ward study (*1*). Among these, 28 died of lung cancer that developed after entry in the registry. Of all 689 patients, 235 were reported to have had acute beryllium disease and 17 of these died of lung cancer. Dr. Steenland has provided me with the Beryllium Case Registry admission numbers for 27 of the 28 patients who developed cancer. One patient was evidently omitted inadvertently, but this omission is of no consequence. It is of particular significance that all 17 of the patients with lung cancer who had a history of acute beryllium disease were employed in one plant in Lorain, Ohio, which ceased operation in 1948. Of the seven facilities studied by Ward et al. (*3*), the plant at Lorain was also the one that had the greatest excess of lung cancer. After correction for smoking, the standardized mortality ratio (SMR) for lung cancer at this plant was 1.49.

The Lorain plant extracted beryllium from ore and operated at a time when the toxicity of beryllium was not yet recognized. The levels of exposure were higher by orders of magnitude than the levels that have been allowed since the early 1950s when the first industrial hygiene standards were established (*4*). The Lorain plant had employed 145 (61%) of all the patients who had acute beryllium disease that was reported to the registry. The remaining 90 patients had worked in plants that manufactured fluorescent lamps, in nonferrous foundries, in several metallurgical laboratories, or in another beryllium refinery.

It is necessary to explain why no cases of lung cancer were found among the 90 employees who developed acute beryllium disease at these other facilities. The acute cases were generally associated with concentrations of beryllium in excess of 100 $\mu g/m^3$. During an industrial hygiene survey of the Lorain plant, exposures as high as 4700 $\mu g/m^3$ were reported (*5*). Higher levels of exposure were known to have existed in another one of the seven plants (*6*).

There was evidently a confounding factor in the Lorain cohort. This factor may have been cigarette smoking, for which any correction must always be associated with a degree of uncertainty. It is also possible that traces of another carcinogen may have been present at Lorain but not at the other six locations.

One must also question the relevance of the findings of Steenland and Ward (*1*) and Ward et al. (*3*) to the question of whether beryllium is carcinogenic to humans under the conditions of exposure that have existed in recent years. During the past four decades, major changes have taken place in the way beryllium is used. The current limit for occupational exposure to beryllium is 2 $\mu g/m^3$, which is orders of magnitude lower than the exposures that existed more than 40 years ago when the Lorain employees were exposed. The SMR reported by Ward et al. (*3*) for the seven plants studied was 1.12 after correction for smoking. The SMR for the Lorain plant was 1.49. The excess risk becomes inconsequential if one assumes that beryllium is the causative agent and uses the linear hypothesis favored by regulatory agencies to assess the risk of developing lung cancer under present-day conditions. Exposures to workers have

been reduced more than 100-fold below those that existed when the Lorain plant was in operation. Such extrapolation would reduce the SMR from exposures at current levels of exposure from 1.49 to less than 1.0049.

MERRIL EISENBUD, Sc.D.
711 Bayberry Dr.
Chapel Hill, NC 27514

References

(*1*) Steenland K, Ward E. Lung cancer incidence among patients with beryllium disease: a cohort mortality study. J Natl Cancer Inst 83:1380–1385, 1991
(*2*) Saracci R: Beryllium and lung cancer: adding another piece to the puzzle of epidemiologic evidence. J Natl Cancer Inst 83:1362–1363, 1991
(*3*) Ward E, Okun A, Ruder A, et al: A mortality study of workers at seven beryllium processing plants Am J Ind Med 22:285–904, 1992
(*4*) Eisenbud M. The origins of the standards for control of beryllium disease (1947-1949). Environ Res 27:79–88, 1982
(*5*) Laskin S, Turner RAN, Stockinger HE: An analysis of dust and fume hazards in a beryllium plant. *In* Pneumonoconiosis (Vorwald AJ, ed). Leroy U. Gardner Memorial Vol. New York Hoeber, 1950
(*6*) Shilen J, Koppenhaver FB, Cleland JG, et al: Beryllium extraction, reduction and alloy fabrication. Ind Med Surg 23:291–299, 1954

Note

Dr. Eisenbud is Professor Emeritus of Environmental Medicine at the Nelson Institute of Environmental Medicine, New York University Medical Center. He is currently Scholar in Residence in the Division of Occupational Health, Duke University Medical Center, and is serving as Chairman of the Beryllium Industry Scientific Advisory Committee.

Response

Dr. Eisenbud refers to our mortality study (*1*) of 689 patients with beryllium disease who were identified from the Beryllium Case Registry, which showed an excess of lung cancer (standardized mortality ratio [SMR] = 2.00; 95% confidence interval [CI] = 1.33-2.89) on the basis of 28 lung cancer deaths. This excess was more pronounced among patients with acute beryllium disease (n = 237; SMR = 2.32; 95% CI = 1.35-3.72) than among those with chronic disease (n = 439; SMR = 1.57; 95% CI = 0.75-2.89). Acute cases are similar to a chemical pneumonitis that occurs shortly after a high exposure, while chronic cases represent a progressive granulomatous disease, which may occur decades after exposure.

Dr. Eisenbud states that all the lung cancer deaths among the patients with acute beryllium disease (n = 17) were among employees of the Lorain plant. He suggests that this finding is surprising and speculates that exposures at Lorain were unique, perhaps involving other carcinogens or excessive cigarette smoking.

Table 1 presents the data for Beryllium Case Registry patients with acute or chronic beryllium disease and compares Lorain with other plants. Because information about plants was missing for some patients in the Beryllium Case Registry, data on these patients are not included in Table 1.

While these data do show a higher lung cancer risk for Lorain employees with acute disease versus employees with acute disease who worked in other plants, the opposite is true for those with chronic disease. For both disease types, the sparse numbers make it difficult to draw any conclusions about lung cancer risk at Lorain versus that risk at other plants.

We agree that exposures at Lorain, which operated for only a few years in the 1940s, were likely to have been very high. The data in Table 1 support that view, given the preponderance of acute cases at Lorain (acute cases generally are reflective of high exposures). The ratio of acute to chronic cases in the Beryllium Case Registry from Lorain was 5.4, while it was 0.26 at other plants.

Additional evidence of the lung cancer risk at Lorain versus that at other plants is provided by the cohort study of 9225 beryllium workers at seven beryllium plants by Ward et al. (*2*). The Lorain plant had the highest SMR for lung cancer in that study, which is not surprising, given the presumably higher exposures and longer potential latency. However, that study also found substantial evidence for the finding of increased lung cancer risk at plants other than Lorain when the data are restricted to those hired in the 1950s, who therefore had sufficient potential latency to develop lung cancer. The SMRs for those hired in the 1950s were elevated at the Reading (SMR = 1.42), Elmore (SMR = 1.42), Hazelton (SMR = 1.86), and Cleveland (SMR = 1.32) plants, but the findings were not statistically significant. Beryllium exposures at these plants during the 1950s are presumed to have been substantially lower than those at Lorain in the 1940s, but the SMRs for lung cancer are similar (possibly because of longer duration of exposure at plants other than Lorain).

In summary, although both the Beryllium Case Registry (*1*) study and the cohort mortality study (*2*) found the greatest risk of lung cancer among workers at the Lorain plant, in neither study was the increased risk of lung cancer confined to this group. Some of the difference in the magnitude of

Table 1. Lung cancer SMRs for Beryllium Case Registry patients, by plant and berylliosis disease type*

	Lorain	Other plants
Acute disease		
No. of cases	146	78
No. of lung cancer deaths	14	2
SMR (95% CI)	2.86 (1.56-4.80)	0.99 (0.12-3.59)
Chronic disease		
No. of cases	27	385
No. of lung cancer deaths	0	10
SMR (95% CI)	0 (–)	1.70 (0.81-3.12)

*Our data on the plant where the acute-disease lung cancer decedents worked differ slightly from those of Dr. Eisenbud. Differences between the number of beryllium disease cases reported at Lorain by Ward et al. (*2*) and by Steenland et al. (*1*) are due to differing criteria regarding cohort definition in the two studies: e.g., women in the Beryllium Case Registry were not eligible for the cohort in Ward et al. (*2*). Because information about plants was missing for some patients in the Beryllium Case Registry, data on these patients are not included.

the SMRs between the workers at the Lorain plant and other groups studied was probably due to higher exposures and longer latency for those working at Lorain. It is not necessary to invoke cigarette smoking or other carcinogens to explain the differential increase in lung cancer risk at Lorain.

Unfortunately, existing data do not permit the development of lung cancer risk estimates by quantitative level of exposure, and we do not believe that Dr. Eisenbud is on solid ground in suggesting that today's risks are inconsequential, given that exposures are so much lower than they were at Lorain in the 1940s. To date, no study has been done relating quantitative level of exposure, and exposure to different forms of beryllium, to lung cancer risk. Investigators at the National Institute for Occupational Safety and Health are currently attempting to make a detailed assessment of exposure at one of the plants in the study where the data may be adequate to support such an assessment. If such an assessment is successful, these data will be used in a case–control study to evaluate the relationship between quantitative level of exposure and type of exposure to lung cancer risk.

KYLE STEENLAND
ELIZABETH WARD
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention
Cincinnati, Ohio

References

(1) Steenland K, Ward E: Lung cancer incidence among patients with beryllium disease: a cohort mortality study. J Natl Cancer Inst 83:1380–1385, 1991
(2) Ward E, Okun A, Ruder A, et al: A mortality study of workers at seven beryllium processing plants. Am J Ind Med 22:285–904, 1992

Note

Correspondence to. Kyle Steenland, Ph.D., Department of Epidemiology/MSR-13, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 4676 Columbia Parkway, Cincinnati, OH 45226.