# EDITORIALS

## Beryllium and Lung Cancer: Adding Another Piece to the Puzzle of Epidemiologic Evidence

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The identification of environmental carcinogens is based on the observation of an excess cancer risk in exposed human groups. This effort is indirectly guided by experimental results, among which those of long-term carcinogenicity tests in animals (mostly rodents) play a key role. All of the agents in group 1 of the International Agency for Research on Cancer evaluation scheme (*1*), namely those definitely carcinogenic in humans, tested positive when adequately investigated in long-term carcinogenicity tests. These results point to the high sensitivity of animal testing. However, of the agents (n = 258) for which "sufficient evidence" of carcinogenicity in animals was judged to exist, less than 15% can be demonstrated to be definitely carcinogenic in humans: for more than half, no human data are available; for the rest, the evidence in humans is either inadequate or positive but limited. The first reason for this state of affairs is the difficulty of obtaining informative epidemiologic data. Groups of subjects exposed to the agent of interest in numbers, levels, and durations sufficient to make an excess risk of cancer detectable often do not exist; or the exposure may be inextricably mixed with exposure to other carcinogens; or, simply, suitable study populations may not have been sought diligently enough. (As for the latter point, clear excesses of cancers may remain unnoticed unless properly searched for, as one is reminded by the recent detection of a focus of mesotheliomas in a town in northern Italy (*2*), most probably related to neighborhood contamination from a work site.)

The case of beryllium highlights in a typical way several of the difficulties in using mortality studies to identify carcinogens in situations of past exposure in humans. Occupational exposure to beryllium, a bivalent light metal, and to its derivatives occurs in mining, extraction, refining, and alloy manufacture, as well as in a number of industries, including the nuclear industry (where the metal is used as a neutron moderator) and the aerospace industry (where it is used, for example, in the manufacture of high-performance brakes) (*3*). Environmental exposure of the general population occurs usually at levels several orders of magnitude lower than exposures found at workplaces. However, levels materially higher than "permissible" have been reported following a nuclear plant accident at Ust' Kamenogorsk, Kazakh Republic (*4*). In experimental animal studies, the evidence of carcinogenicity of beryllium-containing compounds is strikingly consistent and goes back almost half a century. The carcinogenic effects of beryllium have been demonstrated in a substantial number of studies using oral administration, inhalation, and intratracheal administration, as well as intravenous and intramedullary injection in the bone (*3*). Beryllium appears to be by far the most potent inorganic pulmonary carcinogen tested in rats (a thousand times more active per unit weight than crysotile in producing lung tumors) (*5*). Contrasted with this abundant evidence are the results of six epidemiologic studies (*6-11*), which are derived from the observation of only two U.S. occupational cohorts (totaling about 4300 workers), and of a nationwide disease registry population affected by acute or chronic berylliosis, which in part includes cases arising from the same two cohorts.

The results of these studies show an excess of lung cancer, on the order of 50%, 15 years after (and, more clearly, reaching formal statistical significance 25 years after) onset of exposure. If this increase is, in toto or in part, due to the exposure to beryllium, one would expect that the greater the exposure, the higher the risk. In fact, in one of the cohorts (*7*), six (75%) of eight lung cancers observed at the 1967 follow-up were concentrated in the subgroup of workers (15% of the cohort) who had experienced acute berylliosis and, presumably, the high exposure often encountered in the 1940s. Consistent with this finding, a twofold to threefold lung cancer excess was observed among the subjects included in the nationwide registry as being affected by acute berylliosis (*9*). However, and quite inconsistently, no excess at all (actually a deficit, based on very small numbers) was observed among those affected by chronic berylliosis. This inconsistency now appears removed by the results of Steenland and Ward (*12*), who found an increase of about 50% of lung cancer (not statistically significant) among subjects with chronic berylliosis. The authors have updated to the end of 1988 and (unlike the previous, end of 1975, follow-up) included data on women. Furthermore, they excluded subjects (for example, those registered after the lung cancer occurrence) whose presence could contribute to spuriously increasing the association between berylliosis and lung cancer. For approximately one-third of the subjects, they collected information on smoking habits as of 1965, finding that at that time there were more former and fewer current smokers among the registry members than among the corresponding U.S. population. Taking into account known relative risks for lung cancer among smokers, these differences in smoking habits would have produced a slight deficit of lung cancer among the registry members in relation to the general population, supporting the contention that the actual observed excess can hardly be attributed to smoking. The study also confirmed the more than twofold (and statistically

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significant) excess of lung cancer already noted among subjects with acute berylliosis in the previous follow-up.

In their article, Steenland and Ward address the involved question of the mechanisms through which beryllium can be carcinogenic: directly or via the intermediate lesions in the pulmonary tissues characterizing chronic berylliosis. Whereas acute berylliosis is a form of chemical pneumonia, chronic berylliosis is an interstitial granulomatosis of the lung, closely resembling sarcoidosis in its pathological features. The long-term fibrotic evolution of berylliosis brings in a common element with such diseases as silicosis and asbestosis. For each of these conditions, the question has been raised, based on a variable amount of epidemiologic evidence (*13,14*), of whether fibrosis is a necessary precursor of lung cancer. In a narrow etiologic sense, the question is irrelevant: whatever the mechanism, the issue is whether an agent is carcinogenic or not. Yet, a plausible biological mechanism may by itself increase the credibility of a causal link. More importantly, different mechanisms may, directly or via a fibrosis step, generate different shapes of the dose (exposure)-response curve for lung cancer; this would imply that there would be different estimates of the likely risk for an exposed population at a given level of exposure. For beryllium, unlike silica and asbestos, however, this issue may be more of academic than potentially practical interest, because the inadequacy of the measurements of exposure for the studied cohorts has prevented the defining of a dose (exposure)-response relationship for lung cancer.

The results of the Steenland and Ward study go one step toward reinforcing the causal interpretation of the association between occupational exposure to beryllium and lung cancer (*15*). They make it even more important that the follow-up of the two U.S. occupational cohorts is updated (also exploring whether better information on exposure might be retrieved through a case-control study within the cohort) and that the data is analyzed in depth. Clarification is needed of the finding in the most recent follow-up (which stops as early as the end of 1976) (*11*) that the lung cancer excess was concentrated among workers employed for less than 5 years (and less than 1 year); a plausible explanation for this finding, though not the only explanation, is that past short exposures, particularly up to about 1950, may have entailed much higher accumulated doses than did long exposures in more recent periods, when airborne concentrations of beryllium contaminants became considerably lower. Ideally, fresh and independent confirmation of the existing evidence could be obtained by seeking out cohorts of workers suitable for study in countries other than the U.S. If such cohorts are available, which is by no means certain, the worth of the effort should be weighed against the need of epidemiologically investigating some of the many agents that have a less clear relation to cancer than does beryllium.

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