HARVARD SCHOOL OF PUBLIC HEALTH

Department of Epidemiology

Dimitrios Trichopoulos, M.D.
Vincent L. Gregory Professor of Cancer Prevention and
Professor of Epidemiology

RECEIVED
JUN 1 1999

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3127
MD:EC-14, P.O. Box 12233
Research Triangle Park
NC 27709, U.S.A.

Dear Dr. Jameson,

I was asked by BISAC to send you the enclosed statement concerning the alleged human carcinogenecity of beryllium, together with a Curriculum Vitae. I am currently in Athens, Greece, but I will be back in Boston on June 3.

Sincerely,

[redacted]

Dimitrios Trichopoulos, MD

677 Huntington Avenue Boston, MA 02115 Tel: 617 432-4560 Fax: 617 566-7805 Email: dimitrio@epi.harvard.edu

On the alleged human carcinogenecity of beryllium

Dimitrios Trichopoulos, MD*

The Threshold Limit Values Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) has stated, in a 1999 draft document, that it "... feels that the weight of evidence supports the view that beryllium is a confirmed human carcinogen. However, only persons exposed at levels similar to those that existed in the Lorain and Reading plants in the '40s would be at significant risk of developing lung cancer". The concentration in Lorain and Reading as quoted in the ACGIH document was 1,000 $\mu g/m^3$, as contrasted to less than 5 $\mu g/m^3$ in today's plants. MacMahon has noted that even if the concentrations in Lorain and Reading "... were carcinogenic, their relevance to occupational experience of the last three decades is nil" (1)**. Yet, the academic question whether beryllium concentrations more than hundred times higher than those currently found in the beryllium industry could cause cancer in humans preoccupies major scientific bodies. What makes the issue all but incomprehensible is that the evidence for human carcinogenicity, from even extreme concentrations of beryllium, is the weakest ever advanced for any compound that has been characterized as a human carcinogen. There is also general agreement that, among workers employed in beryllium plants after 1959, the overall risk of death from lung cancer is, if anything, lower than the national average, perhaps significantly so (1, 2).

* Vincent L. Gregory Professor of Cancer Prevention and Professor of Epidemiology, Harvard School of Public Health; Director of International Research, Harvard Center for Cancer Prevention; Professor of Hygiene and Epidemiology, University of Athens Medical School; Adjunct Professor of Medical Epidemiology, Karolinska Institute Sweden; and Member, Beryllium Industry Scientific Advisory Committee.

**To facilitate the reader, I have opted for citing only the major sources, in which all other information is cross-referenced.

Authoritative evaluations of whether occupational exposure to beryllium compounds increases the risk of lung cancer, published until 1987, were generally critical of the quality of the evidence available up to that time. Indeed, the authors of the early beryllium and cancer studies were criticized in CDC and EPA documents for their tendency to under-emphasize or attack any findings inconsistent with the hypothesis that beryllium is carcinogenic to humans (quoted in 1). Thus, studies published after 1987 should have generated indisputable results, in order to lead to a revision of the regulatory status of beryllium and its compounds. There were two major studies (2, 3) on the carcinogenicity of beryllium published during the last decades and not even their authors were as definitive in their conclusions as were some major scientific bodies that invoked them (4).

The IARC report (4) suggests that post 1987 beryllium and lung cancer studies represent only the latest contribution to an accumulating body of human evidence on the topic. However, the six retrospective cohort investigations reviewed in the IARC monograph do not provide independent evidence, because they all utilize largely overlapping groups of workers from the same study base. The investigation by Ward and her colleagues (2) is simply the most recent, most powerful and most reliable. The results of this study, however, do not complement those of the five previous retrospective cohort investigations, they simply override them. The investigation by Steenland and Ward (3) is a sound analysis of data from the Beryllium Case Registry, that was created with little control over the enormous potential for selection and confounding bias. Moreover, the study base of the Steenland and Ward analysis (3) is also largely subsumed in that of the

study by Ward *et al* (2). Had the study of Ward *et al* been interpreted as "negative", there would be little epidemiological evidence to incriminate beryllium as a cause of human lung cancer, and the results of this study were anything but conclusive

No other compound or agent has been considered as carcinogenic on the basis of a slight relative risk elevation reported after multiple analyses relying on essentially the same study base. The reported marginal increase of lung cancer risk (relative risk 1.26) would have merited serious consideration had it not been largely confounded by tobacco smoking, as the authors of the best of these studies readily admit (2). Tobacco smoking is a powerful cause of lung cancer and was estimated as being more frequent among beryllium workers than in the population at large. The authors of the Ward *et al* study (2) used an indirect method to achieve some degree of adjustment for smoking, but this method cannot take into account factors such as duration of the smoking habit and other important smoking-related variables. Even this partial control, however, reduced the relative risk from 1.26 to a non-significant 1.12, a more than 50% reduction of excess risk. This is in itself a warning sign of residual confounding by the factor partially controlled for, that is, the indirectly estimated smoking (5). The lack of an association between risk of lung cancer and duration of exposure to beryllium also argues against a causal link between these two entities (1).

This is the first time that a non-significant and partially confounded 12% excess risk derived from a single study has been invoked to characterize a compound, agent or process as definitively carcinogenic. This excess risk is only one third as large as the

increment attributed to passive smoking and the latter estimate is derived from a meta-analysis of some 30 studies (6). The 12% excess risk is also substantially lower than the meta-analyses derived excess risk linking red meat intake to colorectal cancer, extremely low frequency magnetic fields to childhood leukemia and coffee intake to bladder or ovarian cancer, eventhough none of these agents has been designated as definitively carcinogenic by any official agency.

In the study by Ward *et al* (2), workers from seven beryllium processing plants were included, but after adjustment, however partial, for tobacco smoking, the excess risk for lung cancer remained significantly elevated, at a relative risk of 1.49, only among the workers of the oldest plant, that in Lorain, Ohio. It is the excess risk in the Lorain plant that is mostly responsible for the overall non significant 1.12 relative risk among all workers combined. For the Reading workers the relative risk was only 1.09 ($p\sim0.35$) and among the remaining plants it was exactly 1.00 (2, 6). The crucial question posed by these data is: "What process or circumstance was unique or unusual in the Lorain plant, that could have affected the incidence of lung cancer?".

The Lorain plant was in operation from 1936 to 1948, when it was destroyed by fire. During this period, the plant at Lorain was the only commercial beryllium plant that used a sulfuric acid-depended process with limited ventilation, because the occupational inhalation risk associated with air-born beryllium (pneumonitis) had not yet been established. There are no extant measurements of sulfuric acid mists and fumes at the Lorain plant, but existing data indicate that concentrations of sulfuric acid were as high as

subjectively tolerable (6). Occupational exposures to mists and fumes from sulfuric acid and other strong inorganic acids have now been conclusively established as carcinogenic to humans (7). Because the beryllium exposure was universal in the beryllium processing plants, but a sulfuric acid-depended process with limited ventilation was unique in Lorain, which was the only plant characterized by a significantly increased incidence of lung cancer (after partial adjustment for tobacco smoking), it can be inferred that sulfuric acid mists were responsible for the excess incidence of lung cancer in Lorain (6). It should also be noted that the trivial risk elevation in Reading, after partial adjustment for tobacco smoking (relative risk 1.09), could be reflecting either residual confounding by smoking, or confounding by hydrofluoric acid mists that were present in that plant due to poor ventilation, or both. Shifting the emphasis from beryllium to acid mists has strong precedents. Manufacture of isopropanol by the strong-acid process had been evaluated earlier as an "exposure circumstance", as had exposure to lead-acid battery manufacture, before attention was focused on acid mists and fumes (6, 7). I argue, therefore, that *the process and circumstances* at the Lorain plant were probably carcinogenic to humans. The apparent effect of "beryllium and beryllium compounds" was the result of exposure to excessive tobacco smoking in all plants and to sulfuric acid mist and fumes in the Lorain plant, the latter factors acting as typical confounding variables (6).

Some have argued that the study by Steenland and Ward (3) using the national Beryllium Case Registry supports the hypothesis that beryllium is carcinogenic to humans, because the relative risk for lung cancer among those in the registry was twice the expected. Moreover, patients registered with acute beryllium disease, which is caused by higher

beryllium exposure, had higher relative risk for lung cancer than those registered with chronic beryllium disease, that may occur even after exposure to moderate levels of beryllium (relative risks 2.3 and 1.6, respectively). However, smoking among the patients in the registry was ascertained when they already had respiratory disease. It is well known that a substantial fraction of smokers stops smoking as soon as they develop lung disease and ignoring this is equivalent to assuming that those who stopped smoking immediately eliminate their excess risk for lung cancer. In addition, the excess risk for lung cancer among patients with acute pneumonitis in the Beryllium Case Registry was restricted to workers from the Lorain plant, whereas patients with acute pneumonitis from other plants did not have an excess lung cancer risk (1). It seems again that Lorain was unusual and it is not a coincidence that acute pneumonitis, as well as lung cancer, can be caused by mists and fumes from sulfuric acid (6, 7).

Conclusion

The studies by Ward *et al* (2), and Steenland and Ward (3) were adequately conducted and analyzed, given the constrains imposed by the study design (inaccessible study subjects and reliance on recorded information). The conclusions drawn from them, however, did not take into account the powerful confounding of tobacco smoking that cannot be fully accounted for with indirect techniques. Moreover, the authors of these two studies were not aware of the unusual circumstances prevailing in the Lorain plant and did not take into account the confounding that could be generated by the carcinogenic potential of strong inorganic acids used for beryllium extraction.

REFERENCES

1. MacMahon B. The epidemiological evidence on the carcinogenicity of beryllium in humans. J Occup Med 1994;36:15-24.
2. Ward E, Okun A, Ruder A, Fingerhut M, Steenland K. A mortality study of workers at seven beryllium processing plants. Am J Industr Med 1992;22:885-904.
3. Steenland K, Ward E. Lung cancer incidence among patients with beryllium disease: a cohort mortality study. J Natl Cancer Inst 1991;83:1380-5.
4. International Agency for Research on Cancer. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry: working group views and expert opinions. Lyon, 9-16 February, 1993. IARC Monogr Eval Carcinog Risk Hum 1993;58:1-415.
5. MacMahon B, Trichopoulos D. Epidemiology: Principles and Methods. 2nd Edition. Little Brown, Boston, 1996. page 253.
6. Beryllium Industry Scientific Advisory Committee. Is beryllium carcinogenic in humans? J Occup Environ Med 1997;39:205-8.
7. International Agency for Research on Cancer. Occupational exposures to mists and vapours from strong inorganic acids, and other industrial chemicals: working group views and expert opinions. Lyon, 15-22 October, 1991. IARC Monogr Eval Carcinog Risk Hum 1992;54:1-310.