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Review of Beryllium Human Studies (H-1 to H-4) by Wagoner, Bayliss and Infante: "Beryllium: an etiologic agent in the induction of lung cancer, nonneoplastic respiratory disease and heart disease among industrially exposed workers"

(Reviewed by Carl M. Shy for the 10/9/78 meeting at CDC)

The four drafts reporting the results of the NIOSH study of workers employed at a beryllium plant in Reading, Penn. present the most important extant human evidence concerning a potential association between occupational exposure to beryllium and excess lung cancer. The four drafts, dating from 1/31/78 to 8/28/78 are apparently successive revisions, corrections and elaborations of an earlier report submitted at the 1977 OSHA Beryllium Hearings under the authorship of Bayliss, D.L. and Wagoner, J.K. and entitled "Bronchogenic cancer and cardio-respiratory disease mortality among white males employed in a beryllium production facility" (OSHA Beryllium Hearing, 1977, Exhibit 13-F). The latter report was rigorously scrutinized by Brian MacMahon (Chairman of Epidemiology at the Harvard School of Public Health), serving as a consultant to a beryllium company, in a written commentary and analysis entitled "OSHA Beryllium Hearings, 1977. Evaluation of Epidemiological Materials". In the latter report MacMahon independently analyzed the epidemiological data as contained on the NIOSH computer tape. In addition, an in-house CDC Beryllium Panel successively reviewed the first three drafts of the Wagoner, Bayliss and Infante reports (H-1 to H-3) and wrote specific criticisms and suggestions that were largely responded to by the authors and resulted in the final draft dated 8/28/78 (H-4). My review comments will primarily be directed to the final draft dated 8/28/78, hereafter referred to as the Wagoner report. I will also refer to several critical points made by the in-house CDC Beryllium Panel, hereafter

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referred to as the CDC Panel, and in the MacMahon evaluation.

The Wagoner report is a retrospective cohort study of 3055 workers employed at some time between January 1, 1942 and September, 1968 at a beryllium extraction, processing and fabrication facility in Reading, Pennsylvania. Only white male workers engaged in extraction, processing or fabrication, or involved in on-site administrative, maintenance and support activities were reported as included in the study cohort. The observed mortality experience of the cohort for specific causes of death was compared with expected mortality, the latter derived from the age, calendar time-period and cause-specific mortality rates for the white male population of the United States. Vital status of 97% of the study cohort was determined.

The salient results of the Wagoner study are as follows:

1. Table 5: A statistically significant excess of observed/expected deaths was reported for lung cancer (47 observed, 34.3 expected) and for heart disease (396 observed, 349.3 expected).

2. Table 6: For lung cancer deaths, excess deaths were largely distributed among workers with less than 5 years employment (40 observed, 28.6 expected), while workers with 5 or more years employment did not show a statistically significant excess (7 observed, 5.7 expected).

3. Table 7: Excess non-neoplastic respiratory disease deaths were similarly distributed, the excess occurring only among workers employed for less than five years (29 observed, 15.6 expected).

4. Table 8: Excess heart disease deaths were more heavily distributed among workers employed for 5 or more years (78 observed, 60.4 expected, SMR = 129) than for less than 5 years (318 observed, 288.9 expected, SMR = 110), but differences were statistically significant only for the total cohort.

5. Table 6: When lung cancer deaths were analyzed according to interval since first employment and duration of employment, a statistically significant excess appeared only among those followed for 25 or more years since first employment and employed for less than five years. Notably, a significant excess was not seen for the group employed for 5 or more years and followed for 15-24 years or for 25 or more years.

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6. Table 10: Exess lung cancer deaths occurred only among workers initially employed before 1950. No lung cancer deaths were observed in the relatively small portion of the cohort employed since 1950, whereas 2 lung cancer deaths would be expected.

7. Tables 13 & 14 : The 1968 distribution of smoking habits in a sample of the beryllium plant workforce was such that a smoking factor could have accounted for a 14 percent excess in observed lung cancer deaths, whereas a 37 percent excess was reported. Analysis of the distribution of histologic types of lung cancer from 25 of the 47 lung cancer decedents revealed 28 percent (7 of 25) to be adenocarcinomas, while two series of pathologically verified lung cancer deaths in the U.S. suggest an expected adenocarcinoma distribution of 15 to 15.7 percent. This reported shift in histologic types is suggestive of the operation of an epidemiologic risk factor other than cigarette smoking alone.

8. Table 14: The observed lung cancer mortality excess may have been underestimated by 19% because the lung cancer mortality experience of the U.S. as a whole is 19% greater than that of Berks County, in which the plant is located.

Many of the above points were made in response to prodding by the CDC Panel. Early versions of the Wagoner report, as well as the version submitted by Bayliss and Wagoner at the 1977 OSHA Beryllium Hearing, were grossly deficient in providing adequate description of methods, accurate reporting of results,[1] or scientifically cautious interpretation of findings. In my opinion, these deficiencies justified the concern of many about the validity of the early reports. The final draft is a considerable improvement and much of the needed clarification and extension of observations should probably be credited to the careful reviews and constructive suggestions of the CDC Panel.

The MacMahon evaluation, while directed towards the NIOSH report presented at the 1977 OSHA Beryllium Hearing, still makes several crucial observations that are applicable to the final Wagoner report. The major observations of MacMahon bearing on current interpretations of the Wagoner study are as follows:

1. Since U.S. lung cancer mortality rates were not available for the 1968-75 period, expected numbers of deaths for this interval were calculated by applying 1965-67 U.S. rates to the cohort person-years of observation for 1968-75. However, since lung cancer rates in the U.S. have continued to increase significantly, a larger expected value would have been obtained if actual 1968-75 U.S. lung cancer rates were applied, thus decreasing the ratio of observed to expected lung cancer deaths. MacMahon proposed that the above computations could have increased the expected lung cancer deaths to 37.5 and that this value would reduce the observed/expected ratio to less than statistical significance. This observation is particularly important in view of the lack of significant observed/expected ratios for the subcohort employed 5 years or more. Thus, these findings of the Wagoner study may indeed be chance observations, and we must turn to other features of the analysis to find support for the Wagoner conclusions. It is very unfortunate that Wagoner et al. have not re-computed their expected lung cancer deaths, since 1968-75 national mortality data are now available. The CDC Panel report notes that at least one of the authors has suggested this approach and the Panel agreed that these re-calculations would be desirable. We should not be forced to speculate on such an essential element of the study when more accurate data are accessible.

2. MacMahon points out that the NIOSH study failed to subdivide the relatively large segment of the cohort employed for less than 5 years, among whom much of the excess in lung cancer deaths was observed. MacMahon goes on to carry out this analysis by smaller intervals of duration of employment (cf. Table 7 in MacMahon's evaluation), and the results are extremely important to the interpretation of the study. Yet Wagoner et al. failed completely to provide this analysis in their subsequent drafts or even to recognize its significance. The MacMahon table is reproduced here because of its significance.

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Observed/expected deaths from lung cancer
according to duration of employment
and years since first employment

(Source: MacMahon, B.)

Years since first employment	Duration of Employment					Total
	<2 mos.	2-11 mos.	1-4 yrs.	5-14 yrs.	15+ yrs.	
0- 4	0/0.5	0/0.3	0/0.7	-	-	0/1.5
5-14	1/1.9	6/2.1	0/2.0	1/1.9	-	8/7.9
15-24	7/4.6	6/4.5	3/2.7	1/0.7	2/2.2	19/14.7
25+	6/3.5	5/3.9	6/2.7*	2/1.0	1/1.0	20/12.1*
Total	14/10.7	17/10.8	9/8.1	4/3.6	3/3.2	47/36.2

* $p < 0.05$

The lung cancer excess occurs nearly entirely in workers employed less than one year, and there is little evidence for a latency effect for each column of MacMahon's table. MacMahon points out that the total lung cancer experience of the cohort is heavily influenced by individuals with less than one year employment in the plant and simultaneously having long follow-up since that employment. This finding strongly suggests that the short-term workers, in whom most of the excess lung cancer appears, may have gone on to other work exposures associated with excess lung cancer risk, or that some of these workers were early on affected by beryllium exposure to the point where they developed a beryllium pneumonitis and were forced to drop out. Other investigators have suggested workers developing acute pulmonary reactions to beryllium are at increased risk of lung cancer later in life. MacMahon further postulates that cigarette smokers are more likely to develop acute pulmonary reactions to occupational dust exposures and would also be at increased risk of lung cancer. It is not unreasonable to suggest, then, that workers employed less than one year experienced excess lung cancer for the following reasons:

i) A larger population of these workers were smokers; they experienced acute pulmonary reactions to beryllium dust and left the industry. Their subsequent excess lung cancer mortality may be accounted for by the combination of continued smoking and the initial acute pulmonary reaction.

ii) A significant proportion of the short-term workers went on to work in high lung cancer risk industries. Even if the initial beryllium dose to the short-term workers was high, it is not credible to postulate that the dose to workers employed for 5 or more years would not be significantly greater than for the less-than-one-year workers. Failure to find a significant lung cancer excess for the 1241 workers employed for one year or more (cf. Table 2

in Wagoner report) is a telling argument against a beryllium-related lung cancer risk in this particular cohort. MacMahon's vigorous assertion of this point is entirely unanswered in all drafts of the Wagoner paper.

3. MacMahon notes that the 1968 distribution of smoking habits among 379 workers at the plant may well be unrepresentative of smoking habits for plant employees in earlier times. Indeed the evidence for the disproportionate lung cancer excess among short-term workers, most of whom were employed prior to 1960 (cf. Table 2 in Wagoner report) suggests heavier cigarette smoking among this group.

Concerning the issue of histopatholic classification of the lung cancers from the plant, Smith and Suzuki reported 7 adenocarcinomas in 25 of lung cancer patients (28%) for whom pathology specimens were received. (The Wagoner report cites 8 adenocarcinomas). However, among the 7 cases for which histologic reports but not pathology specimens were available for review, only 1 adenocarcinoma (14%) was found. If the latter proportion were applicable to the remaining 15 cases for which neither specimens nor reports were available, we would expect a total of 10 adenocarcinomas out of 47 lung cancer cases, or 21%, a figure not dramatically different than the 15 to 15.7 expected from two other series.

Conclusions

While the Wagoner study gives evidence of excess lung cancer among the 3055 workers at the beryllium plant, there are very sound reasons for doubting that this excess is indeed causally related to beryllium exposure. Adequate calculation of expected numbers of lung cancer cases, based upon actual 1968-75 U.S. lung cancer rates, may very well have shown the reported excess to be a chance observation, not statistically significant. More importantly, nearly all of the excess occurs in workers employed for less than one year. Smoking, acute pulmonary reactions, and/or migration to high risk industries could well account for this excess. This possibility was not adequately addressed in the Wagoner study and would not even be identified were it not for the MacMahon analysis. I do not believe, therefore, that the Wagoner study of itself provides reasonably convincing scientific evidence for an association between beryllium exposure and lung cancer in exposed workers.

These uncertainties could probably be resolved if the suggestion of the CDC Panel for a case-control study is followed. Detailed work and smoking histories can be obtained for the 47 lung cancer cases and for an appropriate number of matched controls from the same plant. The total study population could possibly be as few as 141. The question of smoking and other work exposures can be readily addressed in this approach. The importance of this data set justifies an expeditious follow-up to the CDC Panel suggestion.