REVIEWER'S COMMENTS ON:
"Cause-Specific Mortality Among Male Chemical Workers"
By Bond, McLaren, Cartmill, Wymer, Sobel, Lipps, and Cook
[Revised Version]

March 3, 1987

I am extremely disappointed with this draft, which is no revision at all, but merely the original version with the methods section slightly rearranged (for the better, I should add). The authors seem to have taken great pains not to address seriously any of the queries or suggestions I brought up in my original review, preferring instead to dismiss them in their cover letter. While their evasion looks more like an attempt to get out of doing more work, rather than to cover anything up, I believe the readers of this Journal deserve a better response.

My first unanswered question concerned the distribution of "empty" person-years. These are person-years of exposure to risk of dying observed in strata in which the reference death rates are so low that there is effectively no statistical power. Observations below age 30 fall into this category. If, for example, one-half of all person-years observed in this study fell in that age group (which they obviously do not), there would be no point to doing a mortality study at all. Mortality studies of Vietnam veterans are a similar example. Death is the wrong endpoint for studies of health effects in young people. Tables XI and XII, referred to in the authors' response letter, do not, contrary to their statement, give the distribution of deaths by age. They give the distribution of deaths according to how old the employee was when he was first hired, which could have been decades ago. That's not what I asked about.

My second question concerned short-term service. Bond asserts in his response letter that short-term workers were worth studying because they might later have excess disease, as with asbestos workers. This is theoretically true, until one examines Table X, and sees the trivial number of deaths upon which to base a possible analysis. My question, rephrased, still stands: are there sufficient person-years (i.e., power) to do a satisfactory analysis?

I appreciate the authors' concern not to overburden this general study with specific exposure information. In this case, however, Table XIII is inadequately labeled, and I hope I may be forgiven if I incorrectly concluded that its contents were directly relevant to the study at hand. The table mentions no references, so it is natural to assume that it comes directly from the data in the preceding twelve tables. I am still not certain who in the present cohort the table refers to, or how the risks were arrived at. It is perhaps the most interesting table in the entire report, and, juxtaposed with the title of the report itself may lead the inattentive reader to unwarranted conclusions.

The response in Dr. Bond's letter which mentions Table VII (concerning comparisons of his cohort with different standard rates) is self-contradictory. True, "many of the SMRs do not vary," but many do. In any event, my original question still stands: "what have we learned about this cohort's experience from the data in Table VII?"

Bond's final two responses concerning table VIII and the use of exotic statistical tests (bottom of page 2, top of page 3) are entirely inadequate. I said these points need more discussion, and I meant it.

I have made considerable mention of the use of several control groups, which is a strength of this paper, not a weakness. However, the intrusion of yet another standard (the NIOSH/Waxweiler rates, pp. 23, 26) is a little too much. Why were these supplemental rates brought in only for connective tissue and brain cancer, and why only for white collar workers at that?

In addition to these unanswered concerns, there are one or two further points I would like to raise, now that I have reread the paper. On page 21, there is some speculation on why the Dow cohort mortality is slightly less than that of a supposedly comparable Tecumseh, Michigan population. Possible absence of occupational hazards, health and safety education, and "progressive medical surveillance" are invoked, but absent any actual evidence, speculation it is anyway. [The giveaway word (para. 1, line 12) is "perhaps."] The 7 percent lower cancer rate is insignificant and not worth mentioning.

The following paragraph (p. 21, para. 2) concerning lifestyle differences is also sheer speculation. I found the statement that "Ott found that cigarette smoking differences alone accounted for about one-half of the mortality differentials observed between three socioeconomic groups ..." not credible on its face; unfortunately, the reference is to Dr. Ott's thesis, which is not readily available. "Lifestyle" is a convenient whipping-boy when actual data are not at hand. I suggest the authors confine themselves to the basic facts, which are more than adequate.

The paragraph (p. 22, para. 1) which describes this study as "hypothesis-generating" subjects the authors to a logical trap, and should be re-worded. It seems to be a knee-jerk reaction these days that when your data base exceeds a certain size, such that numerous statistical tests are inevitable, you have to pacify the statistical lions with that odious phrase. If this were literally true, then practically no conclusions of any substance could be drawn about this -- or any -- large study. On the other hand, the techniques currently in fashion to deal with multiple comparisons, such as Bonferroni, etc., are so gross as to demolish otherwise interesting -- and informative -- results. I see no reason to apologize for looking critically at one's own data, but let it be done by epidemiologists, not statisticians.

Finally, the original and the revised version give different "explanations" for why women were not included. If the authors intend to publish the female data in a separate report, let them say so explicitly. If not, why not?

This article is a descriptive study of the mortality of nearly 38,000 male employees of Dow Chemical Company. The goals of the study do not include my etiological hypotheses, at this stage the study aims at creating better premises for future etiological studies.

The investigation is well conducted and well reported. I could not find any flaws in it. However, it is regrettable that the female mortality could not be studied. I think 22.3% or 10,843 females is not a "small proportion" as stated on p. 10. Mortality studies of such cohort sizes of females are utterly rare in the literature.

The report is very long even without female mortality and it may be difficult to find space for it. However, the length is a consequence of the size of the study, not of unnecessary wordiness or undue dwelling on irrelevant details. I cannot see how a report based on such a large study could be significantly abbreviated without loosing information and quality. Hence I feel it should be published as such or not at all.

The pertinent problem, in my view, is the purely descriptive nature of this study. The population is heterogenous, and the mortality of "chemical workers" as such is not very exciting in 1986, after two decades of epidemiologic mortality studies of different categories of workers. True, several subdivisions are made by latency time, hourly or salaried status, period and age of hire, etcetera, but all the time one has the feeling that the real goodies will be served in subsequent reports (and there certainly seem to exist goodies in this material, eg. lymphatic and hematopoietic cancers, some well defined exposed groups, etc). So this is rather a data base for further study than a scientific piece of work. Hence the decision to publish or not publish this article would be one of editorial policy.

Finally one critical remark. The beginning of the "Results" section is a description of the study materials. The aim of the investigation was not to study the age, occupational, racial and hiring date distribution, etc. of Dow's workers, but rather their mortality. Therefore, everything that is listed under "descriptive statistics" belongs under "Materials and methods", including Tables I-V. This change is simple to carry out just by moving a subheading, but the conceptual implication is significant.

AMERICAN JOURNAL OF EPIDEMIOLOGY

624 N. BROADWAY, ROOM 225, BALTIMORE, MARYLAND 21205 USA TELEPHONE 301-955-3441

October 13, 1986

Gregory G. Bond, Ph.D.
The Dow Chemical Company
Epidemiology, H&ES
1803 Building
Midland, MI 48674

RE: MS #86-414
"CAUSE-SPECIFIC MORTALITY AMONG MALE CHEMICAL WORKERS"

Dear Dr. Bond:

I am sorry to report that neither of two outside reviewers recommended that we publish your paper. Both reviewers were concerned that your work did not attempt to focus more specifically on particular hypotheses. I think that the reviewer who suggested that the healthy-worker effect is a bias that should be avoided, not emphasized, has a reasonable point. It would strengthen your work to rely on internal comparisons of the workforce rather than on biased comparisons with the general population. As it is, the paper reads as if it is an attempt to indicate that working at Dow is not so hazardous overall, when compared with the general population. My impression is that the reviewers thought that an analysis that tried more actively to find specific hazards might be more productive and of interest to more epidemiologists. (It is also true that you are more likely to find something if your look harder, and thus a more intense focus on specific associations would be more persuasive whether it was "positive" or "negative.")

Perhaps the enclosed suggestions will enable you to redirect this effort into a form that might satisfy our referees. It would clearly have to be a completely different paper, with new objectives and different analyses. I would second the recommendation to avoid using statistical significance for interpretation. We would be happy to review a new paper that addressed these concerns, but clearly what we are describing would be more than just a revision of the current manuscript. Obviously, you may be reluctant to set aside the current work on these recommendations, since it is an informative paper that might be acceptable at a number of other journals. In its present form, however, we must pass the opportunity to publish it.

I am sorry I could not be more positive. We are extremely appreciative for the chance to consider this interesting work.

Yours sincerely,

Kenneth J. Rothman/bsw

Kenneth J. Rothman, Dr.P.H.
Editor

KJR:bsw
Dictated but not read
Enclosures

S11S/866

PUBLISHED BY THE SCHOOL OF HYGIENE AND PUBLIC HEALTH OF THE JOHNS HOPKINS UNIVERSITY
SPONSORED BY THE SOCIETY FOR EPIDEMIOLOGIC RESEARCH

This manuscript reports on a cohort mortality study of over 37,000 males employed in Michigan between 1940 and 1982 by the Dow Chemical Company. The authors use well standardized procedures in this study. They compare observed mortality with expected levels of mortality in the United States, in all of Michigan, and in the seven Michigan counties immediately surrounding the Dow Chemical plants.

The authors found that overall mortality in the cohort was less than expected. Among hourly employees they noted significant excess mortality for cancer of other lymphatic tissue and for motor vehicle accidents. Both hourly and salaried workers experienced significantly increased mortality from poorly defined cancers. The authors also found statistically significant increases in mortality from brain cancer and from bladder cancer among workers aged 50-54 years; however, there are no consistent trends in those findings. In their examination of mortality patterns in workers with specific exposures, the authors found a two-fold increase in mortality for respiratory cancer among workers exposed to arsenic, a five-fold increase in respiratory cancer among those exposed to asbestos, and a non-significant, but approximately two-fold increase in leukemia among those exposed to benzene.

This manuscript presents the results of a massive amount of competently performed work. Unfortunately, however, this massive exercise was entirely hypothesis-generating in nature; the authors state explictly that they undertook this survey in order to conduct mortality surveillance among the work force of the Dow Chemical Company. As a result, the authors had no stated hypotheses to guide them in their endeavor.

In my opinion, this exercise represents a very competently performed piece of practical public health. However, the methodology used was entirely standard, and in the absence of a stated hypothesis, it does not qualify as research. The notion of doing mortality surveillance among large workforces is not a new one. Although important, it has been done numerous times in the past by the Dow Chemical Company as well as by other chemical firms and government agencies. The findings of this summary might appropriately be presented in an abridged form in a public health journal, such as the American Journal of Public Health or in the Journal of Occupational Medicine. In my opinion, however, the data from this sort of study are no longer sufficiently novel to belong in a research journal.

AMERICAN JOURNAL OF EPIDEMIOLOGY
624 N. BROADWAY, ROOM 802
BALTIMORE, MARYLAND 21205, U.S.A.
(301) 955-3441

Continue on second page if necessary.

[redacted] [redacted]

Review of MS 86-414:

"Cause-specific mortality among male chemical workers."

The authors refer to this study as hypothesis-generating, but I do not see any new hypotheses. Instead, the principal conclusion is that several comparisons to the general population "consistently demonstrated lower mortality in the cohort from each of the major causes of death, including total malignant neoplasms" (abstract, p. 19). Apparently, the authors do not include as "major" causes of death cancers of the liver, testis, brain, lymphatic system and leukemias, all of which are in excess compared to the general population (table 6). Results that refer to specific types of cancer or to certain types of workers are dismissed as "several isolated findings" (p. 14). Thus, instead of providing us with leads about possible effects of chemicals, the authors emphasize "the absence of major occupational hazards, a progressive medical surveillance program, and worker education" (p. 20).

As for the elevated death rates from many causes seen among hourly compared to salaried workers, and long-term compared to short-term workers, we are told that: (a) "the hourly experience still compared favorably to that of the U.S. population," (b) "Ott found that smoking differences alone accounted for about one-half of the mortality differentials observed among three socioeconomic groups defined in a very similar manner to our three pay status groups," and (c) "selection effects and/or other lifestyle differences, possibly including occupational exposures, are likely to be responsible for the remaining mortality differences." The first statement is not an explanation of mortality differences among employees, although this result is easily explained by the healthy worker effect. The second explanation must be rejected since, to my knowledge, smoking does not cause cancers of the liver, stomach, large intestine, prostate, lymphatic system and leukemias (table 9). Confounding due to unspecified lifestyle factors is always an unevaluable possibility. Consequently, these results are about as suggestive as could be expected from such data regarding hypotheses of chemical effects. Persons with twenty or more years of employment experienced a death rate from total malignant neoplasms that was about twenty percent greater than the rate

among persons with fewer than five years of employment. With 476 cancer deaths observed, this result translates into approximately 80 excess cancer deaths. Yet the known carcinogenic exposures in this cohort can explain only about half of these deaths (table 13). Thus, I concur with the authors that occupational factors should be considered as a possible explanation. But if this possibility exists, I think it is misleading to state that "the generally favorable mortality experience of this cohort would suggest that major hazards are unlikely, and that the consequences of multiple chemical exposures to cause synergistic effects may have been greatly exagerated." (The reference given (43) provides no estimate of synergistic effects.)

Several problems remain:

1. A method can only be criticized with respect to its objective, but the rubric of "general mortality survey" or "hypothesis generating study" should not excuse us from having clearly focused aims that motivate particular methods. The major objective stated is "to describe the cause-specific mortality experience of chemical industry employees so as to give better perspective regarding the hazards of employment" (p. 1), but not "to link cause-specific mortality to particular exposures" (p. 25). Other than particular exposures, however, I do not know what the hazards of employment might be, or what perspective is in need of revision. If they are interested in learning about occupational causes of disease, instead of selection factors, a useful principle is that comparison groups should be identical (with respect to disease risk), except for the exposure of interest. Therefore, unless the authors can provide arguments to support their analyses, I would discard comparisons to the general population. Lacking scientific objectives to provide direction, this study utilizes a variety of methodologies that produce lots of results. A repetitive and perfunctory description of which results were statistically significant and which were not is offered in lieu of explanation.

2. I do not think that the concept of statistical significance is helpful. Reliance on statistical significance can easily focus attention on trivial statistical differences while distracting us from important biologic concerns. Thus, these authors draw a distinction between relative risks of 1.1 and 1.2 for total cancer, while "cancers of the stomach, large intestine and prostate were significantly elevated among those with twenty or more years of service relative to those with less than five years of service, however, although also higher than ~~than~~ expected relative to the U.S., the differences were not statistically significant" (p. 15).

3. It is helpful to provide observed and expected numbers of deaths in the tables, however, the expected number given should be the same one used to calculate the effect (RR) estimate (see, e.g., table 9).

The confused purpose of this study can be seen in the last two paragraphs. It looks to me like the investigators emphasize another demonstration of the healthy worker effect, whereas I believe that bias is something to be avoided, not emphasized. Subsequent studies may be performed more easily as a result of this effort, but I think this result is of limited interest. Even with the major revisions I would recommend, the informativeness of this study would be severely limited due to the absence of exposure information. It may be possible to extract some interesting leads, but the authors would have to revise their objectives, methods, and interpretation. Perhaps it would be best to wait for their subsequent studies which, they promise (p. 26), "will have more focused hypotheses."