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Mr. James Morgan
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N 27678

Dear Jim:

This is in response to your memorandum of September 20th requesting our reaction to the NIOSH critique of the lead chromate study. I will take up the criticisms in order, as they occur in the memorandum.

First, there is a typographical error on page 1 of the NIOSH report. The figure 131 for Plant 1 "Hired before 1960" should be 181, and the total hired before 1960 should be 384.

The statement that the "most apparent serious deficiency of this study is the short latent period of this worker cohort" was based upon a misreading of the data. Table 5 shows that 384 men had been hired before 1960. There is nothing that could be construed as indicating that the latent period was 17 years at most. Parenthetically, I would prefer a term other than "latent period", which implies that a condition related to some specific causative event has actually occurred and that the interval between the two is known. What we are really concerned with is: how many men were observed over time periods sufficiently long after their first exposures to lead chromate for conditions with long latent periods to become manifest? Of the 548 men whose vital status was known, 384 (70%) had been hired before 1960, so had had 15 or more years of observation since their first potential exposure. A more detailed analysis of hire dates shows the following:

Hire years	Observation period thru 1974	Plant Number			Total	Cumulative %
		1	2	3		
Pre-1930	45+	1	1	12	14	2.5
1930-39	35-44	2	2	21	25	7.1
1940-44	30-34	4	5	15	24	11.5
1945-49	25-29	69	3	80	152	39.2
1950-54	20-24	79	11	30	120	61.1
1955-59	15-19	26	23	0	49	70.1
1960-64	15	57	107	0	162	100.0



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In other words, over half the study population could have been observed during periods where there was an opportunity for conditions with latency over 20 years to be manifest; 29% where latent periods over 25 years could have been manifest and 12% where latent periods of 30 or more years could have been manifest...

That the statement that "latent period" was 17 years at most is manifestly incorrect is shown by other portions of the report. On page 4 it is made plain that the study population in plant 3 was limited to workers on the wage roll as of June 30, 1957, which made the minimum observation period approximately 17 years, not the maximum observation period.

The comment by NIOSH that the extremely small sample size was a noticeable limitation is not an original observation. It was pointed out by us and was due to the fact that there are not many groups of workers in the United States who have had work exposures limited to inhalable lead chromate.

The criticism that the age distribution of the cohort should be included in the report is valid, and we regret that it was omitted. Although it does not change the conclusions, since age (i.e. year of birth) is included in determining expected rates, it should be available so that biostatisticians can compare our study population with those in other studies. A table showing birth years is included as a postscript.

The problem of racial differences in certain causes of death is recognized. Personnel records do not ordinarily show race, so the actual composition of the study population cannot be determined with precision. Estimates based on the recollection of personnel officers provide only a general guideline and do not always reflect trends over the study period. We used the cause and age specific death rates for "all males" to determine expected rates. The effect of varying mixes of white and non-white workers could be tested, but it must be remembered that in doing this the distributions in each age group are not available for analysis.

We recognize that the choice of control group is important; however it is not necessarily true that the rate for each plant location is more appropriate than a broader population base. There are important differences in different subgroups within each state. Employed vs. non-employed, and socioeconomic status are probably more important than geography. This is an inherent source of error in epidemiologic studies using standardized mortality ratios and one reason why modest deficits and excesses for specific SMR's must be treated with caution especially if based upon small numbers of expected cases.



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The confirmed smoking history of nearly all of those who died of lung cancer is of interest and we presented it only as an additional problem in interpreting the study. As is well known, for some occupational cancers, there is synergism between smoking and the occupational agent, e.g. asbestos. There is no reason to postulate this for lead chromate, and our data should not be construed as showing this. Smoking histories were obtained from medical records and recollections of associates and fellow-workers. We do not see how longer latency and study of cell types would resolve the problem of the importance of smoking. Only a prospective study is likely to provide conclusive evidence. Cell types were not recorded on death certificates for most of the lung cancers. It is probable that going back to hospital records might permit some to be obtained but such records are not readily available to us. Only if there were dramatic predominance of one cell type, such as in bis-chlor-methyl-ether cancers, would such a finding help elucidate cause and effect.

The statement that a possible association between lead chromate and stomach cancer should be discounted because there is no mention of such a relationship in the scientific literature was an unfortunate choice of words. It would have been better to state merely that such an association had not been suggested by any other studies or by experimental work and that further investigation was needed before a final conclusion could be reached based on 6 cases.

One page 2 of Ms. Robinson's critique (line 10 from the bottom) there is an expression that puzzles me, that the mixed exposures in plant 3 resulted in consistently elevated SMR's for respiratory and digestive cancer, "consistently elevated due to cohort composition; a statistical artifact." I am not sure that I know exactly what is meant. Incidentally men who worked before 1957 were included. It is my understanding that inability to start the cohort earlier was due to the fact that in 1957 workers were classified as to whether or not they had worked in lead chromate areas. Those who had left employment before 1957 had no indication in their records.

We believe that our original conclusions were sound and nearly all that could be derived from limited data. The results are consistent with the hypothesis that "lead chromate is a respiratory carcinogen" but they do not prove it. The known carcinogenicity of hexavalent chromium, the fact that lead chromate is not absolutely insoluble, and the fact that other metallic chromates are carcinogenic make the association plausible. I believe that extended observations will confirm the initial impressions. Continued followup of this and similar populations is more important than attempts to extract more information from the figures now at hand.



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I certainly agree that individualized study of gastrointestinal tract cancers is important.

Again, thanks and best wishes.

Sincerely,

W. Clark Cooper, M.D.

WCC/jpm

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Postscript

Years of Birth of Study Population

<u>Year of birth</u>	<u>Plant 1</u>	<u>Plant 2</u>	<u>Plant 3</u>	<u>Total</u>
1890-99	1	-	11	12
1900-09	12	7	38	57
1910-19	47	8	61	116
1920-29	86	45	47	178
1930-39	45	63	1	109
1940-49	38	26	-	64
1950-59	<u>9</u>	<u>3</u>	<u>-</u>	<u>12</u>
TOTAL	238	152	158	548
MEDIAN	1926	1932	1916	1924