

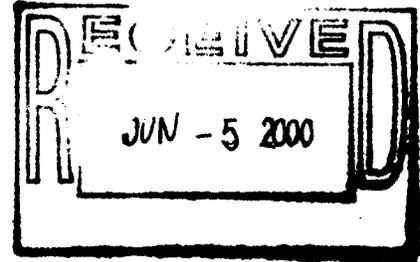
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June 2, 2000

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709



Dear Dr. Jameson:

The International Lead Zinc Research Organization would like to submit the enclosed commentary in response to the proposed listing of lead and lead compounds for the 10th Annual Report on Carcinogens. In addition to the ILZRO commentary, you will find an *in press* manuscript by Wong and Harris detailing the results of an update recently conducted of an epidemiology study investigating US battery workers and lead smelter employees.

Should you have any questions, or require additional clarification, regarding any of the materials raised in this commentary please feel free to contact me. My address, telephone and fax particulars are as on the letterhead. I may be reached via email at cboreiko@ilzro.org.

Thank you for your time and consideration.

Best regards,

Craig J. Boreiko, Ph.D.
Manager, Environment and Health

CJB:ac

ILZRO Commentary on Lead Carcinogenicity

The International Lead Zinc Research Organization notes with surprise the proposed listing of lead in the 10th Annual Report on Carcinogens based upon “recent published data that indicates an excess of cancers in workers exposed to lead and lead compounds.” We have been advised by your office that the technical support document on the classification of lead as a human carcinogen will not be available until the fall of this year. Furthermore, it is our understanding that the “recent published data that indicates an excess of cancers in workers exposed to lead and lead compounds” is based on an editorial published in the Scandanavian Journal of Work Environment and Health in which Harri Vainio of the International Agency for Research on Cancer (IARC) summarized the recent epidemiological findings on this subject. In the absence of defined articulation of the issues of concern, we can only offer the following observations as they relate to the nonpeer reviewed editorial.

The editorial by Vainio correctly notes that the carcinogenicity of lead compounds was recognized by the International Agency for Research and Cancer in 1987. Based on the human and animal evidence available to the Agency at that time, it was determined that there was sufficient evidence of carcinogenicity in experimental animals for soluble lead compounds such as lead acetate and lead phosphate, but inadequate evidence for carcinogenicity in humans. On that basis the Agency classified lead compounds as a group 2B carcinogen.

The Vainio editorial cites ten epidemiological studies that have been published since 1987 to support his statement that “When all the available evidence is taken into account, occupational exposure to lead and lead compounds should therefore be considered as carcinogenic to humans”. A close review of the literature on lead and cancer, along with the recent updates on the Swedish lead smelter and the U.S. lead smelter and battery plant studies, indicates that the evidence that lead is a human carcinogen is even weaker today than it was when IARC last reviewed the evidence in 1987.

Animal Studies

Because the 1987 classification was based on the limited animal evidence on carcinogenicity it will only be briefly discussed in our comments. Previous studies with experimental animals have shown that lead compounds such as lead acetate and lead phosphate are capable of inducing cancer in rodents. Cancers observed are typically renal cell carcinomas against a background of proximal tubular cell hyperplasia, cytomegaly and cellular dysplasia, with a tendency for male animals to be more susceptible to tumors than females. The overall pattern of tumor induction, combined with a largely negative profile for genotoxicity, have caused many to doubt the relevance of these findings for humans. For example, Goyer (1993) has suggested that carcinomas induced by lead in rodents occur only as a consequence of cystic changes in the renal cortex that follow chronic lead nephropathy. Given the susceptibility of the rodent kidney, particularly that of the male rat, to nephropathy the relevance of the results obtained with experimental animals to humans is at best questionable.

Over the years ILZRO has conducted studies of lead compounds in experimental animals. These include limited inhalation studies in rats (no findings of carcinogenicity) and mechanistic studies of the time- and dose-dependent changes that occur in the male rat kidney as a consequence of oral lead acetate administration. These latter studies support the hypothesis of Goyer that tumor induction in the male rat kidney is preceded by a series of degenerative and hyperplastic changes that are likely unique to the rodent kidney. Given that the focus of the present discussions appears to be human epidemiology, these studies will not be discussed further. The results of these studies could be made available upon request

Human Epidemiological Studies

In IARC's 1987 monograph on the evaluation of lead as a human carcinogen, the Agency evaluated six epidemiological studies and concluded that there was inadequate evidence for carcinogenicity to humans resulting from occupational exposures to lead. The six studies evaluated by the Agency in the 1987 monograph represent the worst case scenario as far as the level of lead to which the workers were exposed. The more recent studies have been conducted

on worker populations for which there were no exposure histories available or have experienced blood lead levels several times lower than in these earlier studies.

From these earlier studies the Agency concluded that the “Excesses of respiratory cancer in these studies were relatively small, showed no clear-cut trend with length of exposure, and could have been confounded by factors such as smoking or exposure to arsenic”. The new evidence published since that time does not establish a definitive relationship between occupational lead exposure and cancer. To the contrary, additional evidence has emerged to confirm that confounding factors account for the excess cancers reported in some of the epidemiological studies. As will be described in the following comments, there is even less evidence for a causal relationship between lead and human cancer than in 1987.

Most of the major epidemiological studies that have been conducted since the 1987 IARC review have been summarized by Fu and Boffetta (1995) in a critical review that included a meta-analysis of case control and cohort studies carried out through 1992. This review noted that modest elevations of cancer were evident at sites such as lung, stomach, bladder and kidney, but that there was limited evidence to support the hypothesis of a causal association with lead exposure. The authors noted that most studies did not take into account potential confounders such as other occupational exposures, smoking and dietary habits. For example, the relative risk observed for lung cancer (RR 1.29) was comparable to that suggested to be expected in studies that lacked correction for confounding exposures to cigarette smoke. Although some studies reported modestly higher relative risks, these were noted to potentially be due to confounding exposures to other carcinogens in the workplace.

Increased incidence of stomach cancer was also reported in some studies, but the incidence of stomach cancer was noted by Fu and Boffetta to be inversely related to socio-economic status and to vary as a function of dietary and other lifestyle factors. Although the incidence of stomach cancer in some studies was somewhat higher than might be expected due just to lifestyle factors, other occupational exposures suspected to be associated with risk of stomach cancer were noted to be potentially present.

In the case of bladder cancer, elevations were suggested to likely be the result of publication bias since only four of fourteen studies reviewed presented results for bladder cancer. Given the known association between bladder cancer and cigarette smoking, lifestyle confounding in those studies reporting excess risk was judged probable. Finally, Fu and Boffetta noted that a non-statistically significant increased risk of kidney cancer was evident in their meta-analysis. This observation was of interest due to the specificity of lead for the induction of renal adenomas and carcinomas in rodents. However, based upon the relatively small number of tumors observed, Fu and Boffetta concluded that evidence was “still inadequate to either confirm or rule out an association between kidney cancer and exposure to lead.” Indeed, Fu and Boffetta suggest that suggestions of excess kidney cancer are, like bladder cancer, probably reflective of publication bias.

Finally, of the 18 epidemiological studies that Fu and Boffetta included in their meta-analysis, only seven had any meaningful data on the level of lead to which the workers in the studies were exposed. This meta-analysis thus provides little new information to change the conclusions on lead and cancer that were made by IARC in their 1987 reviews.

Since the conduct of this review, data has become available from several new studies and/or from updates of existing cohort mortality studies. Several of these studies were noted with concern by Vainio (1997). For example, a registry-based analysis of occupational exposure to lead and lung cancer in Finland by Anttila et al. (1995) evaluated workers from the battery industry, lead smelting, metal foundries, railroad machine shops and chemical manufacturing. Overall mortality for the cohort was less than expected (SMR 84) while the SMR for cancer mortality, all causes, had an SMR of 93. An internal cohort analysis of cancer incidence rates was conducted and a small excess of total cancer and lung cancer was found among workers who had blood lead levels above 21 µg/dL. However, the incidence of cancer did not vary as a function of elevated lead exposure level and strong interactions were observed with concomitant exposures to engine exhaust. The lack of an exposure-response relationship between lead and lung cancer makes causality doubtful. Approximately 90% of the cases were also noted to be

long-term smokers although, oddly enough, no relationship between lung cancer and smoking was found. The treatment of this confounder in the analysis is thus somewhat suspect. Such registry-based studies are best regarded as hypothesis-generating due to the lack of precision they possess with respect to actual work history and/or exposures experienced by the study subjects. Overall, the results of the study add little to the existing epidemiological database on which the classification of lead is currently based.

Gerhardsson et al. (1995) evaluated a cohort of 664 male lead battery workers. A non-significant increase in cancer of the gastrointestinal tract was evident in the cohort as a whole and increased to a “barely significant level” in the exposure quartile with the highest cumulative lead exposures. However, no clear dose response pattern was evident upon more refined analysis of the database nor was cancer incidence related to latency. The authors indicated that the results “must also be interpreted with caution because of limited numbers, and lack of information on dietary and smoking habits.” Given tissue sites of concern in other studies, it is interesting to note that cancer of the respiratory tract, kidney and bladder were not elevated in response to occupational exposure to lead.

A second Swedish study by Lundström et al. (1997) evaluated relationships between cumulative lead exposure and mortality from lung cancer. Interpretation of the results of this study are difficult since lead production was occurring as a co-generation product of copper smelting and significant elevation of lung cancer rates was evident at the entire facility. However, there appeared to be a dose-dependent relationship between indexes of cumulative lead exposure and the incidence of lung cancer. Cancers of the gastrointestinal tract, kidney and bladder were not elevated.

Finally, a study by Cocco et al. (1997) evaluated patterns of mortality at a lead smelter in Italy. This study reported a possible association between lead exposure and kidney cancer, although these findings were based upon a relatively small number of observations and were not found to be statistically significant. This study thus provides little new evidence that long-term

employment in lead smelting plants increases the risk of kidney cancer. Mortality from cancer of the stomach and the lung were lower than expected.

Thus, the studies conducted up through 1997 continued to display the same inconsistent pattern of results that characterize the earlier database. Most studies did not observe increases in cancer of the kidney and/or gastrointestinal tract. Those that did generally failed to observe an increase in lung cancer. Conversely, increases in lung cancer were sometimes seen, unaccompanied by increases in kidney and/or intestinal tract cancer, but the significance of these observations was judged uncertain due to the probable influence of lifestyle confounders and/or the presence of other carcinogens in the workplace.

Recent Updates on Studies Related to Lead and Cancer

ILZRO has maintained a long-standing research portfolio encompassing issues of occupational exposure to lead and cancer. Several of these studies have recently been completed or are nearing completion and bear upon the issue of lead carcinogenicity. The dose-dependent relationship between occupational exposure to lead and lung cancer reported by Lundström et al. (1997) was of interest and more detailed exposure assessments and case-control analyses were supported by ILZRO's research funding program. Analysis of mortality at this Swedish facility is complex in that it is primarily a copper smelting facility with a small volume of lead production as a co-generation product. Overall mortality from lung cancer is elevated at the facility as a whole, an observation suspected to be due to concomitant exposures to the arsenic that is also present in copper ore bodies.

In results presented at a conference convened by IARC in June 1999, provisional data was presented on the results of this more refined analysis. The 1997 publication of Lundström et al. had focused upon 14 cancers of the lung reported in the "lead subcohort". This cohort was defined not so much by job activity as by blood lead measurements. A substantial proportion of the lung cancers reported are now known to have occurred in maintenance workers, builders and truck drivers who worked in all departments of the facility and hence had exposures to a number of other confounders within the plant. Most of the cases examined to date had extensive

exposure to arsenic. A case referent study is presently underway to more fully define the nature of confounding exposures present in this cohort and is scheduled for completion in mid-2000. Given the arsenic exposures now being quantified in this cohort, and the fact that a number of the cancers reported earlier were not actually in persons who many would view to be true lead smelter workers, the investigators now caution that it would be premature to assume a causal relationship between lead exposure and lung cancer based upon their previously published data. Details of this study should be "in press" later this year.

ILZRO has also completed an update of a large cancer mortality study of employees at U.S. lead battery production plants and lead smelters. The cohort consists of 4,518 workers at battery plants and 2,300 workers at lead smelters and constitutes the single largest study conducted on occupational lead exposure. The results of this study are now in press in the American Journal of Industrial Medicine. A copy of this *in press* manuscript is enclosed with these comments.

This recent update by Wong and Harris contributes significantly to understanding cancer at sites that have traditionally been of concern with occupational lead exposure. The study reports a deficit (just lacking in statistical significance) of kidney cancer and a statistically significant deficit in bladder cancer mortality. The study thus supports the earlier observation of Fu and Boffetta that publication bias likely influenced earlier suggestions that cancer at these sites was associated with lead exposure.

As has been noted by some studies, an excess of stomach cancer was observed by Wong and Harris in the study as a whole. However, given the well-known impact of lifestyle confounders and socio-economic factors upon stomach cancer incidence, the authors conducted a nested case-control study of stomach cancer. Odds ratios were calculated for multiple exposure indices and none were found to correlate with the incidence of stomach cancer. The lack of an exposure-response relationship is naturally inconsistent with causality. Instead, it was observed that a disproportionate number of the stomach cancer cases were present in foreign-born workers. In particular, 40% of the cases were born in Ireland or Italy, countries which have a higher rate of

stomach cancer than is present in the US population at large. The excess of stomach cancer in this study is thus likely a product of confounding and not due to lead exposure.

The recent update by Wong and Harris also observed a small but statistically significant increase in lung cancer (SMR=116). This increase in lung cancer is on the order of that generally expected in databases that are not corrected for confounding by smoking and is statistically significant mainly due to the large size of the study cohort. The authors caution that definitive statements cannot be made regarding the observation of lung cancer risk, particularly in the absence of smoking data. They note that the risk of lung cancer did not increase with length of employment and further determined that the excess in lung cancer was primarily present in workers hired after 1946 and not in workers hired before 1946. Excess lung cancer thus occurred in individuals with lower overall levels of lead exposure. The failure of lung cancer incidence to correlate with exposure duration or intensity suggests that it is not causally related to lead. In consideration of this observation, it should be noted that death from nephritis increased as a function of both metrics of exposure duration and intensity. The correlation of this lead-related disease endpoint with these indices indicates that the exposure metrics used are appropriate and that the failure to observe exposure-related correlations with lung cancer is evidence for lack of an exposure-response relationship with lead. ILZRO is presently planning to implement a nested case-control study of lung cancer in this cohort to further evaluate the relative roles of lead exposure and lifestyle confounders upon the modest excess lung cancer risk observed.

The only other finding of note in this study is an increase incidence of thyroid cancer. However, the authors note that the number of deaths observed was small and potential confounding exposures in some of the deaths cannot be ruled out. Excess cancer of the thyroid and other endocrine glands has not been reported in other studies of lead exposed workers. This is presumably due to their failure to observe cancer excess.

Summary

The last comprehensive review of relationships between occupational exposure to lead and human cancer (Fu and Boffetta 1995) observed no consistent relationship between occupational lead exposure and cancer. Sporadic increases of lung, kidney, stomach and bladder cancer have been reported. However, the findings between the different studies are disparate and fail to provide a consistent pattern of elevated cancer mortality. Although aspects of this analysis suggested lead exposure could be correlating with cancer at some sites, little data firmly implicated lead as a human carcinogen. Studies conducted since that time have continued this pattern of results. Some studies reported modest excesses in lung cancer but not kidney, stomach or bladder. Others have reported excesses in kidney cancers but not for cancers at other sites.

Recent ILZRO studies have focused upon elucidation of potential relationships between occupational lead exposure and cancer. Ongoing studies at a Swedish smelter, previously reported to have a dose-dependent relationship between lead exposure and lung cancer (Lundström et al. 1997) have instead revealed extensive arsenic confounding that presently precludes establishment of causal relationships with lead exposure. A case control analysis of lung cancer at this facility is ongoing and should be completed by mid-2000. A major epidemiological study update has also been completed by ILZRO. This study reports deficits of kidney and bladder cancer, although only the bladder cancer deficit is statistically significant. An increase in stomach cancer was observed in this mortality study, but case-control analysis suggests that it is not causally related to lead exposure. Rather, excess stomach cancer appears to be occurring in foreign-born workers from countries with higher rates of stomach cancer. A small but statistically significant excess of lung cancer is present in the current update, but does not correlate with metrics for intensity or duration of exposure. Although this cancer excess is unlikely to be causally-related to lead exposure, case-control studies are planned and should be completed by the end of 2001.

The results of these two most recent studies confirm the earlier suggestions of Fu and Boffetta that publication bias is likely the source of suggestions that lead exposure can be associated with

bladder and kidney cancer. Furthermore, where available data have permitted more refined analysis of excesses of cancer at sites such as the stomach or the lung, confounders such as differences in ethnicity or the presence of exposure to other carcinogens were related to the excess cancer incidence. IARC's 1987 evaluation of the human epidemiology data deemed it to be inconclusive. Data generated since that time make it even less probable that lead functions as a human carcinogen.

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RE: AJIM 99-153
Cancer mortality study of employees at lead
Battery plants and lead smelters

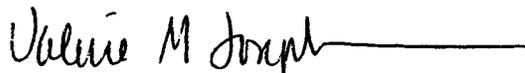
Dear Dr. Wong:

We have received your revised manuscript and comments. We are pleased to accept the manuscript for publication in the *American Journal of Industrial Medicine*.

The manuscript will be sent off to Production today and you should receive proofs in six to eight weeks. We are working with new typesetters and copyeditors who are located abroad. They have been satisfactory except for a few glitches with large tables. Please pay particular attention to your Tables when you receive proofs.

We look forward to seeing your manuscript in print. As of yet, we have no date for the special issue.

Sincerely,



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Cancer Mortality Study of Employees at Lead Battery Plants and Lead Smelters, 1947-1995

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Short title: Cancer mortality in lead battery and lead smelter workers

Grant sponsor: The study was supported by a research grant from the International Lead and Zinc Research Organization.

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ABSTRACT

Background: This study examined cancer mortality of a cohort of male US workers exposed to lead.

Methods: The cohort consisted of 4,518 workers at lead battery plants and 2,300 at lead smelters. Vital status was ascertained between 1947 and 1995. Site-specific cancer standardized mortality ratios (SMRs) and 95% confidence intervals (95% CIs), based on the mortality rates of the US male population and adjusted for age and calendar time, were calculated for the total cohort as well as subcohorts stratified by various exposure parameters. In addition, a nested case-control study of stomach cancer (30 cases and 120 age-matched controls) was also conducted.

Results: Mortality from all cancers was as expected (897 observed deaths, SMR=103.8, 95%CI: 97.1-110.8). Mortality was significantly raised for stomach cancer (SMR=147.4, 95%CI: 112.5-189.8), lung cancer (SMR=116.4, 95%CI: 103.9-129.9), and cancer of the thyroid and other endocrine glands (SMR=308.0, 95%CI: 133.0-606.8). There was a non-significant mortality deficit from kidney cancer (SMR=63.6, 95%CI: 33.9-108.7). For bladder cancer, mortality was significantly lower than expected (SMR=55.5, 95%CI: 31.7-90.1). Non-significant mortality deficits were also reported for cancer of the central nervous system (SMR=74.8, 95%CI: 41.9-123.4) and lymphatic and hematopoietic cancer (SMR=92.2, 95%CI: 72.4-115.7). Additional analyses by type of facility (lead battery plants v. lead smelters), length of employment, latency, and period of hire were also performed. In the nested case-control study of stomach cancer, odds ratios were calculated for various exposure indices, and none was found to be elevated. Furthermore, no exposure-response relationship between lead exposure and stomach cancer was found in the nested case-control study.

Conclusions: A significant mortality increase from stomach cancer was found. However, based on the analyses in the cohort study and the nested case-control study, the increase did not appear to be related to lead exposure. A small, but statistically significant mortality increase from lung cancer was also observed. The small increase, in the absence of an exposure-response relationship, could be the result of confounding due to smoking, and was not likely causally related to lead exposure. Although the significant increase in cancer of the thyroid and other endocrine glands appeared to be consistent with an occupational interpretation, the small number

of deaths (8), the lack of information on potential confounding factors and the lack of reporting of a similar increase in other studies underscore the need to view this finding with caution. No increased mortality was found for kidney cancer, bladder cancer, cancer of the central nervous system, or lymphatic and hematopoietic cancer.

KEYWORDS

Lead; lead battery; lead smelter; epidemiology; mortality; stomach cancer; lung cancer; thyroid cancer; kidney cancer; bladder cancer; brain cancer; lymphatic and hematopoietic cancer

ACKNOWLEDGMENTS

The authors are grateful to the participating companies in the original study for their participation, to Dr. Clark Cooper (retired) for assembling the original cohort, to the National Death Index (NDI) of the National Center for Health Statistics for providing vital status information, to Robert Bilgrad at NDI for his valuable assistance, to state health departments for providing copies of death certificates, to the International Lead and Zinc Research Organization (ILZRO) for sponsoring the project, and to Dr. Craig Boreiko at ILZRO for his continuing support.

INTRODUCTION

Occupational exposure to lead has long been associated with lead poisoning, neuropathy, and renal diseases. Results on cancer from studies of workers exposed to lead, however, have been inconsistent, and the carcinogenic potential of lead is still unresolved. In an evaluation in 1987, the International Agency for Research on Cancer [IARC, 1987] classified lead and inorganic lead compounds as “possible human carcinogens” (Group 2B). The evaluation was based on “*sufficient evidence for carcinogenicity in experimental animals but insufficient evidence for carcinogenicity in humans.*” In 1995, Fu and Boffetta at IARC performed a literature review and a meta-analysis of published data on cancer in workers exposed to lead [Fu and Boffetta, 1995]. Based on the literature review and meta-analysis, significant excess risks of stomach cancer and lung cancer were reported. The summary relative risks and 95% confidence intervals (95%CI) were 1.33 (95%CI: 1.18-1.49) for stomach cancer and 1.29 (95%CI: 1.10-1.50) for lung cancer, respectively. The authors concluded that the findings provided some evidence for an association between occupational exposure to lead and stomach cancer or lung cancer, but could not rule out the effects of confounders such as smoking and non-occupational factors. Finally, Fu and Boffetta [1995] also reported excess risks for kidney cancer and bladder cancer, but suggested that the results could have been influenced by possible publication bias.

Included in the IARC [1987] evaluation and the Fu and Boffetta [1995] review was a cohort mortality study of US lead battery and lead smelter workers [Cooper and Gaffey, 1975; Cooper, 1976; Cooper et al., 1985]. The cohort consisted of 4,519 male lead battery workers and 2,300 male lead smelter workers, who were employed at these facilities for at least one year between 1946 and 1970. Mortality of the cohort in the last update [Cooper et al., 1985] was ascertained through the end of 1980. With respect to cancer, mortality from stomach cancer and lung cancer was elevated. Among lead battery workers, the standardized mortality ratios (SMRs) and 95% CIs were 168 (95%CI: 116-235) for stomach cancer and 124 (95%CI: 102-150) for lung cancer, respectively. Among lead smelter workers, the SMRs and 95%CIs were 146 (95%CI: 67-278) for stomach cancer and 125 (95%CI: 89-169) for lung cancer, respectively. The

authors commented that *“Ethnicity, diet, alcohol and cigarette smoking could not be ruled out as possible confounding etiologic factors for the cancer deaths.”*

The present investigation was based on the data of the study of US lead battery and lead smelter workers previously reported by Cooper et al. [1985]. The primary objectives of the present investigation were: (1) to update the vital status of the cohort, and (2) to analyze the updated site-specific cancer mortality data (particularly stomach cancer, lung cancer, kidney cancer, bladder cancer, cancer of the central nervous system, and lymphatic and hematopoietic cancer) in relation to employment pattern (type of facility, length of employment, and period of exposure). In addition, a nested case-control study of stomach cancer was also conducted. The primary objective of the case-control study was to analyze stomach cancer risk in relation to length and cumulative exposure to lead, based on a detailed classification of jobs by exposure category.

MATERIALS AND METHODS

The selection of the original cohort was based on a questionnaire survey in 1968. Questionnaires outlining the proposed study were sent to plants of member companies of the International Lead and Zinc Research Organization, the Lead Industry Association, or the Battery Council International. Information regarding operation history, workforce and personnel records was solicited. Of the 101 plants contacted, 84 indicated willingness to participate. Based on a consideration of operation history, the size of workforce, and the quality and availability of personnel records, 10 lead battery plants and 6 lead smelters (1 primary smelter, 2 secondary smelters, and 3 recycling plants) were chosen to be included in the study.

The cohort was defined as male workers with at least one year of employment between January 1, 1946 and December 31, 1970 at one of the selected facilities. A total of 4,519 lead battery employees and 2,300 lead smelter employees were included in the previous study. In the present update, the same cohort definition was used. However, based on a thorough review of the cohort data, one duplicate record was discovered among lead battery workers. In the present update, the duplicate record was removed, reducing the number of lead battery workers to 4,518.

The lead battery plants were located in California, Illinois, Pennsylvania (3 plants), Oregon, Texas (3 plants) and Wisconsin. Approximately 70% of the lead battery workers were employed at the 3 plants in Pennsylvania. The lead smelters were located in California (2 smelters), Indiana, Montana, Nebraska, and Pennsylvania. Approximately 35% of the lead smelter workers were employed at the Nebraska smelter, 23% at the Indiana smelter, and 19% at the Montana smelter.

In the last update of the study [Cooper et al., 1985], vital status was ascertained through December 31, 1980. In the present investigation, the vital status of the cohort was updated through December 31, 1995. The primary sources for vital status information in the update was the National Death Index (NDI) developed and maintained by the National Center for Health Statistics (NCHS). The Death Master File (DMF) maintained by the Social Security

Administration (SSA) was also utilized. Dates and causes of death were obtained from either death certificates or NDI reports. Underlying causes of death were coded according to the International Classification of Diseases, 8th Revision (ICD-8).

In assembling the original cohort, employment histories through 1970 were collected, which included jobs, departments, and the corresponding effective dates. Subsequently, employment status (i.e., active, terminated or retired) was updated through 1981. In the present investigation, employment status was not further updated. In other words, employment status for all cohort members was known through 1981 only.

As stated in the previous report by Cooper et al. [1985], there was no exposure data for the entire cohort. However, biological monitoring data were collected on some of the cohort members between 1947 and 1972, with the majority of the measurements made after 1960. In total, urinary lead measurements were available for 2,275 men, and blood lead concentrations for 1,863 men (Table 1). There were 1,550 men with 10 or more urinary lead measurements. In this group of workers, the average urinary lead measurements were 129.7 $\mu\text{g/l}$ (6.3 $\mu\text{mol/l}$) among lead battery workers and 173.2 $\mu\text{g/l}$ (8.4 $\mu\text{mol/l}$) among lead smelter workers, respectively. In both groups, there were many individuals with average urinary lead levels above 200 $\mu\text{g/l}$ (9.7 $\mu\text{mol/l}$). Among the 1,083 lead battery workers with 3 or more blood lead analyses, the average was 62.7 $\mu\text{g}/100\text{ g}$ (3.0 $\mu\text{mol/l}$). For 254 lead smelter workers with at least 3 blood lead samples, the average blood lead level was 79.7 $\mu\text{g}/100\text{ g}$ (3.9 $\mu\text{mol/l}$). However, for a number of lead battery or smelter workers, the average blood lead level was more than 100 $\mu\text{g}/100\text{ g}$ (4.8 $\mu\text{mol/l}$).

In comparison, the current (1999) ACGIH Biological Exposure Index (BEI) for blood lead is 30 $\mu\text{g}/100\text{ ml}$. BEIs represent the levels of determinants which are most likely to be observed in specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure to the threshold limit value (TLV). Thus, historically the worker in the study were exposed to lead at levels far exceeding the current TLV of 0.05 mg/m^3 .

No separate analysis of mortality was made for cohort members with biological monitoring data, since all the measurements were made between 1947 and 1972 and the majority after 1960. Thus, these measurements might not accurately reflect earlier exposure levels. Furthermore, many workers began employment prior to the implementation of monitoring programs, and, therefore, might not have any recorded measurements. Recorded measurements presented in Table 1 served, however, as evidence that many cohort members had been exposed to lead in amounts far exceeding the current standards.

Site-specific cancer SMRs and corresponding 95% CIs were calculated for the entire cohort as well as for subcohorts stratified by type of facility (battery plants v. smelters) and other exposure parameters. In the calculation of SMRs, the expected deaths were based on mortality rates of the male population in the US, and were adjusted for age and calendar time. Statistical analysis was performed using the Occupational Cohort Mortality Analysis Program (OCMAP) developed by the Department of Biostatistics at the University of Pittsburgh [Marsh et al., 1998].

In addition to the cohort study, a nested case-control study of stomach cancer among lead battery workers was also conducted. For practical reasons, the case-control study was limited to the largest participant in the study, which contributed half of the stomach cases. It was felt that exposure assessment and collection of additional information would be more efficient if resources and efforts were limited to one single facility. The study consisted of 30 stomach cancer deaths at a lead battery plant in Philadelphia (the largest participant in the study) and 120 age-matched controls from the same facility. Job titles of these 150 workers were reviewed to determine the potential for lead exposure. Based on the review, jobs were classified by level of lead exposure into low, intermediate, and high categories (Appendix). Several lead exposure indices were used in the case-control analysis: months of overall employment at the plant, months of employment in areas with intermediate or high lead exposures, and weighted cumulative exposure in months (1=low, 2=intermediate, 3=high). Comparisons were made using total work histories prior to the deaths of the index cases, as well as exposures 10 (or 20) or more years prior to the deaths of the index cases. Means of various exposure indices were calculated and compared between the cases

and controls. Odds ratios based on the Mantel-Haenszel chi-square procedure were calculated for various exposure indices, and trend tests based on conditional logistic regression were performed for exposure-response analysis.

RESULTS

Table 2 presents some descriptive statistics of the cohort. Two-thirds of the cohort were lead battery workers. Close to 70% of the lead battery workers were employed for 20 years or longer, and 57% were hired prior to 1946. On the other hand, approximately 40% of lead smelter workers were employed for 20 years or longer, and 21% were hired before 1946. With respect to vital status, more than half of the cohort (N=3,713) had been identified to have died. Death information was obtained from either death certificates or NDI reports for all workers identified to have died except for 18 decedents (0.5%). These 18 deaths were included in overall mortality analysis but not in cause-specific analysis. In the previous follow-up through 1980, there were 432 (6.3%) individuals whose vital status was not determined. In the present update, the number of workers with unknown vital status was reduced to 356 (5.2%). Person-years of observation of these 356 individuals were counted up to the last known date of employment.

Site-specific cancer mortality analysis for the combined cohort of lead battery and lead smelter workers is presented in Table 3. A small but statistically significant increase of overall mortality was found (SMR=104.5, 95%CI: 101.2-108.0). Three cancer sites showed significant increases: stomach cancer (SMR=147.4, 95%CI: 112.5-189.8), lung cancer (SMR=116.4, 95%CI: 103.9-129.9), and cancer of the thyroid and other endocrine glands (SMR=308.0, 95%CI: 133.0-606.8). On the other hand, significant deficits were observed for cancer of the buccal cavity and pharynx (SMR=58.1, 95%CI: 30.9-99.4) and bladder cancer (SMR=55.5, 95%CI: 31.7-90.1). Mortality from other cancer sites were as expected. In particular, there was no increase in mortality from kidney cancer (SMR=63.6, 95%CI: 33.9-108.7), cancer of the central nervous system (SMR=74.8, 95%CI: 41.9-123.4), or lymphatic and hematopoietic cancer (SMR=92.2, 95%CI: 72.4-115.7). There were 34 deaths attributed to leukemia, with 33.30 expected (SMR=102.1, 95%CI: 70.7-142.7). The OCMAP program did not provide separate analyses for non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM). However, additional separate analyses indicated that the SMR for NHL was 73.3 (95%CI: 49.5-104.7; 22 observed deaths), and the SMR for MM was 57.7 (95%CI: 26.5-109.5; 9 observed deaths).

Tables 4 and 5 show cancer mortality analysis separately for lead battery and lead smelter workers. To a large extent, mortality patterns were similar between the two groups. In particular, mortality increases were observed in both groups for stomach cancer, lung cancer, and cancer of the thyroid and other endocrine glands, although some of the individual increases were no longer statistically significant because of the reduced number of deaths in separate analyses. There was no increased mortality in either lead battery or lead smelter workers for kidney cancer, bladder cancer, cancer of the central nervous system, or lymphatic and hematopoietic cancer.

Mortality analysis by hire date (<1946 v. 1946+) for the total cohort of lead battery and smelter workers is depicted in Table 6. Mortality from stomach cancer was elevated regardless of hire date, but the increase among those hired before 1946 was significant (SMR=142.6, 95%CI: 103.2-192.1), whereas that among those hired in or after 1946 was not (SMR=161.3, 95%CI: 94.0-258.3). In contrast, mortality from lung cancer was significantly elevated among those hired in or after 1946 (SMR=135.0, 95%CI: 114.3-158.3), whereas lung cancer mortality was as expected among those hired prior to 1946 (SMR=103.4, 95%CI: 88.3-120.4). For cancer of the thyroid and other endocrine glands, non-significant increases of approximately the same magnitude were observed for both groups (SMR=306.0 for those hired before 1946, and SMR=311.4 for those hired in or after 1946). No increased mortality was seen in either group by hire date for kidney cancer, bladder cancer, cancer of the central nervous system, or lymphatic and hematopoietic cancer.

Mortality analysis by hire date is shown separately for lead battery and lead smelter workers in Tables 7 and 8, respectively. For stomach cancer, only lead battery workers hired before 1946 experienced a significantly higher risk (SMR=148.6, 95%CI: 104.6-204.8), whereas for lung cancer, only lead battery workers hired in or after 1946 had a significantly elevated risk (SMR=153.4, 95%CI: 121.3-191.5).

Mortality analysis by length of employment in lead battery and lead smelter workers is presented in Table 9. For stomach cancer and lung cancer, only those with 10-19 years of employment experienced significantly increased risks (SMR=203.7 and SMR=144.7,

respectively). All eight deaths from cancer of the thyroid and other endocrine glands were among workers with 20 or more years of employment, resulting in an SMR of 462.7 (95%CI: 199.8-911.6). No increase in kidney cancer, bladder cancer, cancer of the central nervous system, or lymphatic and hematopoietic cancer was seen for any group by length of employment.

Table 10 shows cause-specific mortality analysis by latency. There were significant increases from stomach cancer among lead battery and lead smelter workers with <20 and 20-34 years of latency (SMRs of 222.2 and 160.2). Among those with a latency of 35+ years, there was a small non-significant increase (SMR=118.4). For mortality from lung cancer, only workers with 20-34 years of latency experienced a significant increase (SMR=138.4, 95%CI: 115.4-164.7). For mortality from cancer of the thyroid and other endocrine glands, workers with 35+ years of latency had a significant SMR of 518.5 (95%CI: 190.3-1128.5).

In addition to the cohort study, a nested case-control study was also conducted at a large battery plant in Philadelphia (the largest participant in the cohort study). The nested case-control study consisted of 30 stomach cancer cases and 120 age-matched controls. The means of various lead exposure indices for the stomach cancer cases and controls are presented in Table 11. Cases had either similar or slightly lower mean exposures than the controls. However, none of the differences were statistically significant. The results of the case-control analysis of stomach cancer are summarized in Table 12. Odds ratios were calculated for each quartile of exposure category, and trend tests were also performed. There was no indication of any association between lead exposure and stomach cancer, based on either individual odds ratios (ORs) or trend test. For example, based on the total weighted cumulative exposure, the ORs were 1.00, 0.62, 0.82 and 0.61 for the lowest, second, third and highest quartile, respectively, with a p-value of 0.47 for the trend test. On the other hand, it was noted that there were more foreign-born workers among the stomach cancer cases than among their age-matched controls (OR=1.29, 95%CI: 0.61-3.06). In particular, 40% cases were born in Ireland or Italy, compared to only 23% controls (OR=2.30, 95%CI: 0.99-5.36).

DISCUSSION

Similar to the previous analysis, in the present updated cohort study there was a small increase in overall mortality for the entire cohort of lead battery and lead smelter workers (SMR=104.5). The increase occurred among lead battery workers only (SMR=106.7), but not among lead smelter workers (SMR=99.8). However, in either subcohort there was no evidence for the commonly observed healthy worker effect.

In terms of specific cancers, among lead battery workers, there was a significantly elevated mortality from stomach cancer (SMR=152.8). A slightly smaller non-significant increase was observed among lead smelter workers (SMR=133.4). These increases in stomach cancer mortality were similar to, but somewhat smaller than those reported in the previous analysis. There was no pattern of an increase of stomach cancer by length of employment in the cohort study. In fact, the lowest SMR was observed in the group with the longest employment (20+ years).

For stomach cancer, a nested case-control study was conducted in addition to the cohort study. Jobs were classified into three categories (low, intermediate, and high) according to potential for exposure to lead. A weighted cumulative exposure index was created for each subject. No difference in terms of exposure was found between the stomach cancer cases and their age-matched controls. Furthermore, no elevated odds ratios or upward trends were reported for any exposure categories. Thus, the results from both the cohort and the nested case-control studies argued against a causal role of occupational exposure.

On the other hand, there were more foreign-born workers among the cases than among the controls, particularly for those born in Ireland or Italy (OR=2.30, 95%CI: 0.99-5.36). Epidemiologic studies have reported a higher risk of stomach cancer among immigrants in the US. In a review, Howson et al. [1986] compared stomach cancer mortality rates during two time periods (1950-52 and 1977-79) among 18 countries, including Ireland, Italy and the US. Although stomach cancer mortality rates declined drastically for all three countries between the two time periods, the rates for Ireland and Italy were two to four times higher than those for the US during

the same time periods. Based on the nested case-control study, the increase in stomach cancer mortality observed in the cohort study appeared unlikely to be related to lead exposure. On the other hand, being foreign-born might have accounted for at least part of the increase.

Likewise, results on stomach cancer from other studies of workers exposed to lead have suggested a small increase but no exposure-response relationship. Gerhardsson et al. [1986] reported a significant increase of stomach cancer mortality in a cohort of 3,832 workers exposed to lead at a copper smelter in northern Sweden (SMR=143, 95%CI: 105-191, 46 observed deaths). In a subgroup of 437 workers with "verified high lead exposure," there was no increase (SMR=95, 95%CI: 19-274, 3 observed deaths). The mean blood lead level in 1950 in the subgroup with high exposure was 58.2 $\mu\text{g}/100\text{ ml}$. In another small study of 664 workers at a secondary lead smelter in southern Sweden, Gerhardsson et al. [1995] reported 3 cases of stomach cancer, compared to 1.6 expected (standardized incidence ratio, SIR=188, 95%CI: 39-550). In a cohort study of 1,990 workers at an Idaho lead smelter, Steenland et al. [1992] reported a nonsignificant increase of stomach cancer mortality (SMR=136, 95%CI: 75-224). However, in the subcohort with high lead exposure, the increase was somewhat smaller (SMR=128, 95%CI: 61-234). Finally, in a cohort of 1,388 Italian lead smelter workers, Cocco et al. [1997] reported a significant mortality deficit from stomach cancer (SMR=49, 95%CI: 29-79) when compared to national mortality rates, but the significant deficit disappeared when regional mortality rates were used for comparison (SMR=97, 95%CI: 53-162).

At present, a causal relationship between lead exposure and stomach cancer cannot be established based on the current data. In fact, the lack of exposure-response relationships in these studies argues against a causal interpretation. To further investigate the relationship between lead exposure and stomach cancer, additional nested case-control studies, incorporating quantitative lead exposure, personal and lifestyle information, are desirable.

With respect to lung cancer, similar to the previous analysis, a small but statistically significant increase was observed in the present update (SMR=116.4, 95%CI: 103.9-129.9). The increase in lung cancer mortality was restricted to workers hired in or after 1946 (SMR=135.0,

95%CI: 114.3-158.3), and no increase was seen in workers hired earlier (SMR=103.4, 95%CI: 88.3-120.4), who were likely to have been exposed to higher levels of lead. Furthermore, no exposure-response relationship was evident based on length of employment analysis. The lowest lung cancer mortality (SMR=110.1, 95%CI: 95.9-125.8) was observed among the group with the longest duration of employment (20+ years). The lack of an upward trend by length of employment further argues against a causal interpretation of the small lung cancer excess in the study.

It is impossible to draw firm conclusions regarding lead exposure and the small increase in lung cancer mortality reported in the present update. An increase of approximately 15% (such as the one in this study), in the absence of a positive exposure-response relationship between lead exposure and lung cancer, could be the result of confounding due to smoking. For example, if we assume that smoking produces a lung cancer relative risk of 10-fold in general, a 15% increase in lung cancer risk can easily be explained by a 10%-15% difference in smokers between the study cohort and the comparison population [Wong and Musselman, 1994]. Unfortunately, smoking information was not available in the present investigation. However, the small magnitude of the increase and the lack of a positive exposure-response relationship in the present investigation tend to argue against a causal interpretation.

Results on lung cancer from other studies of lead exposed workers are inconsistent. For example, in the Idaho lead smelter study, Steenland et al. [1992] reported a small nonsignificant increase in lung cancer mortality (SMR=1.18, 95%CI: 0.92-1.48) for the entire cohort. In the subcohort of workers with high exposure, the increase was somewhat lower (SMR=1.11, 95%CI: -0.82-1.47). Steenland et al. [1992] concluded that there was little epidemiologic evidence implicating lead exposure, and that excess smoking in the cohort might have contributed to the lung cancer increase. In the Italian study of lead smelter workers [Cocco et al., 1997], a significant deficit in lung cancer was reported when compared to national death rates (SMR=62, 95%CI: 43-86), but the deficit was reduced when regional mortality rates were used (SMR=82, 95%CI: 56-116). In the Swedish study of copper smelter workers [Gerhardsson et al., 1986], a significant increase of lung cancer mortality was reported (SMR=218.4, 95%CI: 176.1-268.3) for the overall cohort, and a reduced excess for the subgroup with high lead exposure, which was not

statistically significant (SMR=160.0, 95%CI: 58.6-348.6). It should be pointed out that potential confounding due to arsenic exposure was likely at this Swedish copper smelter. In the second Swedish study of secondary lead smelter workers, Gerhardsson et al. [1995] reported a nonsignificant increase based on 6 cases (SIR=1.32, 95%CI: 0.49-2.88).

Except for the study of Swedish copper smelter workers, lung cancer mortality increases reported in individual studies were small, and could have been due to smoking. In the Swedish copper smelter study, arsenic exposure was a potential confounding factor. Similar to stomach cancer, nested case-control studies of lung cancer, incorporating quantitative lead exposure, arsenic exposure and lifestyle (particularly smoking) information, are needed to further investigate the relationship between lead exposure and lung cancer.

In the present investigation, a significant mortality increase from cancer of the thyroid and other endocrine glands was found (SMR=308.0, 95%CI: 133.0-606.8). Three deaths were from cancer of the thyroid gland (ICD8 193) and 5 from cancer of other endocrine glands (ICD8 194). All 8 deaths occurred among workers with 20 or more years of employment (SMR=462.7, 95%CI: 199.8-911.6). The highest increase was among workers with a latency of 35 years or longer (SMR=518.5, 95%CI: 190.3-1128.5). Thus, the data seemed to suggest a potential association between employment at lead battery plants or lead smelters and cancer of the thyroid and other endocrine glands. However, it should be noted that the number of deaths was small (8), and potential confounding exposures in some of the deaths could not be ruled out. One of the known risk factors for thyroid cancer is therapeutic radiation to the head and neck for tonsillitis, eczema, acne, and thymus enlargement. Such information was not available in the present study. Furthermore, it is unfortunate that results of cancer of the thyroid and other endocrine glands have not been reported in other studies of lead exposed workers, presumably because the number of deaths from cancer of the thyroid and other endocrine glands (relatively rare cancer) was small and/or no excess was found in these other studies. As such, a comparison to other studies of lead workers was not possible.

No increase in mortality from kidney cancer, bladder cancer, cancer of the central nervous system, or any of the lymphatic and hematopoietic cancers was found in the present study. In their review and meta-analysis, Fu and Boffetta [1995] commented that the increases in kidney cancer and bladder reported in the literature could have been the result of publication bias. The only way to resolve this issue is to conduct a comprehensive meta-analysis based on data in all studies (published or otherwise). In some cases, authors may have to be contacted for data not reported in their publications.

The findings of the cohort study should be interpreted in conjunction with its limitations. One of the limitations of the study was the lack of quantitative exposure data for the entire cohort. As such, quantitative exposure-response analysis in terms of lead exposure levels was not possible. Furthermore, employment histories were truncated in 1981. For chronic diseases with long latent periods, exposure within the last decade or two before death generally has little impact on the disease. Therefore, ignoring exposure after 1981 in the analysis should have little influence on the results. In addition, information on confounding factors for some of the diseases of interest (such as diet and ethnicity in stomach cancer, smoking in lung cancer, and radiation in thyroid cancer) was not available. The collection of such personal, lifestyle or medical history data was beyond the scope of the cohort study. Some of the inadequacies in the cohort study can be alleviated by nested case-control studies, such as the one on stomach cancer reported here.

In summary, a significant mortality from stomach cancer was found in the cohort study. However, based on analyses in the cohort study and the nested case-control study, the increase did not appear to be related to lead exposure. A small, but statistically significant mortality increase from lung cancer was also observed. The small increase, in the absence of an exposure-response relationship, could be the result of confounding due to smoking, and was not likely causally related to lead exposure. Although the significant increase in cancer of the thyroid and other endocrine glands appeared to be consistent with an occupational interpretation, the small number of deaths, the lack of information on potential confounding factors and the lack of reporting of a similar increase in other studies underscore the need to view this finding with

caution. No increased mortality was found for kidney cancer, bladder cancer, cancer of the central nervous system, or lymphatic and hematopoietic cancer.

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Appendix: Examples of jobs by exposure category in the case-control study

Low exposure		Intermediate exposure	High exposure
air clean tubes	mix soda	air casting	assayer
ash man	motor tender	battery man	assembly
assembly finish	mould maker	bench hand	assemble in jigs
batteries on skids	oiler	chain hoist	ball caster
blacksmith	order filler	cleaner [machine]	battery assembly
bricklayer box maker	oxygen attendant	cleaner [manual]	box plates
cable trimmer	painter/sprayer	clean up	burner assembler
car man	pickling	connector burner	burning machine
carpenter	pile containers	conveyer loader	burn spines
cell filler	plug batteries	drying oven	crane follower
cell finisher	powerhouse	experimental work	crane operator
chauffeur	printer	finish grids	cut apart
checker	process inspector	finish, slam and trim	disassemble cells
clerk	process oven	floating crew	dumper
cover assembly	pump hand	floorman	feed elements
electrician	remove saw burrs	gang boss	forming
electrolyte leveler	saw adjuster	grid caster	furnace man
elevator operator	saw fiber	grinding	grid paster
embossing machine	sawyer	helper	mill operator
emergency man	shipping	hydraulic casting machine	mixer
engineer	solderer	janitor	mix oxide
fill and finish	spray booth cleaner	laborer	paste mixer
fill batteries	switchboard	leading hand	plate burner
finisher	timekeeper	machine operator	plate cleaner
fireman	tool maker	maintenance	plate cutter
glue hand	trim castings	material handler	plate finisher
gravity and adjuster	truck repair	monorail hooker	plate handler
grid stock	unload coal	moulder	plate parter
guard	unload lumber	packer	plate paster
hardware man	vulcanizing	porter	plate wiper
instrument assembly	wash and stamp	pressman	prepare plates
jig cutter	washer	puddling grids	reclaim scrap
lead roller	watchman	punch press	saw and brush
mechanical	wax sprayer	repair batteries	saw lugs
messenger	welder	shipping machine	shaker
		supply man	shaker hand
		sweeper	skimmer
		tank man	slag man
		truck driver	
		utility	
		wireman	

Table 1

Urinary and blood lead concentrations among lead battery and lead smelter workers, 1947-1972

Urinary lead concentrations							
Type of facility	Total no. of workers sampled	Analysis of data based on workers with 10 or more samples			No. of workers whose averages exceeded		
		No. of workers	Average ($\mu\text{g}/\text{l}$)	150 $\mu\text{g}/\text{l}$	200 $\mu\text{g}/\text{l}$	250 $\mu\text{g}/\text{l}$	300 $\mu\text{g}/\text{l}$
Battery	1286	1053	129.7	249	59	17	7
Smelter	989	497	173.2	289	164	70	27
Total	2275	1550	142.9	538	223	87	34

Blood lead concentrations							
Type of facility	Total no. of workers sampled	Analysis of data based on workers with 3 or more samples			No. of workers whose averages exceeded		
		No. of workers	Average ($\mu\text{g}/100\text{ g}$)	40 $\mu\text{g}/100\text{ g}$	70 $\mu\text{g}/100\text{ g}$	80 $\mu\text{g}/100\text{ g}$	100 $\mu\text{g}/100\text{ g}$
Battery	1326	1083	62.7	1009	278	102	24
Smelter	537	254	79.7	241	89	56	18
Total	1863	1337	64.0	1250	367	158	42

Table 2

Descriptive statistics of a cohort of lead battery and lead smelter workers

Description	Lead battery	Lead smelter	Total
Cohort size	4,518	2,300	6,818
Length of employment as of December 31, 1981			
< 10 years	417 (9.2%)	836 (36.3%)	1,253 (18.4%)
10-19 years	991 (21.9%)	559 (24.3%)	1,550 (22.7%)
20 + years	3,110 (68.8%)	905 (39.3%)	4,015 (58.9%)
Year of Hire			
< 1946	2,571 (56.9%)	485 (21.1%)	3,056 (44.8%)
1946 +	1,947 (43.1%)	1,815 (78.9%)	3,762 (55.2%)
Vital status as of December 31, 1995			
Alive	1,710 (37.8%)	1,039 (45.2%)	2,749 (40.3%)
Dead	2,613 (57.8%)	1,100 (47.8%)	3,713 (54.5%)
With death certificates	2,600 (99.5%)	1,095 (99.5%)	3,695 (99.5%)
Without death certificates	13 (0.5%)	5 (0.5%)	18 (0.5%)
Unknown	195 (4.3%)	161 (7.0%)	356 (5.2%)

Table 3

Observed and expected deaths, standardized mortality ratios and 95% confidence intervals by cause of death among 6,818 lead battery and lead smelter workers, 1947-1995

CAUSE OF DEATH	OBS	EXP	SMR	95% CONFIDENCE LIMITS	
				LOWER	UPPER
All Causes of Death	3713	3551.81	104.5 **	101.2	108.0
All Malignant Neoplasms	897	864.17	103.8	97.1	110.8
Cancer of Buccal Cavity & Pharynx	13	22.37	58.1 *	30.9	99.4
Cancer of Digestive Organs & Peritoneum	254	230.53	110.2	97.0	124.6
Cancer of Esophagus	22	20.20	108.9	68.2	164.9
Cancer of Stomach	60	40.70	147.4 **	112.5	189.8
Cancer of Large Intestine	81	81.52	99.4	78.9	123.5
Cancer of Rectum	22	23.03	95.5	59.9	144.6
Cancer of Biliary Passages & Liver	14	16.09	87.0	47.6	146.0
Cancer of Pancreas	41	44.30	92.6	66.4	125.6
Cancer of All Other Digestive Organs	14	8.51	164.5	89.9	276.0
Cancer of Respiratory System	330	286.98	115.0 *	102.9	128.1
Cancer of Larynx	9	11.26	79.9	36.5	151.7
Cancer of Bronchus, Trachea, Lung	317	272.40	116.4 **	103.9	129.9
Cancer of All Other Respiratory	4	3.21	124.6	34.0	319.1
Cancer of Prostate	75	88.81	84.5	66.4	105.9
Cancer of Testes and Other Male Genital Organs	0	2.93	0.0	0.0	125.9
Cancer of Kidney	13	20.45	63.6	33.9	108.7
Cancer of Bladder and Other Urinary Organs	16	28.83	55.5 *	31.7	90.1
Malignant Melanoma of Skin	9	10.53	85.4	39.1	162.2
Cancer of Central Nervous System	15	20.05	74.8	41.9	123.4
Cancer of Thyroid & Other Endocrine Glands	8	2.60	308.0 *	133.0	606.8
Cancer of Bone	3	2.96	101.2	20.9	295.8
Cancer of All Lymphatic, Haematopoietic Tissue	74	80.28	92.2	72.4	115.7
Lymphosarcoma & Reticulosarcoma	6	11.85	50.6	18.6	110.2
Hodgkins Disease	8	6.14	130.3	56.2	256.7
Leukemia & Aleukemia	34	33.30	102.1	70.7	142.7
Cancer of All Other Lymphopoietic Tissue	26	29.00	89.7	58.6	131.4
Benign Neoplasms	2	8.12	24.6 *	3.0	89.0

* significant at 5% level

** significant at 1% level

Table 4

Observed and expected deaths, standardized mortality ratios and 95% confidence intervals
by cause of death among 4,518 lead battery workers, 1947-1995

CAUSE OF DEATH	OBS	EXP	SMR	95% CONFIDENCE LIMITS	
				LOWER	UPPER
All Causes of Death	2613	2449.83	106.7 **	102.6	110.8
All Malignant Neoplasms	624	596.05	104.7	96.6	113.2
Cancer of Buccal Cavity & Pharynx	11	15.54	70.8	35.3	126.7
Cancer of Digestive Organs & Peritoneum	183	161.95	113.0	97.2	130.6
Cancer of Esophagus	16	13.84	115.6	66.1	187.8
Cancer of Stomach	45	29.45	152.8 **	111.5	204.5
Cancer of Large Intestine	59	56.80	103.9	79.1	134.0
Cancer of Rectum	14	16.53	84.7	46.3	142.1
Cancer of Biliary Passages & Liver	10	10.94	91.4	43.8	168.1
Cancer of Pancreas	30	30.79	97.4	65.7	139.1
Cancer of All Other Digestive Organs	9	6.18	145.6	66.6	276.3
Cancer of Respiratory System	219	194.41	112.6	98.2	128.6
Cancer of Larynx	7	7.81	89.7	36.1	184.8
Cancer of Bronchus, Trachea, Lung	210	184.31	113.9	99.0	130.4
Cancer of All Other Respiratory	2	2.21	90.5	10.9	326.9
Cancer of Prostate	54	62.93	85.8	64.5	112.0
Cancer of Testes and Other Male Genital Organs	0	1.96	0.0	0.0	188.4
Cancer of Kidney	7	13.95	50.2	20.2	103.4
Cancer of Bladder and Other Urinary Organs	10	20.53	48.7 *	23.4	89.6
Malignant Melanoma of Skin	4	6.89	58.0	15.8	148.6
Cancer of Central Nervous System	10	13.34	75.0	35.9	137.9
Cancer of Thyroid & Other Endocrine Glands	5	1.80	277.9	90.2	648.5
Cancer of Bone	2	2.11	94.7	11.5	342.1
Cancer of All Lymphatic, Haematopoietic Tissue	53	55.06	96.3	72.1	125.9
Lymphosarcoma & Reticulosarcoma	4	8.38	47.7	13.0	122.2
Hodgkins Disease	6	4.18	143.5	52.6	312.2
Leukemia & Aleukemia	26	23.07	112.7	73.6	165.2
Cancer of All Other Lymphopoietic Tissue	17	19.43	87.5	51.0	140.1
Benign Neoplasms	2	5.51	36.3	4.4	131.0

* significant at 5% level

** significant at 1% level

Table 5

Observed and expected deaths, standardized mortality ratios and 95% confidence intervals
by cause of death among 2,300 lead smelter workers, 1947-1995

CAUSE OF DEATH	OBS	EXP	SMR	95% CONFIDENCE LIMITS	
				LOWER	UPPER
All Causes of Death	1100	1101.99	99.8	94.0	105.9
All Malignant Neoplasms	273	268.12	101.8	90.1	114.6
Cancer of Buccal Cavity & Pharynx	2	6.83	29.3	3.5	105.8
Cancer of Digestive Organs & Peritoneum	71	68.58	103.5	80.9	130.6
Cancer of Esophagus	6	6.37	94.2	34.6	205.1
Cancer of Stomach	15	11.25	133.4	74.6	220.0
Cancer of Large Intestine	22	24.72	89.0	55.8	134.7
Cancer of Rectum	8	6.50	123.0	53.1	242.4
Cancer of Biliary Passages & Liver	4	5.15	77.7	21.2	199.0
Cancer of Pancreas	11	13.51	81.4	40.6	145.7
Cancer of All Other Digestive Organs	5	2.33	214.8	69.7	501.3
Cancer of Respiratory System	111	92.58	119.9	98.6	144.4
Cancer of Larynx	2	3.46	57.8	7.0	208.9
Cancer of Bronchus, Trachea, Lung	107	88.09	121.5	99.5	146.8
Cancer of All Other Respiratory	2	1.00	200.2	24.2	723.2
Cancer of Prostate	21	25.88	81.1	50.2	124.0
Cancer of Testes and Other Male Genital Organs	0	0.97	0.0	0.0	379.2
Cancer of Kidney	6	6.50	92.3	33.9	201.0
Cancer of Bladder and Other Urinary Organs	6	8.30	72.3	26.5	157.4
Malignant Melanoma of Skin	5	3.64	137.2	44.5	320.3
Cancer of Central Nervous System	5	6.71	74.5	24.2	173.9
Cancer of Thyroid & Other Endocrine Glands	3	0.80	375.7	77.5	1098.0
Cancer of Bone	1	0.85	117.4	2.9	654.4
Cancer of All Lymphatic, Haematopoietic Tissue	21	25.22	83.3	51.5	127.3
Lymphosarcoma & Reticulosarcoma	2	3.46	57.7	7.0	208.6
Hodgkins Disease	2	1.96	102.1	12.4	368.9
Leukemia & Aleukemia	8	10.24	78.2	33.7	154.0
Cancer of All Other Lymphopoietic Tissue	9	9.57	94.0	43.0	178.5
Benign Neoplasms	0	2.61	0.0	0.0	141.4

* significant at 5% level

** significant at 1% level

Table 6

Mortality analysis by date of hire in lead battery and smelter workers

CAUSE OF DEATH	< 1946		1946+	
	OBS	SMR	OBS	SMR
All causes	2472	103.9	1241	105.8 *
All malignant neoplasms	547	98.3	350	113.7 *
Cancer of buccal cavity & pharynx	9	62.8	4	49.8
Cancer of digestive organs & peritoneum	176	111.6	78	107.2
Cancer of esophagus	14	113.8	8	101.3
Cancer of stomach	43	142.6 *	17	161.3
Cancer of large intestine	58	104.8	23	87.9
Cancer of rectum	18	107.1	4	64.2
Cancer of biliary passages & liver	12	121.0	2	32.4
Cancer of pancreas	20	68.7	21	138.1
Cancer of all other digestive organs	11	172.7	3	140.3
Cancer of respiratory system	174	102.4	156	133.2 **
Cancer of larynx	6	83.0	3	74.4
Cancer of bronchus, trachea & lung	166	103.4	151	135.0 **
Cancer of all other respiratory organs	2	99.8	2	165.9
Cancer of prostate	48	70.5 *	27	130.3
Cancer of testes & other male genital organs	0	0.0	0	0.0
Cancer of kidney	7	56.5	6	74.4
Cancer of bladder & other urinary organs	12	55.5 *	4	55.4
Malignant melanoma of skin	4	79.2	5	91.2
Cancer of central nervous system	7	67.1	8	83.1
Cancer of thyroid & other endocrine glands	5	306.0	3	311.4
Cancer of bone	2	97.5	1	109.7
Cancer of lymphatic & hematopoietic tissues	50	99.2	24	80.3
Lymphosarcoma & reticulosarcoma	5	61.4	1	27.0
Hodgkin's disease	5	142.7	3	113.8
Leukemia	22	100.7	12	104.7
Cancer of other lymphopoietic tissue	18	106.6	8	66.0
Benign neoplasms	1	19.6	1	33.0

* significant at the 0.05 level

** significant at the 0.01 level

Table 7

Mortality analysis by date of hire in lead battery workers

CAUSE OF DEATH	< 1946		1946+	
	OBS	SMR	OBS	SMR
All causes	2087	108.3 **	526	100.7
All malignant neoplasms	458	100.0	166	120.2 *
Cancer of buccal cavity & pharynx	8	67.1	3	82.9
Cancer of digestive organs & peritoneum	151	116.3	32	99.7
Cancer of esophagus	13	127.2	3	83.0
Cancer of stomach	37	148.6 *	8	175.8
Cancer of large intestine	50	110.4	9	78.3
Cancer of rectum	14	101.1	0	0.0
Cancer of biliary passages & liver	9	110.6	1	35.7
Cancer of pancreas	19	79.1	11	162.6
Cancer of all other digestive organs	9	170.9	0	0.0
Cancer of respiratory system	140	99.1	79	148.5 **
Cancer of larynx	6	99.9	1	55.5
Cancer of bronchus, trachea & lung	132	98.9	78	153.4 **
Cancer of all other respiratory organs	2	120.4	0	0.0
Cancer of prostate	41	75.1	13	155.7
Cancer of testes & other male genital organs	0	0.0	0	0.0
Cancer of kidney	5	48.8	2	54.0
Cancer of bladder & other urinary organs	10	57.0	0	0.0
Malignant melanoma of skin	3	71.6	1	37.0
Cancer of central nervous system	5	57.1	5	109.0
Cancer of thyroid & other endocrine glands	4	294.8	1	226.2
Cancer of bone	2	117.4	0	0.0
Cancer of lymphatic & hematopoietic tissues	42	101.4	11	80.6
Lymphosarcoma & reticulosarcoma	4	59.1	0	0.0
Hodgkin's disease	5	170.5	1	80.0
Leukemia	20	111.8	6	116.0
Cancer of other lymphopoietic tissue	13	94.1	4	71.3
Benign neoplasms	1	24.1	1	73.0

* significant at the 0.05 level

** significant at the 0.01 level

Table 8

Mortality analysis by date of hire in lead smelter workers

CAUSE OF DEATH	< 1946		1946+	
	OBS	SMR	OBS	SMR
All causes	385	85.2 **	715	109.9 *
All malignant neoplasms	89	90.4	184	108.5
Cancer of buccal cavity & pharynx	1	41.4	1	22.6
Cancer of digestive organs & peritoneum	25	89.6	46	113.1
Cancer of esophagus	1	48.0	5	116.7
Cancer of stomach	6	114.1	9	150.3
Cancer of large intestine	8	79.5	14	95.5
Cancer of rectum	4	135.5	4	112.7
Cancer of biliary passages & liver	3	168.7	1	29.7
Cancer of pancreas	1	19.7	10	118.5
Cancer of all other digestive organs	2	180.8	3	245.6
Cancer of respiratory system	34	118.8	77	120.4
Cancer of larynx	0	0.0	2	89.6
Cancer of bronchus, trachea & lung	34	125.7	73	119.6
Cancer of all other respiratory organs	0	0.0	2	304.4
Cancer of prostate	7	51.8	14	113.2
Cancer of testes & other male genital organs	0	0.0	0	0.0
Cancer of kidney	2	93.5	4	91.8
Cancer of bladder & other urinary organs	2	49.1	4	94.7
Malignant melanoma of skin	1	116.1	4	143.8
Cancer of central nervous system	2	119.2	3	59.6
Cancer of thyroid & other endocrine glands	1	360.9	2	383.6
Cancer of bone	0	0.0	1	199.0
Cancer of lymphatic & hematopoietic tissues	8	89.2	13	80.0
Lymphosarcoma & reticulosarcoma	1	72.8	1	47.8
Hodgkin's disease	0	0.0	2	144.2
Leukemia	2	50.6	6	95.5
Cancer of other lymphopoietic tissue	5	153.0	4	61.5
Benign neoplasms	0	0.0	0	0.0

* significant at the 0.05 level

** significant at the 0.01 level

Table 9

Mortality analysis by length of employment in lead battery and smelter workers

CAUSE OF DEATH	< 10 years		10-19 years		20+ years	
	OBS	SMR	OBS	SMR	OBS	SMR
All causes	423	99.6	542	140.3 **	2748	100.3
All malignant neoplasms	101	85.8	143	129.6 **	653	102.7
Cancer of buccal cavity & pharynx	0	0.0	5	150.2	8	50.5 *
Cancer of digestive organs & peritoneum	24	84.1	31	107.3	199	115.0
Cancer of esophagus	3	103.2	1	35.7	18	124.2
Cancer of stomach	8	170.2	11	203.7 **	41	134.0
Cancer of large intestine	6	61.2	5	53.9	70	112.1
Cancer of rectum	1	37.6	6	202.3	15	86.2
Cancer of biliary passages & liver	1	45.6	0	0.0	13	108.6
Cancer of pancreas	4	69.4	7	122.4	30	91.4
Cancer of all other digestive organs	1	95.1	1	79.1	12	193.7 *
Cancer of respiratory system	51	119.9	54	139.6 *	225	109.3
Cancer of larynx	1	64.9	1	64.5	7	85.7
Cancer of bronchus, trachea & lung	49	121.1	53	144.7 *	215	110.1
Cancer of all other respiratory organs	1	197.4	0	0.0	3	134.3
Cancer of prostate	4	56.3	8	125.3	63	83.6
Cancer of testes & other male genital organs	0	0.0	0	0.0	0	0.0
Cancer of kidney	3	97.8	3	100.6	7	48.6
Cancer of bladder & other urinary organs	3	111.2	3	109.0	10	42.8 **
Malignant melanoma of skin	0	0.0	3	148.1	6	95.9
Cancer of central nervous system	2	47.3	5	128.0	8	67.1
Cancer of thyroid & other endocrine glands	0	0.0	0	0.0	8	462.7 **
Cancer of bone	0	0.0	1	215.3	2	100.1
Cancer of lymphatic & hematopoietic tissues	5	39.3 *	17	150.2	52	92.5
Lymphosarcoma & reticulosarcoma	0	0.0	1	52.7	5	61.8
Hodgkin's disease	2	118.6	1	76.2	5	159.2
Leukemia	1	20.4	8	181.2	25	104.3
Cancer of other lymphopoietic tissue	2	46.9	7	189.0	17	80.8
Benign neoplasms	0	0.0	2	199.3	0	0.0 **

* significant at the 0.05 level

** significant at the 0.01 level

Table 10

Mortality analysis by length of latency in lead battery and smelter workers

CAUSE OF DEATH	< 20 years		20-34 years		35+ years	
	OBS	SMR	OBS	SMR	OBS	SMR
All causes	465	148.3 **	1243	130.4 **	2005	87.7 **
All malignant neoplasms	197	114.0	309	115.8 *	481	95.6
Cancer of buccal cavity & pharynx	4	123.1	3	35.3	6	56.6
Cancer of digestive organs & peritoneum	29	112.2	87	120.0	138	104.4
Cancer of esophagus	0	0.0	10	143.0	12	108.0
Cancer of stomach	13	222.2 *	22	160.2 *	25	118.4
Cancer of large intestine	2	27.1 *	25	107.7	54	106.1
Cancer of rectum	6	193.6	5	65.0	11	89.9
Cancer of biliary passages & liver	0	0.0	4	88.0	10	96.7
Cancer of pancreas	6	122.8	14	97.1	21	84.0
Cancer of all other digestive organs	2	130.0	7	243.6	5	122.0
Cancer of respiratory system	36	122.9	129	133.0 **	165	102.7
Cancer of larynx	2	146.2	2	48.9	5	86.2
Cancer of bronchus, trachea & lung	34	124.3	127	138.4 **	156	101.8
Cancer of all other respiratory organs	0	0.0	0	0.0	4	251.0
Cancer of prostate	5	161.2	16	98.3	54	77.8
Cancer of testes & other male genital organs	0	0.0	0	0.0	0	0.0
Cancer of kidney	1	39.8	2	28.5	10	91.6
Cancer of bladder & other urinary organs	4	188.2	4	54.0	8	41.5 **
Malignant melanoma of skin	1	47.9	3	82.2	5	104.2
Cancer of central nervous system	4	88.7	2	25.9 *	9	114.9
Cancer of thyroid & other endocrine glands	0	0.0	2	215.2	6	518.5 **
Cancer of bone	0	0.0	1	94.4	2	164.7
Cancer of lymphatic & hematopoietic tissues	9	74.5	29	121.0	36	81.4
Lymphosarcoma & reticulosarcoma	1	36.4	2	45.7	3	63.5
Hodgkin's disease	1	40.4	6	293.0 *	1	61.9
Leukemia	4	84.3	13	138.0	17	88.8
Cancer of other lymphopoietic tissue	3	140.4	8	98.5	15	80.0
Benign neoplasms	1	105.7	1	42.9	0	0.0 *

* significant at the 0.05 level

** significant at the 0.01 level

Table 11

Comparison of employment/exposure histories of cases and controls based on employment prior to death dates of index cases

Employment/exposure histories*	Cases (n=30)		Controls (n=120)		Cases v. controls	
	Mean	SD	Mean	SD	Difference	SD
<u>Months employed at the plant</u>						
Total pre-death	275.4	149.2	302.6	138.1	-27.1	30.0
10 years pre-death	234.9	139.5	245.7	139.0	-10.8	28.5
20 years pre-death	149.5	117.1	156.1	121.3	-6.6	24.1
<u>Months in intermediate or high exposure areas</u>						
Total pre-death	185.8	163.0	202.0	156.8	-16.3	33.0
10 years pre-death	163.3	150.0	165.7	146.2	-2.5	30.5
20 years pre-death	108.1	110.3	108.5	117.9	-0.3	22.2
<u>Weighted exposures</u>						
Total pre-death	485.0	298.1	555.1	327.5	-70.1	62.1
10 years pre-death	407.3	267.7	444.8	315.4	-37.5	56.7
20 years pre-death	257.2	214.7	287.4	267.9	-30.3	46.2

* see text for a full description of exposure classification.

Table 12

Results of conditional logistic regression analysis in a nested case-control study of stomach cancer among lead battery workers

Exposure category*	Employment at the plant			Employment in intermediate or high exposure areas			Weighted exposure		
	Cases/controls	OR	p	Cases/controls	OR	p	Cases/controls	OR	p
<u>Total exposure pre-death</u>									
Lowest quartile	10/31	1.00	-	13/30	1	-	10/30	1.00	-
2nd quartile	3/29	0.30	0.11	3/30	0.25	0.04	6/30	0.62	0.39
3rd quartile	13/30	1.70	0.34	5/30	0.43	0.14	8/30	0.82	0.72
Highest quartile	4/30	0.43	0.19	9/30	0.75	0.55	6/30	0.61	0.39
		Trend test	0.58		Trend test	0.48		Trend test	0.47
<u>Exposure 10 years pre-death</u>									
Lowest quartile	11/30	1.00	-	7/30	1	-	10/30	1.00	-
2nd quartile	3/30	0.03	0.07	8/30	1.13	0.84	4/30	0.39	0.15
3rd quartile	9/30	0.91	0.87	4/30	0.6	0.43	9/30	0.87	0.78
Highest quartile	7/30	0.68	0.55	11/30	1.73	0.34	7/30	0.61	0.45
		Trend test	0.62		Trend test	0.56		Trend test	0.74
<u>Exposure 20 years pre-death</u>									
Lowest quartile	10/30	1.00	-	-	-	-	8/30	1.00	-
2nd quartile	4/30	0.40	0.16	15/60	1.00	-	8/30	1.00	1.00
3rd quartile	8/30	0.81	0.73	5/30	0.66	0.45	5/30	0.61	0.47
Highest quartile	8/30	0.78	0.72	10/30	1.48	0.46	9/30	1.08	0.91
		Trend test	0.85		Trend test	0.59		Trend test	1.00

* see text for a full description of exposure classification.