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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 11th Annual Report on Carcinogens. 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:jp

ILZRO Commentary on Lead Carcinogenicity

The following comments are being submitted by the International Lead Zinc Research Organization in response to the call for public comment by the National Toxicology Program (NTP) on the proposed listing of occupational exposure to lead or lead compounds in the 11th Annual Report on Carcinogens. According to the NTP this decision is based on recent published data that indicate an excess of cancers in workers exposed to lead and lead compounds. As reflected in this commentary, the latest findings from multiple studies are disparate and do not support the agency's suggestion that recent studies indicate occupational exposure to lead or lead compounds pose excess cancer risk.

Studies with experimental animals have reproducibly shown that several lead compounds (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, has 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 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 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. In view of the fact that the focus of the present discussions appears to be limited to the occupational exposure to lead and lead compounds, these studies will not be discussed further. However, the results of these studies could be made available upon request.

A number of epidemiological studies have been conducted of occupationally exposed groups. The most recent published comprehensive review of this literature was by Fu and Boffetta (1995) and 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 found 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 expected in studies lacking correction for confounding exposures to cigarette smoke. Although some studies reported modestly higher relative risks, these findings 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 to just lifestyle factors, other occupational exposures suspected to be associated with risk of stomach cancer were reported in some studies.

In the case of bladder cancer, elevations were suggested to likely be the result of publication bias since only 4 of 14 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."

Since the conduct of this review, data have become available from several new studies and/or from updates of existing cohort mortality studies. These more recent studies indicate that there is

little reason to suspect lead is a human carcinogen at most any tissue site. Indeed, a recent brief review of this literature by Steenland and Bofetta (2000) concludes: "Overall, there is only weak evidence associating lead with cancer."

Only a small number of studies have been published in recent years. 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 sectors. 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 with increasing lead exposure level and strong interactions were observed with concomitant exposures to engine exhaust. Approximately 90% of the cases were also long-term smokers although, oddly enough, no relationship between lung cancer and smoking was found. 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. Altogether, the results of the study add little to the existing epidemiological database.

A similarly inconclusive registry-based study of occupational lead exposure and brain cancer was conducted by Cocco et al. (1998) and suggested an association between the two. However, the authors note that poor detail in the occupation and industry coding system and incomplete working histories are major limitations of their study. Little actual lead exposure data was available for the study subjects, further limiting the power of the study. Excess risk was heavily influenced by mortality patterns within the "printing industry" and undefined manual occupations. As is appropriate for such a registry-based study, the authors frame their results as being hypothesis generating. The significance to be attached to this observation is questionable, particularly in light of the general absence of excess risk in cohort mortality studies.

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 the results of other studies, it is relevant to note that cancer of the respiratory tract, brain, kidney and bladder were not elevated in response to occupational exposure to lead.

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. Cancer of the stomach, brain and lung were not elevated, but as was noted by Vainio (1997), there was a 4.5 fold excess mortality from diseases of the respiratory system in the cohort which could have masked a small lung cancer excess.

Finally, a second Swedish study by Lundström et al. (1997) evaluated relationships between cumulative lead exposure and mortality from lung cancer. Interpretation of this study is difficult since lead production was occurring as a co-generation product of copper smelting and a significant elevation of lung cancer rates was evident at the entire facility. However, the authors report that 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, brain, kidney and bladder were not elevated. The suggestion of a dose-dependent relationship between lead exposure and lung cancer was noted by Vainio (1997) to be a finding of some significance.

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, brain 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. In spite of the high intensity of lead

exposure in many of these cohorts, no consistent pattern of excess risk has emerged. Indeed, isolated suggestions of risk have, in several instances, now been shown to be the likely product of confounding.

The excess lung cancer risk reported in the Lundström et al. study was the focus of more detailed investigations by Englyst et al. (2001). 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. 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 personnel, builders and truck drivers who worked in all departments of the facility. Indeed, most of the cases were found to have extensive exposure to arsenic and other carcinogens. In contrast to the earlier paper, which concluded that a dose-dependent correlation between lead and lung cancer was evident in this cohort, the more recent study concludes that "arsenic exposure, which occurred among these workers, is probably a main contributing factor to the development of lung cancer."

A case control study has also just been completed at this smelter. The results of the study are as yet unpublished, but have determined that there is a strong interaction between arsenic and cigarette smoking for the incidence of lung cancer in the "lead cohort" at this smelter. A relationship between lead exposure and lung cancer is not evident. These findings are presently in preparation for publication (V. Englyst, personal communication).

The results of an update for a large cohort mortality study of employees at US lead acid battery production plants and smelters has been published by Wong and Harris (2000). The cohort in this study consists of 4518 workers at battery plants and 2300 workers at lead smelters and represents the single largest study conducted of occupational lead exposure. The study findings contribute significantly to an understanding of cancer incidence at sites that have traditionally been of concern. The study reports a deficit, just lacking in statistical significance, for kidney cancer and a statistically significant deficit in bladder cancer mortality. No elevation of central nervous system cancer was seen. As has been observed by some studies, an excess of stomach

cancer is evident in the cohort 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 lead exposure indices and none were found to correlate with the incidence of stomach cancer. The lack of an exposure-response relationship is not consistent 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 that have a higher rate of stomach cancer than is present in the US population. The excess of stomach cancer in this study is thus likely a product of factors relating to country of origin and not lead exposure.

Wong and Harris further observed a small but statistically significant increase in lung cancer (SMR 116). This increase is on the order of that generally expected in the absence of correction for confounding by smoking and is statistically significant 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 absence of smoking data. They also note that the risk of lung cancer does not increase with the length of employment and have further determined that the excess in lung cancer is present in workers hired after 1946 but not in workers hired before 1946. Excess lung cancer thus occurred in those individuals with lower overall levels of lead exposure. The failure of lung cancer incidence to correlate with exposure duration or intensity indicates that it is not likely causally related to lead exposure. A case control study of lung cancer in the Wong and Harris study is ongoing and should clarify the relative role of confounders in this cohort.

In consideration of the Wong and Harris study, it should further be noted that death from nephritis increased as a function of both exposure duration and intensity. The correlation of this lead-related disease endpoint with these exposure indices indicates that the exposure surrogates 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. It should further be noted that, although exposures were sufficient to produce mortality from kidney disease, there was a relative deficit of kidney cancer in the cohort (SMR 64).

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 had been reported. However, the findings between the different studies were disparate and failed to provide a consistent pattern of elevated cancer mortality. Little data firmly implicated lead as a human carcinogen. Studies conducted since that time have continued this pattern of results. Registry-based suggestions of a linkage to brain cancer have not been verified by cohort studies. Some cohort studies have 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. In most instances, the modest excess of cancer risk reported in some studies has been found to be the likely products of confounding. Taken as a whole, these data indicate that occupational exposure to lead and lead compounds does not pose carcinogenic risk.

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