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September 29, 2003

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,

Signature [redacted]

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

CJB:acw

Enclosure

ILZRO Commentary on Lead Carcinogenicity

The following comments are being submitted by the International Lead Zinc Research Organization in response to the May 8, 2003, Report on Carcinogens Background Document for Lead and Lead Compounds. These comments mirror concerns originally expressed in our commentary filed September 24, 2001, (see attachment 1) with updates as appropriate on key issues and with minor notes concerning technical inaccuracy in the Background document.

As a general observation, the document does an admirable job of condensing a large volume of scientific publications into a more easily digestible format. However, the material as presented is at times lacking with respect to meaningful study analysis that would facilitate a true weight of evidence evaluation of the available data. ILZRO believes that more recent studies do not support suggestions that lead is a human carcinogen.

Comments are offered, presented in the order in which they appear in the document.

Page 3, forms of lead in soil: Things have advanced since the 1977 NSF report cited and what is stated here is only applicable to short time frames after atmospheric deposition. Recognizing the advancements that have been made in this area, the U.S. EPA recently convened a workshop to assess the current state of the science regarding *in vivo* and *in vitro* bioavailability for metals in soil. These new studies are now being compiled by the EPA for use in human health risk assessments. Similarly, this section of the document should be revised to reflect the latest scientific understanding on more recent evidence related to the bioavailability of lead.

The forms of lead in soil can be complex and, as a function of time and local geochemistry, progress towards thermodynamically stable forms tending to have limited bioavailability. This has been demonstrated by the work of Cotter-Howells and Thornton (1991) that investigated lead exposure routes in residents residing near a former mining

community in the United Kingdom heavily contaminated with lead. Hand wipe samples from children in the community revealed relatively high lead concentrations suggesting that elevated levels of lead are transferred to the child by the soil-dust-hand-mouth pathway. However, the blood lead concentrations of the children were within normal UK ranges. Analysis of the soil grains revealed that many were composed of pyromorphite, a stable soil-lead mineral.

A study on the migration of lead at historical lead smelting sites ranging in age between 200 and ~ 1900 years was carried out by Maskall et al. (1995). While the levels of metals present at the site were reported to be elevated, they reported low metal mobility and availability because of the particular regions geochemistry.

Page 19, units: It is a minor matter, but the text drifts between expressing production of different materials as metric tons in some cases, kg in others. Clarity would be enhanced if a single unit of mass were to be uniformly adopted.

Page 24, blood measurement: No citation is given for sensitivity, but numerous laboratories routinely measure blood lead down to concentrations of 1 μg/dL or lower. A 4 μg/dL detection limit does not characterize current analytical capabilities.

Page 26, chelation as an exposure measure: An EDTA provocation test has clinical and research applications in assessing quantities of readily mobilized lead in the body – but is seldom used as an exposure measure per se.

Page 26, Py-5'N: The text implies that this biomarker, and the other biomarkers described in this paragraph, can be routinely applied in exposure assessment. They are not routine and are seldom applied.

Page 27, natural occurrence: Although the average crustal abundance of lead cited is approximately correct, it would be helpful to note that natural occurrence can be 10-100 fold (oil rich shales) or more (mining areas) higher. Quantitative estimates of natural

variability are to be preferred to the statement that it can be "very high". The statement is made that modern body burdens are 300-fold higher than those found in pre-industrial humans. Even if one accepts some of the novel assumptions used to derive this estimate, current US exposures have declined by an order or magnitude since this estimate was offered.

Page 27, air: Fossil fuel combustion can still be one of the major contributors to lead in air. The natural lead content of some fuels (especially coal) can be the single largest contributor to air lead in some regions.

Page 29, long range transport: Perspective would be maintained if the quantities found were to be mentioned. Lead can be measured in polar snow and ice, but the actual concentration is quite low.

Page 31, dermal absorption: quantification of dermal uptake estimates should be provided here. As noted later, the issue is not accurately depicted later in the document.

Page 32, air lead blood lead: The graph is attractive, but misleading in its simplicity. The decline in blood leads depicted came about as a result of multiple policy efforts to eliminate sources of human exposure to lead. An overlay of lead-soldered food can use, or FDA total diet study data, would match equally well. As is discussed in NHANES III blood lead publications, close to half of the recent declines in blood lead are related to declines in lead in food.

Page 33, lead glazes: It should probably be specified that the lead glazes of greatest concern are improperly (low temperature fired) artisan products. Modern ceramics such as fine porcelain china frequently use leaded glazes and are produced to comply with rigid ISO leach test standards. Such standards now also exist for lead crystal.

Page 33, Stauber et al. (1994): Yes, the authors concluded that there was significant uptake, but they did not actually measure it. They simply could not find it. In this paper

and other work by the authors, lead uptake through skin occurs without changing blood lead levels. Novel distribution and excretion pathways are proposed to explain why the supposed high uptake of lead does not lead to an actual increase in blood lead. The older, but more rigorous work of Moore et al. (1980) provides far more reliable estimates of uptake (on the order of 0.2%).

Page 35, solders: It should probably be specified that the solders under discussion are for electronic use. Lead in plumbing solders is banned.

Page 37, OSHA air lead data: If it is available, data of more recent vintage would be better to include.

Page 37, NIOSH data: Do the NIOSH data presented in the table represent exposure with or without appropriate respiratory protection?

Page 49, Lundström et al. (1997): Here and elsewhere, the description of the facility included for study is inadequate. Proper interpretation of epidemiological data requires an understanding of the nature of the facility under study and why (or why not) various issues of confounders might arise. The Lundström et al. (1997) study was conducted at a copper smelter processing a concentrate with significant arsenic content. Lead was produced as a co-generation product in relatively modest quantities. Isolation and study of "lead only" exposed individual in such a setting is challenging, especially when a significant elevation of lung cancer rates was evident at the entire facility. 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." The conclusions of the authors on the arsenic issue were thus worded a bit more strongly then is implied here.

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 (V. Englyst, personal communication).

Similar additional detail would be helpful with respect to other studies. For example, as noted in Selevan et al. (1985) the study was conducted in an area with numerous nonferrous smelters, resulting in an "itinerant" smelter workforce. The employment history of the cohort, and resulting confounding exposures at other smelters, introduces uncertainty with respect to interpretation of the study's findings.

Page 50, 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. The document appears to fault the case control study (p51) for not ensuring that the incidence of Irish and Italian immigrants was in fact higher than that in the US population. The authors probably took it as a given that 40% is higher than US norms.

Page 59 - 60, Jemal et al. (2000), Lustberg and Silbergeld (2002): The Jemal et al. paper is somewhat unfairly represented. The authors recognized some of the limitations discussed regarding the insensitivity of quartile analysis, although points regarding sensitivity of the study are appropriate. They further calculated the relative risk of all cancer mortality relative to a referent blood lead level of 8 μg/dL (Jemal et al., fig. 1) and found no significant trend for men. Indeed the analysis depicts a decline in cancer mortality at blood lead levels in excess of 30 μg/dL. (This is another reason why the findings of Jemal et al. may differ from the subsequently discussed Lustberg and Silbergeld paper). Given the attention subsequently given to the lung cancer issue it is inappropriate to list the RR for women (based on 19 deaths) and not that for men (based on 52 deaths). The male lung cancer RR was 1.2 (0.6 – 2.5), far lower than the risk cited for women. The overall conclusion of the study was that "individuals with blood lead levels in the range of NHANES II do not have increased risk of cancer mortality".

The subsequently discussed Lustberg and Silbergeld analysis, in excluding individuals with blood leads in excess of 30, may have excluded individuals suggested by Jemal et al. to have lower cancer risk. Both studies worked with the oversampled NHANES II data base and never unweighted the data base. The risk, or lack thereof, calculated thus cannot be related to US norms for cancer mortality. The Lustberg and Silbergeld paper, suggesting risk, is applauded for greater use of confounder data but the overall quality of the confounder data used is questionable. For example, note that the Lustberg and Silbergeld analysis extended to confounder interactions in the incidence of cardiovascular disease. How much confidence can be placed upon an analysis that finds body mass index is not a risk factor for cardiovascular disease?

Page 65 – 68, lung cancer: The document suggests a relationship between lung cancer and lead exposure. Meta-analyses are noted that find a RR of 1.3 that declines to 1.14 after exclusion of the Lundström et al. data known to be confounded by arsenic and smoking. The RR after this exclusion is well within the range suggested to be expected in occupational studies that have not corrected for smoking.

A numerical count is then offered of the cohort studies, noting that 15 of 18 studies found an association, but only 8 of these found it to be statistically significant. Less than half the studies thus find a significant association. Such simple number counts are meaningless when dealing with studies known to lack confounder correction – and meta-analyses do not correct underlying difficulties in the databases that they draw upon.

Three occupational cohort studies are then identified as being especially relevant because they relied upon blood lead data. One is the Lundström et al. study generally regarded to be an outlier. Another is that of Gerhardsson et al. (1995) noted to have only a weak increase. No clear evidence of dose response was found in this study, nor was lung cancer related to exposure latency. Finally Antilla et al. (1996) is cited. Although referred to as a cohort study, this was in fact a registry based study with some unusual findings. 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. The three studies with blood lead data thus do not provide more compelling evidence of an association.

The subsequent discussion of other studies somehow manages to miss the salient points of the work of Wong and Harris (2000) who arguably conducted one of the largest and most relevant true cohort studies. Wong and Harris observed a small but statistically significant increase in lung cancer (SMR 116). This increase was on the order of that consistent with correction for confounding by smoking and was statistically significant due to the large size of the study cohort. The authors cautioned that the risk of lung cancer did not increase with the length of employment and further noted that the excess in lung cancer was present in workers hired after 1946 but not in workers hired before 1946. Excess lung cancer thus occurred in those individuals presumed to have lower levels of lead exposure. In support of this assumption, death from nephritis (likely lead related) increased as a function of both exposure duration and intensity. Thus, lung cancer may be elevated in this study to an extent that is statistically significant, but the overall response profile is not consistent with a causal relationship to lead exposure.

The document does not demonstrate a convincing case that the epidemiological data provides a convincing case for an impact of lead exposure upon lung cancer. Statements that "in studies that controlled for cigarette smoking, the relationship between the observed associations between lead exposure and lung cancer remained" are extremely difficult to interpret when the studies that supposedly show this are not identified and placed within the context of the greater whole. The subsequent conclusion that "even a small elevation of risk due to lead exposure would have a significant impact at the general population level, given the ubiquity of low-level lead exposure" is particularly difficult to accept when no real evidence exists for cancer outside the occupational setting and/or though exposure pathways that do not entail inhalation.

Page 69 – 71, stomach cancer: If Cocco et al. (1999) is the strongest evidence in support of an association then evidence is lacking. This was a registry-based study, with estimates of lead exposure estimated primarily based only upon job description. 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 were available for the study subjects, further limiting the power of the study.

Page 109-120, cancer in experimental animals: The document fails to include a discussion of the classic work by Azar et al. (1977), a two -year study in which male and female rats were fed lead acetate at dose levels up to 2000 ppm in their diet. Certainly this study represents the single largest cancer bioassay conducted of lead in experimental animals and therefore should be included in the document.

Page 123-152, genotoxicity: The review provided of genotoxicity is largely factually accurate, but lacking in interpretive depth. Presumably, genotoxicity would provide backing evidence for lead carcinogenicity, but the available data are indeed mixed. Bacterial mutagenesis data are generally negative while mutagenesis studies in mammalian cells are generally of mixed outcome. *In vivo* studies (human and animal) similarly provide mixed evidence. When presented as a series of (+)s and (-)s on charts, the nature of the data base is obscured.

Data on lead genotoxicity are decidedly mixed, a fact that has led many to suggest that if lead is genotoxic, it must be so by indirect mechanisms. This is largely due to:

-difficulty in obtaining a consistent response profile

-the high concentrations required to elicit a response, and the weak responses generally observed

-lack of dose response, or shallow dose response, in a number of studies (e.g., 2-fold increase in effect for a 100-fold increase in dose (e.g., Jagetia et al., 1998)

-lack of evidence of direct interaction with DNA, but rather indirect effects that may be mediated by oxygen radicals

In consideration of the above, it should further be noted that qualitatively different responses are obtained in other studies. Whereas some studies have suggested oxidative damage that manifests as single-strand DNA breaks, other work has suggested impacts at the chromosome level (micronuclei or chromosome aberrations). The two phenomenon are not easily reconciled. Finally, much of the human data is dominated by observations of micronuclei (or failure to observe micronuclei) that are difficult to interpret. For example, the Bulgarian battery worker studies of Vangelov et al. (1997) suggest a doubling of micronucleus frequency in a very heavily exposed worker, but this doubling is difficult to interpret when the effect observed comparable in magnitude to age-related changes in micronuclei as a function of age (Vaglenov and Karadjov, 1997). Such changes are similarly difficult to interpret when they are easily reversed by the simple administration of vitamin pills (Vangelov et al., 1998).

If lead possesses genotoxic activity it is unquestionably extremely weak and likely mediated via indirect mechanisms. Processes that would exhibit effect thresholds would in turn mediate most of the indirect mechanisms hypothesized. If genotoxicity were to be related to carcinogenicity, it in turn follows that non-threshold models would not characterize a carcinogenic response.

Page 155, lead accumulation in bone: While the observations of Aufderheide and Wittmers (1992) are as reported, it is now recognized that older persons also had higher lead exposure in their youth. Most physiologically based pharmacokinetic models of lead metabolism do not predict elevations of lead in bone as a function of age. More modern studies conducted by K-XRF suggest that increase in bone lead as a function of age is a birth cohort effect reflective of exposure history (e.g., Kosnett et al., 1994; Hu et al., 1996).

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ATTACHMENT I

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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