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Lead and Cancer in Humans: Where Are We Now?

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Background *Lead is only weakly mutagenic, but in vitro it inhibits DNA repair and acts synergistically with other mutagens. Lead acetate administered orally, cutaneously, or intraperitoneally causes kidney cancer, brain cancer (gliomas), and lung cancer in rodents, and acts synergistically with other carcinogens. Most cytogenetic studies of exposed workers have shown increases in chromosome aberrations or sister chromatid exchange, including some studies with positive-exposure response trends. There are eight studies of cancer mortality or incidence among highly exposed workers; most are cohort studies of lead smelter or battery workers exposed decades ago.*
Methods *We reviewed the epidemologic studies with regard to cancer.*
Results *These studies provide some evidence of increased risk of lung cancer (RR = 1.30, 1.15–1.46, 675 observed deaths) and stomach cancer (combined RR = 1.34, 1.14–1.57, 181 observed). However, the lung cancer findings are not consistent across studies, and confounding by arsenic may affect the study with the highest lung cancer RR. Exclusion of that study yields a combined lung cancer RR of 1.14 (1.04–1.73). There is little evidence of increased risk of kidney cancer (combined RR = 1.01, 0.72–1.42, 40 observed) or brain cancer (combined RR=1.06, 0.81–1.40, 69 observed). However, two studies show a two-fold increase in kidney cancer, and one study shows a significant excess of gliomas. IARC classified lead as a "possible human carcinogen" based on sufficient animal data and insufficient human data in 1987. Six of the eight studies cited above have been published since 1987.*
Conclusion *Overall, there is only weak evidence associating lead with cancer; the most likely candidates are lung cancer, stomach cancer, and gliomas.* Am. J. Ind. Med. 38:295–299, 2000. *Published 2000 Wiley-Liss, Inc.*†

KEY WORDS: lead; cancer; epidemiology

INTRODUCTION

In 1987 IARC judged the evidence for lead and inorganic lead compounds to be sufficient in animals and inadequate in humans, leading to an overall evaluation of Group 2B, possibly carcinogenic in humans. Since that time, a number of new studies or updates of older studies have been published. We here summarize existing evidence regarding the possible carcinogenicity of lead.

ANIMAL STUDIES

Lead is not genotoxic in vitro, but increases the mutagenicity of other mutagens, possibly acting via inhibition of DNA repair [Hartwig, 1994]. Early animal studies indicated that lead does cause cancer in animal studies [IARC, 1980], principally kidney cancer in two species by different routes of administration. In addition, rats developed brain cancer (gliomas) in one study, and mice developed lung adenomas in another. Lead acetate and lead oxide acted synergistically to increase kidney and lung tumors, respectively, after administration of known carcinogens (nitrosamines,

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benzo[a]pyrene.) In 1980 and again in 1987 IARC deemed these animal studies sufficient for demonstrating animal carcinogenicity for inorganic lead compounds [IARC, 1980, 1987].

However, almost all these studies used one form of lead (lead acetate, a soluble salt), chosen for ease of administration, given orally, subcutaneously, or intraperitoneally, usually at very high doses. Most human exposure to lead, on the other hand, is to lead oxides or lead fumes which are inhaled.

HUMAN GENOTOXICITY STUDIES

Winder and Bonin [1993] reviewed 19 cytogenetic studies of workers done from 1969 to 1986 with documented lead exposure in battery manufacturing and lead smelting. Sixteen of these studies showed increased chromosomal aberrations and/or sister chromatid exchange in peripheral lymphocytes, compared to nonexposed workers, although the authors do not report quantitative results or significance tests. Several studies showed positive exposure–response trends and three were longitudinal studies comparing workers before and after exposure. While a number of these studies were done in the early 1970s and methods for cyogenetic studies have developed and become more standardized, these studies do indicate that lead has cytogenetic effects in vivo.

OCCUPATIONAL EXPOSURE

High exposure has occurred among workers in lead smelters and lead battery plants (50–5000 $\mu g/m^3$ in air, 40–100 $\mu g/dl$ in blood) [Fu and Boffetta, 1995]. Moderate exposure has occurred among welders of metals containing lead or painted with lead (lead fumes), lead glass workers, lead miners, workers repairing automobile radiators, printers using lead type, and production workers using lead (e.g., producing lead chromate paint) (50–1000 $\mu g/m^3$ in air, 20–60 $\mu g/dl$ in blood).

Occupational exposures have decreased markedly since the 1950s in industrialized countries, and today blood levels in most workers in these countries rarely exceed 25 $\mu g/dl$, which might be considered high enough to be an occupational exposure by definition. In the US, for example, in 1976–1980, approximately 9% of U.S. males had blood levels above 25 $\mu g/dl$ (the overall geometric mean for males was 15 $\mu g/dl$), while in 1988–1991 only 1% had levels above 25 $\mu g/dl$ (overall male mean 4 $\mu g/dl$) [Pirkle et al., 1994]. The U.S. Occupational Safety and Health Administration (OSHA) limits for airborne lead are 50 $\mu g/m^3$, and blood levels must be kept below 40 $\mu g/dl$.

EPIDEMIOLOGY STUDIES

The epidemiology is mostly based on highly exposed workers who were exposed decades ago. Ambient nonoccupational levels are much lower than occupational levels. This review of cancer epidemiology will focus on occupational exposures, and particularly on documented occupational exposure (e.g., with measurements of exposure levels or blood leads). Other recent reviews of the epidemiology have been published by Fu and Boffetta [1995] and by Hayes [1997].

Human epidemiology of lead-exposed workers has focused on all cancers: lung, stomach, kidney, and brain. We consider each of these, focusing on eight studies with high documented exposures below (7 cohort studies, 1 nested case-control) (Table I). These studies controlled for age, sex,

TABLE 1. Lead and Cancer: 8 Studies (7 Cohort, 1 Nested Case-Control)

Study	Country	Population	Mean lead levels, comments
Wong et al. (1) [2000]	USA	4518 battery workers, 624 cancer deaths	Blood Pb 63 $\mu g/dl$, 1947-72; external referent
Wong et al. (2) [2000]	USA	2300 smelter workers, 273 cancer deaths	Blood Pb 80 $\mu g/dl$, 1947-72; external referent
Steenland et al. [1992]	USA	1990 smelter workers, 192 cancer deaths	Blood Pb 56 $\mu g/dl$, 1976; external referent
Fanning [1988]	UK	201 cancer deaths among 2073 deaths of battery and other lead-exposed workers	Nested case-control; High ($>$ 40 $\mu g/dl$) vs. low exp
Cocco et al. [1997]	Italy	1388 smelter workers, 132 cancer cases	48 $\mu g/m^3$ air lead, 1977; external regional referent
Lundstrom et al. [1997]	Sweden	2353 smelter workers, 172 cancer cases	Blood Pb 60 $\mu g/dl$ in 1950; external ref; 15-year latency; incident cases
Anttila et al. [1995]	Finland	20741 persons w/blood lead across industries, 274 cases	Apprx. 26 $\mu g/dl$ 1973; RRs for $>$ 20 $\mu g/dl$ vs. external referent; incident cases
Gerhardsson et al. [1995]	Sweden	664 smelter workers, 40 cancer cases	Blood Pb 60 $\mu g/dl$ in 1969; external local referent; incident cases

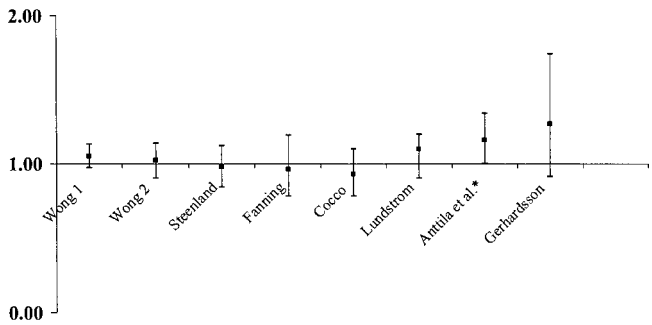


FIGURE 1. Lead and all cancer relative risks: eight studies. (*Internal referent; use of RR with external referent does not change results appreciably.) Meta-analysis results (fixed effects) RR = 1.04 (1.00–1.09).

and calendar time, but not for smoking or diet. Six used external comparisons, while two used internal ones. Most recent published updates are used for all studies.

Eight studies are not too many upon which to base conclusions, despite reasonably large numbers of cancer deaths or cases for most sites (all cancers 1911, lung 675, stomach 181, kidney 40, brain 69). Furthermore, a weakness of most studies is the lack of quantitative data on dose–response, although a few studies do divide workers into high and low exposure groups. In the following, the results of each study are reported based on the whole population of exposed workers.

While there is a plausible mechanism by which lead might increase all cancers (inhibiting DNA repair), the data do not support such a general increase. Results of studies of lead and all cancers are shown in Figure 1. A meta-analysis using a fixed effects model (see below) results in a RR = 1.04 (1.00–1.09). This is a negligible increase, and is not suggestive of a true association.

All eight studies under consideration include results for lung cancer risk (Figure 2). The lung cancer results show significant heterogeneity due to high relative risk in a study of Swedish smelter workers by Lundstrom et al. [1997]. In the presence of significant heterogeneity, a random effects model may be used to combine relative risks across studies. This model assumes that there is no single true relative risk underlying the different study findings, but rather a distribution of true relative risks. Random effects models estimate a kind of average of these true relative risks, using a weighted average of study-specific relative risks in which the weights are the inverse of the variance of each study-specific relative risk plus the variance of the study-specific relative risks. Random effects models typically result in a larger variance for this estimated relative risk than do fixed effects models. Fixed effects models, conversely, are used when different studies yield relatively homogenous relative risks and it can be assumed that there is a single underlying true relative risk. The resulting weighted average of study-specific relative risks uses weights which are the inverse of the study-specific relative risks without an added component for their variance across studies. The variance of the estimated common relative risk is generally smaller than in random effects models.

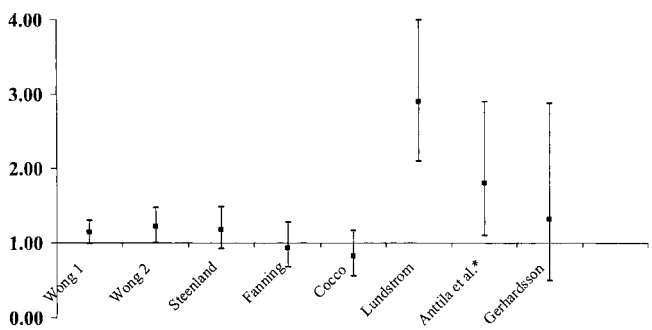
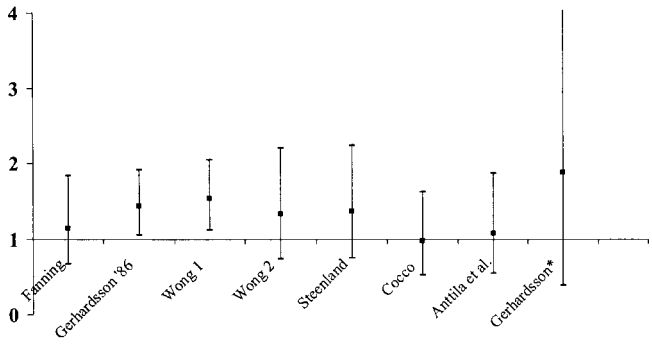


FIGURE 2. Lead and lung cancer relative risks: eight studies. (*Internal referent; use of RR with external referent does not change results appreciably.) Meta-analysis results (random effects): RR = 1.30 (1.15–1.46) with Lundstrom et al. (fixed effects): RR = 1.14 (1.04–1.25).

For lung cancer, analysis using a random effects model yields a RR = 1.30 (1.15–1.46). Without the "outlier" Lundstrom study a fixed effects model can be used, resulting in a RR = 1.14 (1.04–1.25). None of these studies control for smoking, which may be a confounder, especially for those studies in which workers are compared with the general population. The estimated overall relative risk with Lundstrom et al. [1997] included is within the upper range of what could plausibly be explained by smoking differences [Siemiatycki et al., 1992]. Overall, these studies show only a weak evidence of effect, and heterogeneity and possible confounding limit inference.

The lung cancer findings for lead are also potentially confounded by exposures to cadmium and/or arsenic (known lung carcinogens) in the lead smelter studies. On the other hand, in most of the smelter studies there was documentation that cadmium and arsenic levels were low. However, in the study with the highest relative risk [Lundstrom et al., 1997], there was significant exposure to arsenic before 1950, a period also of the highest lung cancer risks; confounding by arsenic in this cohort is a possibility. Recent work in this cohort confirms significant arsenic exposure for the lung cancer cases [Englyst et al., 1999], and the authors state that they cannot conclude whether the observed lung cancer excess is due to lead, arsenic, or a combination of the two. Further case-control studies are in progress in this cohort.

Results for stomach cancer are shown in Figure 3, based on all eight studies (Lundstrom et al., [1997] did not break out stomach cancer; we used the results of an earlier follow-up by Gerhardsson et al., [1986]). A meta-analysis using a fixed effects model results in a RR = 1.34 (1.14–1.57). Confounding by diet is possible, although unlikely to explain completely the observed excess. Data for stomach are again suggestive but not conclusive.



*Upper 95% CI for RR for Gerhardsson is 5.50

FIGURE 3. Lead and stomach cancer relative risks: eight studies. (*Upper 95% CI for RR for Gerhardsson is 5.50.) Meta-analysis results (fixed effects) RR = 1.34 (1.14–1.57).

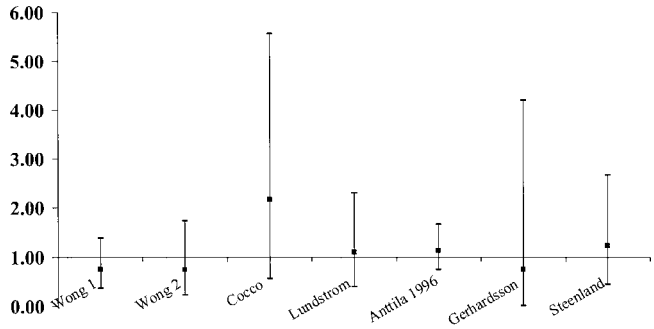


FIGURE 5. Lead and brain cancer relative risks: seven studies. Meta-analysis results (fixed effects) RR = 1.06 (0.81–1.40).

Additional information on stomach cancer is available from four case-control studies. Wong and Harris [2000] conducted a nested case-control study at one battery plant which had 30 stomach cancer deaths (representing half of the 60 stomach cancers in the Wong and Harris cohort study). No dose–response was found using a variety of measures for estimated lead exposure. This study, therefore, weakens the case for a true association between lead and stomach cancer. On the other hand, three recent population-based case-control studies using job-exposure matrices offer some support of a true association. Cocco et al. [1998a] found a significantly (60%) increased risk of cancer of the gastric cardia for men likely to have been exposed to high levels of lead based on death certificate data for disease and usual occupation. Parent et al. [1997] found an odds ratio of 13.7 (2.2–84.6) for substantial exposure to lead, based on only three exposed cases, in a population-based case control study in Montreal. Wingren and Axelson [1987] showed some association between lead exposure and stomach cancer among Swedish glassworkers, but lead exposure could not be separated from exposure to other metals.

Figure 4 shows the results for lead and kidney cancer based on seven studies. A meta-analysis using a fixed effects model yields a relative risk of 1.01 (0.72–1.42). Overall, there is little positive evidence for kidney cancer, the cancer found most consistently in animal studies. Although statistically these studies do not show significant heterogeneity, overall numbers are small (40 deaths or cases total) limiting power to detect heterogeneity, and two studies do show an approximately two-fold excess. This suggests that kidney cancer remains a concern.

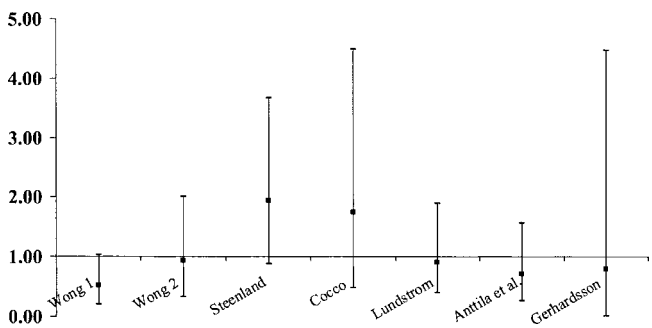


FIGURE 4. Lead and kidney cancer relative risks: seven studies. Meta-analysis results (fixed effects) RR = 1.01 (0.72–1.42).

Figure 5 shows the results for lead and brain cancer relative risks based on seven studies. Meta-analysis results (fixed effects model) yield a relative risk of 1.06 (0.80–1.40). Like kidney cancer, there is little evidence for an excess risk of brain cancer, despite one suggestive study [Cocco et al., 1997], and some animal evidence for this site. The number of deaths or cases is again relatively small (n = 69). However, there is supportive evidence for brain cancer from two other studies not included in Figure 5 because they are not cohort studies of exposed workers or because they have used a more restricted subset of all brain cancers. A U.S. study of death certificates and occupation found an odds ratio of 2.1 (1.1–4.0) for men with high probability of high level exposure (job exposure matrix, 27,000 brain cancer cases) [Cocco et al., 1998b]. Antilla et al. [1996] in a nested case-control study of 16 male glioma cases (a subset of the 26 brain cancers included in Figure 5) found an odds ratio of 11.0 (1.0–6.3) for those with blood lead > 28 μg/dl vs. those with less than 14 μg/dl (p for trend = 0.03). These two studies suggest that brain cancer remains a concern.

While most of the epidemiology concerns inorganic lead, there are two studies of workers exposed while producing tetraethyl lead that has been and in some countries is still used as an additive in gasoline [Robinson, 1974; Fayerweather et al., 1997]. Tetraethyl lead is metabolized to inorganic lead in the body. The study by Robinson [1974] was based on only 51 total deaths and is not informative. The more recent study [Fayerweather et al., 1997] found a significant excess of rectal cancer (odds ratio 3.7, 1.3–10.2) with a positive exposure–response relation-

ship based on estimated exposure. Colon cancer was also elevated, although not as markedly (odds ratio 1.3 (0.7–2.5), 16 exposed cases), and showed a positive exposure response. There is some evidence from one Swedish study of glassworkers who may ingest lead (odds ratio 1.7 (1.0–2.5), 18 exposed cases, Wingren and Axelson [1987]), but the eight principal studies reviewed here show no evidence of an excess of colon or rectal cancer. Differences in findings for digestive cancer could be due to the absorption pattern of inorganic lead vs. organic lead.

CONCLUSIONS

Despite the fact that lead is one of the earliest recognized occupational toxins, there exist relatively few studies of cancer among lead-exposed workers with well-documented high exposures. Such studies are the most informative for identifying whether lead causes cancer.

In the eight principal studies with well-documented high exposures, the evidence is somewhat suggestive of an association with lung cancer and stomach cancer, but remains limited. Possible confounding by arsenic is a concern in the study with the highest lung cancer relative risk. In addition, there is weaker evidence of an association with kidney cancer and gliomas. Most of the epidemiologic studies unfortunately do not have data on dose–response that would be expected to provide a better basis for inference than comparisons of exposed to nonexposed. Future information can be expected from increased follow-up of the newest cohort, 12,000 workers with blood lead levels in Sweden. New developments in measuring bone lead may offer a method of estimating cumulative exposure retrospectively [Borjesson et al., 1997; Hu et al., 1998].

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