



## **Editorial**

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### **Lead and cancer -- association or causation?**

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## *Lead and cancer — association or causation?*

Lead is one of the oldest industrial toxins. It must have begun to take its toll soon after Prometheus made the gift of fire to man. Throughout the centuries, this valuable metal has been used in a variety of ways. Due to the widespread use of lead in pipes for water distribution, lead-based paint, lead additives in gasoline and other applications, lead has since become a general environmental contaminant. It has also turned out to be a human toxin that can affect many organs and their functions, including bone marrow and the nervous system.

Early on, acute toxicity after high-level exposures to lead compounds was the main concern. In the days of the Roman empire, both lead and mercury poisoning were known, for Pliny the Elder included them among the “diseases of slaves” (potters’ and knife grinders’ phthisis). Nowadays, as a result of improved hygiene and increased knowledge, interest has primarily shifted to more subtle changes, such as behavioral problems and mental retardation.

The carcinogenicity of lead compounds was recognized in 1987 by the International Agency for Research on Cancer (IARC) (1), which considered that lead and inorganic lead compounds are possibly carcinogenic to humans (IARC group 2B), on the basis of sufficient evidence of carcinogenicity in experimental animals but inadequate evidence for carcinogenicity in humans.

Fu & Boffetta (2) conducted a meta-analysis of available case-referent and cohort studies on the association between exposure to lead compounds and cancer occurrence available at that time. They concluded that the data from workers with heavy exposure to lead “provided some evidence to support the hypothesis of an association between stomach and lung cancers and exposure to lead [p 73]”.

Since the review by Fu & Boffetta, four other studies have been published: 1 from Finland (3), 2 from Sweden (4, 5) and 1 from Italy (6).

Anttila et al (3) studied 20 700 workers who had been biologically monitored for their blood lead concentrations during 1973—1983. The internal comparison within the cohort showed a 1.4-fold increase in the overall cancer incidence and a 1.8-fold increase in the incidence of lung cancer among those who had ever had a blood-lead level of  $\geq 1.0 \mu\text{mol/l}$ . In the case-referent analysis, an increased odds ratio was found for lung cancer for concomitant exposure to lead and engine exhaust.

In a small Swedish cohort of 664 male lead-battery workers, an increased mortality was noted for all malignant neoplasms (SMR 165, 95% CI 109—244) (4). The incidence of respiratory tract cancer in the total cohort was slightly increased (SIR 132, based on 6 observed and 4.5 expected cases). Another Swedish cohort (5) was formed from 3979 primary lead smelter workers. Lung cancer incidence was increased in the total cohort (SIR 278, 95% CI 205—375) and in the highest lead-exposed subgroup (SIR 305, 95% CI 196—463).

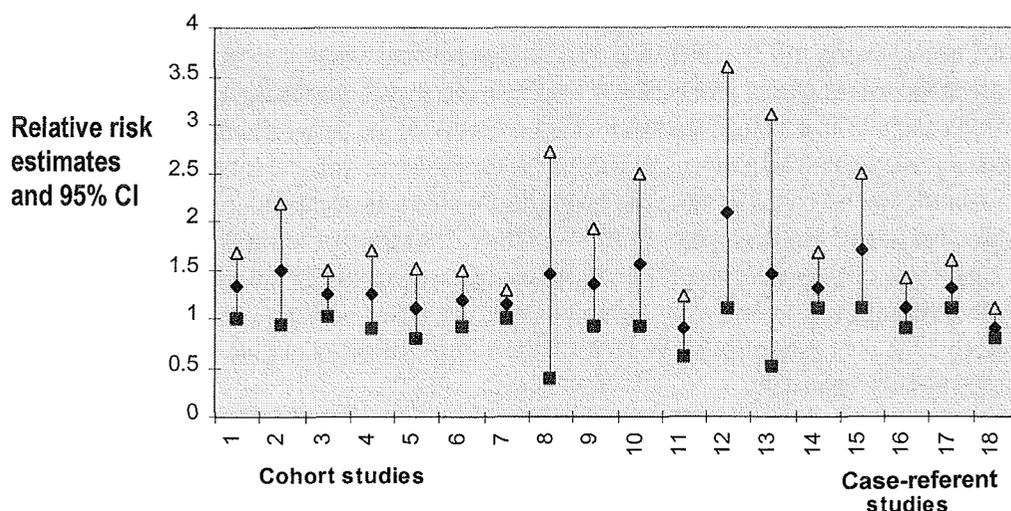
The Italian cohort consisted of 1388 workers in a lead-smelting plant. Mortality from all cancers, stomach cancer, and lung cancer was lower than expected; however, there was a 4.5-fold excess mortality from pneumoconiosis and other diseases of the respiratory system, obviously due to exposure to silica. The lack of excess cancer occurrence is in apparent contradiction with the epidemiologic literature supporting an association between silicosis and lung cancer (7). Therefore, the detection of any possible excess of lung cancer due to lead exposure may also have been masked for the same reasons (eg, by misdiagnosis of lung cancer on the death certificates).

Risks of genitourinary diseases and kidney cancer increased significantly with duration of employment up to 6.6-fold and almost 11-fold, respectively, among smelter workers employed for 21 years or more (6).

Even though the risk estimates for kidney cancer have varied within heavily-exposed lead cohorts, some common features emerge. Increased risks have appeared in studies of lead smelters with long-term exposure to high levels of lead, with a long latency or induction period. Concerning lung cancer, the published cohort and case-referent studies seem to support the hypothesis that exposure to lead causes a significant, but relatively small, increase in risk (figure 1). In three of the recent cohorts, an increased incidence of lung cancer has been observed among lead-exposed workers. The increases in the Finnish and recent Swedish cohorts could not be explained solely by confounding from smoking or by other occupational carcinogens.

Lead and lead compounds have long been recognized as carcinogenic to animals (ie, they have an inherent capacity to induce malignant cell growth) (1, 24). Long-term rodent carcinogenicity studies have shown that the oral administration of lead compounds can lead to an increased occurrence of renal tumors. Lead compounds can also increase tumor yields at other sites. Lead subacetate has increased the incidence of lung adenomas in a screening assay of mice.

In conclusion, the epidemiologic evidence has, until now, been inconsistent. For lung cancer, the 12 cohort studies and 4 case-referent studies (either among battery workers or among lead smelters), included in the meta-analysis by Fu & Boffetta (2), show a fairly consistent increase, although small, in lung cancer risk (figure 1). The relative risks among subpopulations more exposed to lead compounds showed even higher point estimates of risk in certain studies. With the 4 recent cohorts (not shown in figure 1), it seems that long-term, high exposure to lead compounds is associated with an increased risk of lung cancer. While the Italian cohort did not report any increase in lung cancer risk, it had an excess of kidney cancer (6). Animal studies have provided convincing evidence for the induction of kidney tumors after exposure to lead compounds (24). An excess of cancer in the digestive tract has also been reported in some epidemiologic studies; however, this excess risk could be explained, at least in part, by nonoccupational factors (2).



**Figure 1.** Relative risk estimates and 95% confidence intervals (95% CI) for the association of industrial lead exposure with lung cancer in cohort (N = 12) and case-referent (N = 4) studies. Sources of lead exposure and references (in parentheses): 1. batteries (8), 2 = smelters (8), 3 = batteries (9), 4 = smelters (9), 5 = smelters (10), 6 = smelter (11), 7 = smelter (12), 8 = pigments (13), 9 = pigments (14), 10 = printing (15), 11 = printing (16), 12 = glassworks (17), 13 = glassworks (18), 14 = glassworks (19), 15 = glassworks (20), 16 = lead compound (21), 17 = nonferrous smelters (22); 18 = battery and other factories (23).

Should lead and lead compounds now be considered carcinogenic to humans? The weight of evidence is beginning to be convincing enough concerning kidney and even lung cancer. When all the available evidence is taken into account, occupational exposure to lead and lead compounds should therefore be considered as carcinogenic to humans.

### References

1. International Agency for Research on Cancer (IARC). Overall evaluations of carcinogenicity: an updating of IARC monographs, volumes 1 to 42. Lyon: IARC, 1987. IARC monographs on the evaluation of carcinogenic risk to humans, supplement 7.
2. Fu H, Boffetta P. Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data. *Occup Environ Med* 1995;52:73—81.
3. Anttila A, Heikkilä P, Pukkala E, Nykyri E, Kauppinen T, Hernberg S, et al. Excess lung cancer among workers exposed to lead. *Scand J Work Environ Health* 1995;21:460—9.
4. Gerhardsson L, Hagmar L, Rylander L, Skerfving S. Mortality and cancer incidence among secondary lead smelter workers. *Occup Environ Med* 1995;52:667—72.
5. Lundström NG, Nordberg G, Englyst V, Gerhardsson L, Hagmar L, Jin T, et al. Cumulative lead exposure — relationship to mortality and lung cancer morbidity in a cohort of smelter workers. *Scand J Work Environ Health* 1997;23(1):24—30.
6. Cocco P, Fu H, Boffetta P, Carta P, Flore C, Flore V, et al. Mortality of Italian lead smelter workers. *Scand J Work Environ Health* 1997;23(1):15—23.
7. International Agency for Research on Cancer (IARC). Silica, some silicates, coal dust and para-aramid fibrils. Lyon: IARC, in press. IARC monographs on the evaluation of carcinogenic risks to humans, vol 68.
8. Cooper WC, Gaffey WR. Mortality of lead workers. *J Occup Med* 1975;17:100—7.
9. Cooper WC, Wong O, Kheifets L. Mortality among employees of lead battery plants and lead producing plants, 1947—1980. *Scand J Work Environ Health* 1985;11:331—45.
10. Selevan S, Landrigan PJ, Stern FB, Jones, JH. Mortality of lead smelter workers. *Am J Epidemiol* 1985;122:673—83.
11. Steenland K, Selevan S, Landrigan P. The mortality of lead smelter workers: an update. *Am J Public Health* 1992;82:1641—4.
12. Gerhardsson L, Lundström N-G, Nordberg G, Wall S. Mortality and lead exposure: a retrospective cohort study of Swedish smelter workers. *Br J Ind Med* 1986;43:707—12.
13. Davies JM. Long term mortality study of chromate pigment workers who suffered lead poisoning. *BMJ* 1984;41:170—8.
14. Sheffet A, Thind I, Miller AM, Louria DB. Cancer mortality in a pigment plant utilizing lead and zinc chromates. *Arch Environ Health* 1982;37:44—52.
15. Bertazzi P, Zochetti C. A mortality study of newspaper printing workers. *Am J Ind Med* 1980;1:85—97.
16. Michaels D, Zoloth SR, Stern FB. Does low-level lead exposure increase risk of death? a mortality study of newspaper printers. *Int J Epidemiol* 1991;20:978—83.
17. Cordioli G, Goughi L, Solari PL, Berrino F, Crosignani P, Riboli E. Mortality from tumors in a cohort of workers in the glass industry. *Epidemiol Prev* 1987;30:16—8.
18. Wingren G, Englander V. Mortality and cancer in a cohort of Swedish glassworkers. *Arch Occup Environ Health* 1990;62:252—7.
19. Sänkilä R, Karjalainen S, Pukkala E, Oksanen H, Hakulinen T, Teppo L, Hakama M. Cancer risk among glass factory workers: an excess of lung cancer? *Br J Ind Med* 1990;47:815—8.
20. Wingren G, Axelson O. Mortality in the Swedish glassworks industry. *Scand J Work Environ Health* 1987;13:412—6.
21. Siemiatycki J. Risk factors for cancer in the workplace. London: CRC Press, 1991.
22. Ades AE, Kazantzis G. Lung cancer in a non-ferrous smelter: the role of cadmium. *Br J Ind Med* 1988;45:435—42.
23. Fanning D. A mortality study of lead workers, 1926—1985. *Arch Environ Health* 1988;43:247—51.
24. International Agency for Research on Cancer (IARC). Some metals and metallic compounds. Lyon: IARC, 1980:362—3. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, volume 23.

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