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Excess lung cancer among workers exposed to lead

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Objective Studies on experimental animals suggest that inorganic lead is a carcinogen. The purpose of the study was to examine whether occupational exposure to lead increases the risk of cancer.

Methods The study population comprised 20 700 workers who had been biologically monitored for their blood lead (B-Pb) concentrations during 1973—1983. The mortality and cancer incidence rates were followed among the monitored workers and compared with those of the Finnish general population. An internal comparison of the cancer incidence rates was also done between subcohorts formed according to individual B-Pb levels. Questionnaire-based information was also collected on lifetime occupational history and potential confounders, and exposure history was assessed on an individual basis with a nested case-referent design for lung cancer.

Results 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 ≥ 1.0 μmol · l^{-1}. In the case-referent study, an increased odds ratio for lung cancer was found for concomitant exposure to lead and engine exhaust. The odds ratio for squamous-cell carcinoma of the lung was increased even when the blood lead level had been slightly elevated. Bias or confounding did not explain the risks.

Conclusions The results suggest that exposure to lead increases the risk of lung cancer. Co-exposure to engine exhaust and lead may be associated with the risk.

Key terms case-referent study, cohort analysis, incidence, mortality, occupational exposure, record linkage.

Long-term carcinogenicity studies on experimental animals have shown that oral doses of a lead compound can induce renal tumors. Tumor induction has also been noted at other sites. Lead subacetate has increased the incidence of lung adenomas in a short-term carcinogenicity study. Synergistic effects of tumor incidence in the lung have been reported for lead, including co-exposure to lead oxide and benzo[a]pyrene (1—4). According to cytogenetic studies on experimental animals, lead can induce indirect disturbances in DNA (deoxyribonucleic acid) replication, repair, or helical structure, as has been reported also for nickel compounds, cadmium, and chromates (5—6). Cytogenetic studies on heavily exposed workers, for whom smoking was controlled, suggest that lead compounds are genotoxic in humans (7—10).

Excess mortality from lung cancer has been shown in six of eight cohorts of lead workers (11—18). The excess has usually been small, and it has not shown a clear relation with the length or degree of exposure. An excess of cancer of the digestive system has also been reported (11, 13, 16, 18), along with, in one cohort, excess kidney cancer (18). Due to methodological shortcomings in these studies, such as low statistical power, inadequate data on individual exposure, and an absence of information on potential confounders, both the International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (EPA) have concluded that the evidence for the carcinogenicity of inorganic lead is inadequate for humans (2, 3).

The aim of the present study was to examine whether occupational exposure to lead increases the risk of cancer. The study population consisted of workers who were biologically monitored for their blood lead (B-Pb) concentrations during 1973—1983. We followed their mortality and cancer incidence and compared the rates within the study base with those of the general population.

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We also performed an internal comparison of the cancer risk within the cohort, the subcohorts being based on the highest individual B-Pb level. To study the association of lead with the occurrence of lung cancer further, we performed a case-referent study within the cohort, aiming at estimates for which individual exposure history and confounding were controlled.

Subjects and methods

A file of biologically monitored workers was collected from the laboratory documents of the Finnish Institute of Occupational Health. The data included 63 670 blood lead measurements made in 1973—1983. The personal identity was traced from the laboratories, employers, or population catalogues for 22 086 persons (97% of the measurements). Those monitored for nonoccupational purposes were excluded. After the removal of the nonoccupational samples, the data included 20 741 persons, 18 329 men (88%) and 2 412 women (12%). The collection and contents of the data have been described in earlier reports (19—21).

According to instructions based on the Act on Labor Protection (299/1958), if the B-Pb of any worker at a workplace exceeds 2 $\mu mol \cdot l^{-1}$, all workers in similar tasks should be monitored periodically. Most of the workers who were followed more than five times a year were from the battery industry, lead smelting, metal foundries, railroad machine shops, and the manufacture of chemicals. The workers in these industries were monitored an average of about eight times in 2.7 years. For all the other industries combined, the average number of measurements per individual was only 1.9 (for example, in the metal scrap business 2.5 measurements and in automobile repair shops 1.4 measurements per individual).

The geometric mean B-Pb decreased from 1.4 $\mu mol \cdot l^{-1}$ to 0.7 $\mu mol \cdot l^{-1}$ for the men and from 1 $\mu mol \cdot l^{-1}$ to 0.3 $\mu mol \cdot l^{-1}$ for the women during the 10-year span of 1973—1982. The highest monitored levels (the interval from the 99th percentile to maximum) decreased from 4—8 $\mu mol \cdot l^{-1}$ to 3—4 $\mu mol \cdot l^{-1}$ among the men and from 4—5 $\mu mol \cdot l^{-1}$ to 2—2.5 $\mu mol \cdot l^{-1}$ among the women. The mean age for the subjects when entering the cohort (ie, when the first sample was taken) was 33.8 years for the men and 37.5 years for the women (21).

Cohort analysis

The follow-up of cancer incidence for the cohort analyses was done automatically through the files of the Finnish Cancer Register between 1973—1988. The follow-up was started at the date of the first personal measurement. The total number of person-years at risk was 207 270 for the men and 28 872 for the women. The follow-up was complete for the identified cohort members. Mortality data were collected in a similar way through the Cause-of-Death Register maintained by the Central Statistical Office of Finland. Altogether 1007 men and 75 women had died during 1973—1988. A death certificate was not available for nine of the deceased persons, who had died abroad.

The expected numbers were calculated from the rates in the general population, separately for the men and women, and by five-year age groups and four-year calendar periods. Two-sided confidence intervals for the standardized incidence or mortality ratios (SIR and SMR, respectively) were determined using the exact method based on a Poisson distribution. The data were grouped according to the highest personal B-Pb level. A follow-up interval initiated five years after the first individual measurement was also used, for a better control of potential biases in the comparison and allowance for lag time (22).

We also performed an internal comparison of cancer incidence rates within the cohort base. The definition of exposure relied on the administrative reference limit for "occupationally unexposed" (< 1.0 $\mu mol \cdot l^{-1}$) used by the analyzing laboratories throughout the study period. These analyses were done by Poisson regression. Workers aged 30—74 years were included in the analyses, and 15-year age groups, four-year calendar periods, and gender were controlled. Person-years were used as denominators.

Case-referent study

To assess the association of lung cancer with indices of lifetime exposure to lead and to obtain information on potential confounders, a case-referent study on lung cancer was performed within the study base. The record linkage for the case-referent study was done in 1991. There were 116 primary lung cancers [International Classification of Diseases, seventh revision (ICD-7) code 162.0—1] among the men and four among the women eligible for the study during 1973—1990. Only the first primary cancer of a person was accepted. Five pleural cancer cases (ICD—7 code 162.2) were found among the monitored men and two among the women. The number of pleural cancers was too small to assess disease-specific risks. They were included, however, in the data so that information would be obtained on the exposure histories. The data were analyzed both by including pleural cancer in the analyses and excluding it (on the assumption of a better specificity for the disease). Due to the small number of women available for the final population, the study was restricted to men.

Three referents for each case were selected randomly from among the monitored workers who were not regis-

tered for any cancer. The referents were matched with the cases by gender, year of birth, age at the end of follow-up, and vital status. If a case was deceased, two deceased referents and one living referent were selected if available (correspondingly, for a living case, two living referents and one deceased referent were selected).

Thus there were 121 male cases and 363 referents to start with. About 90% of the cases and 60% of the referents were deceased. A postal address was available from the central population register for 102 (84%) cases (or next-of-kin of deceased ones) and 308 (85%) referents. The excluded subjects were those for whom next-of-kin were not available or those who had died or had the cancer diagnosed less than one year earlier than the postal date (to allow a minimum time for grief).

The study used a semi-structured questionnaire to collect information on detailed lifetime occupational history. There were also questions on smoking history (onset of smoking, age at having stopped smoking, average daily numbers of smoked cigarettes for each period of smoking). The covering letter assured that participation in the study was voluntary and that confidentiality would be safeguarded, in accordance with Finnish legislation. The respondents had the possibility to reply either by mail or by telephone. After two reminders, 57 cases (56%) and 179 referents (58%) had replied. The next-of-kin of the deceased subjects responded as often as the living subjects. There were no major differences in the response rate between the cases and referents either in relation to age or the response given via the mail or phone. For four cases and four referents, detailed information on occupational history was missing in the reply, and they were excluded. Nineteen referents were excluded due to nonresponse of the cases in the same strata. Thus the final population included 53 cases and 156 referents.

Table 1. Definitions of the background and low and high levels of exposure for potential occupational confounders. The given concentrations are approximate guideposts rather than precise values. (OES = Finnish hygienic standard for occupational exposure)

Exposure	Background	Low	High
Asbestos (fibers · cm^{-3})	< 0.1	0.1—1	> 1
Metals and their inorganic compounds (arsenic, cadmium, chromates, nickel)	< 1/10 OES[a]	1/10—OES[a]	> OES[a]
Silica (mg · m^{-3})	< 0.02	0.02—0.2	> 0.2
Organic solvents	< 1/100 OES[b]	1/100 OES[b]	> OES[b]
Gasoline (ppm benzene)	< 0.01	0.01—1	> 1
Polycyclic aromatic hydrocarbons (µg benzo[a]pyrone · m^{-3})	< 0.01	0.01—1	> 1
Engine exhaust		Exposure < 30% of the work time	Exposure ≥ 30% of the work time
Radon		Mining workers	

[a] OES values used: arsenic and its inorganic compounds = 0.01 mg · m^{-3}, cadmium and its compounds = 0.02 mg · m^{-3}, chromates = 0.05 mg · m^{-3}, nickel, metal = 1 mg · m^{-3}, nickel compounds = 0.1 mg · m^{-3}.
[b] OES value for solvent mixtures, for which the effects of specific solvents are additive.

An industrial hygienist (PH) classified the exposure histories without knowing the case-referent status. Exposure was assessed for occupational carcinogens (IARC classes 1, 2A, and 2B). The approximate limits of the exposure levels are presented in table 1. Both the personal and workplace-specific mean B-Pb levels were used in the assessment for lead, together with the information on worktasks. For those periods in which no or inadequate measurements were available on an individual basis, exposure was estimated from industry or worktask-specific temporal profiles. These profiles described the average exposure level to lead, based on a comparison of the recorded measurements with the earlier and more recent reports (23—29). The secular trends in the B-Pb were assessed with log-linear regression.

Lead compounds were categorized into the following groups: (i) dust of lead or lead oxide, (ii) fume of lead or lead oxide, (ii) lead pigments in paints (eg, lead chromate, lead molybdate, lead monoxide, lead sulfate and lead carbonate), (iv) lead compounds in polyvinyl chloride plastics (lead stearate, lead sulfate and lead phosphate), (v) alkyl lead compounds (lead tetraethyl and lead tetramethyl) and (vi) leaded engine exhaust (lead oxide, lead bromochloride, and lead sulfate).

The statistical analyses used several indicators of occupational lead exposure, such as the highest personal B-Pb value (µmol · l^{-1}), mean estimated level (µmol · l^{-1}), duration of exposure, and occupational cumulative exposure (time–integrated dose from the log-linear estimation µmol · l^{-1} × year) considering various latency periods. The latency was defined as the time elapsed from first exposure. Lead exposure indicators were tested as continuous, dichotomous, and multilevel categorical variables. The lowest limit for lead exposure ("unexposed," < 0.8 µmol · l^{-1}) was derived from an estimation of the 95th percentile in the Finnish population during the mid-1970s.

The case strata were defined by five-year periods of birth years and three-year age groups. The odds ratios for exposure were estimated with the conditional logistic regression model (30, 31). The statistical significance was tested through a comparison of the standardized regression coefficients with the normal distribution. Those for whom at least one work period lasting several years was reported were included in the final data, with indices of missing information. The information on exposure levels for occupational exposures other than lead was not used in the final models because of the very small number of workers in the high-level categories.

Results

Cohort analysis

The overall mortality for the whole cohort was less than expected [1082/1293, SMR 84, 95% confidence interval (95% CI) 79—89]. The SMR for cancer mortality, all cancers combined, was slightly decreased (SMR 93, 95% CI 81—105). There was also no clear excess mortality for specific causes of death. When grouped according to the highest B-Pb, a clear excess was seen only for external causes (such as accidents and violence, SMR 139 and 95% CI 106—179 for a B-Pb of ≥ 2.0 μmol · l^{-1}).

For the whole cohort, 396 incident cancers, 102 of which were lung cancers, were observed among the men and 73 cancers, of them three lung cancers, among the women. The expected numbers were 399 and 102 for the men and 75 and 3 for the women. There were 17 renal cancers among the men and 1 among the women (18 and 2 expected, respectively). The incidence of bladder cancer was increased (32 observed, SIR 1.6, 95% CI 1.1—2.3), while the incidence of cancer of the buccal cavity and pharynx was decreased (8 observed, SIR 0.5, 95% CI 0.2— 0.9).

Table 2 shows the observed and expected numbers and SIR values of the cancers, grouped by the highest personal B-Pb level and gender of the subjects. The analysis omits five years from the beginning of follow-up. The overall cancer incidence was decreased among the men in the lowest B-Pb group. When data on both genders were combined, a small statistically significant excess was seen in the intermediate B-Pb level for overall cancer (SIR 1.2, 95% CI 1.0—1.4) and for lung cancer (SIR 1.4, 95% CI 1.0—2.0). The SIR of nervous system cancer was slightly increased for the men in the highest B-Pb group and for women in the intermediate group. There was an increase in the risk of nervous system cancer among 45- to 59-year-old persons for a B-Pb of ≥ 1.0 μmol · l^{-1} (8 cases, SIR 2.9, 95% CI 1.2—5.7). The SIR of bladder cancer was elevated in all the B-Pb groups.

In the internal comparison, the incidence of overall cancer and lung cancer was increased for the highest level of B-Pb (≥ 1.0 μmol · l^{-1}) as compared with those with a B-Pb level of < 1.0 μmol · l^{-1}. The rate ratio (RR) was 1.4 (95% CI 1.1—1.7) for overall cancer and 1.8 (95% CI 1.1—2.9) for lung cancer for a B-Pb level of

Table 2. Observed number of cases, standardized incidence ratio (SIR), and 95% confidence interval (95% CI) of cancer incidence in 1973—1988 among the monitored workers, grouped by the highest personal blood lead concentration and gender. Follow-up started five years after the first measurement.

Primary site[a]	Highest blood lead value (μmol · l^{-1})								
	0.0—0.9			1.0—1.9			2.0—7.8		
	Observed (N)	SIR	95% CI	Observed (N)	SIR	95% CI	Observed (N)	SIR	95% CI
Men									
All cancers (140—204)	114	0.8*	0.7—1.0	120	1.2	1.0—1.4	40	1.0	0.7—1.4
Buccal cavity and pharynx (140—148)	2	0.4	0.1—1.3	4	1.0	0.3—2.6	—	0.0	0.0—1.4
Digestive organs (150—159)	31	0.9	0.6—1.3	32	1.3	0.9—1.8	10	1.0	0.5—1.9
Stomach (151)	11	1.0	0.5—1.9	11	1.4	0.7—2.5	1	0.3	0.0—1.8
Pancreas (157)	6	1.1	0.7—2.5	4	1.0	0.3—2.6	2	1.3	0.2—4.8
Respiratory organs (160—164)	30	0.8	0.5—1.1	40	1.4*	1.0—1.9	13	1.2	0.6—2.0
Lung, trachea (162.0—1)	25	0.7	0.5—1.1	35	1.4	1.0—1.9	11	1.1	0.6—2.0
Genital organs (177—179)	14	1.0	0.6—1.7	6	0.6	0.2—1.3	3	0.8	0.2—2.3
Kidney (180)	4	0.6	0.2—1.5	5	1.0	0.3—2.4	—	0.0	0.0—2.0
Bladder (181)	10	1.4	0.7—2.6	10	2.0	1.0—3.6	3	1.5	0.3—4.5
Nervous system (193)	8	1.3	0.6—2.6	6	1.3	0.5—2.7	3	1.6	0.3—4.6
Women									
All cancers (140—204)	35	1.0	0.7—1.3	16	1.4	0.8—2.3	3	0.9	0.2—2.6
Digestive organs (150—159)	8	1.2	0.5—2.3	1	0.5	0.0—2.5	2	3.4	0.4—12
Stomach (151)	2	1.2	0.1—4.2	—	0.0	0.0—6.6	—	0.0	0.0—24
Pancreas (157)	4	4.2*	1.2—11	1	3.2	0.1—18	—	0.0	0.0—47
Respiratory organs (160—164)	1	0.6	0.0—3.5	4	7.8**	2.1—20	—	0.0	0.0—26
Lung, trachea (162.0—1)	1	0.7	0.0—4.0	2	4.5	0.5—16	—	0.0	0.0—30
Breast (170)	11	0.9	0.5—1.6	5	1.4	0.5—3.2	—	0.0	0.0—3.2
Genital organs (171—176)	7	1.1	0.5—2.3	3	1.5	0.3—4.5	—	0.0	0.0—6.2
Kidney (180)	—	0.0	0.0—5.7	1	0.3	0.1—1.7	—	0.0	0.0—41
Bladder (181)	1	2.5	0.1—14	—	0.0	0.0—28	—	0.0	0.0—110
Nervous system (193)	3	1.8	0.4—5.1	2	3.8	0.5—14	—	0.0	0.0—22

[a] Code of the International Classification, seventh revision, in parentheses.
* $P < 0.05$, ** $P < 0.01$.

Table 3. Number of cases and person-years and the rate ratios (RR) for selected cancers in the internal comparison among 30- to 74-year-old cohort members (Poisson regression). Follow-up started five years after the first measurement. The results have been adjusted for 15-year age groups, 4-year follow-up periods, and gender. (95% CI = 95% confident interval)

Primary site	Highest blood lead value (μmol · l⁻¹)									
	0.0—0.9		1.0—1.9				2.0—7.8			
	Cases	Person-years	Cases	Person-years	RR	95% CI	Cases	Person-years	RR	95% CI
All cancers	143	59 000	131	42 510	1.4**	1.1—1.8	43	16 614	1.2	0.9—1.8
Men	112	48 483	115	39 406	1.4**	1.1—1.8	40	15 577	1.3	0.9—1.8
Women	31	10 517	16	3 104	1.7	0.9—3.0	3	1 037	1.0	0.3—3.4
Lung, trachea	26	59 000	36	42 510	2.0*	1.2—3.2	11	16 614	1.5	0.8—3.1
Men	25	48 483	34	39 406	1.8*	1.1—3.1	11	15 577	1.5	0.7—3.1
Women	1	10 517	2	3 104	6.8	0.6—75	—	1 037	0.0	..

* $P < 0.05$, ** $P < 0.01$.

Table 4. Odds ratios (OR) for lung cancer for occupational lead exposure and the number of exposed cases in the final population — 53 cases and 156 referents; the data include pleural cancer. (95% CI = 95% confidence interval, B-Pb = blood lead)

Lead exposure indicator[a]	Cases	Referents	OR[a]	95% CI[a]
Highest B-Pb (μmol · l⁻¹)				
0.0—0.7	15	56	1.0	.
0.8—1.3	23	61	1.6	0.6—3.9
1.4—1.9	10	21	1.7	0.7—3.9
2.0—4.3	5	18	1.5	0.4—5.8
Mean estimated level (μmol · l⁻¹)				
0.0—0.7	16	50	1.0	.
0.8—1.3	28	75	1.3	0.6—3.0
1.4—1.9	9	20	1.9	0.6—5.8
2.0—2.8	0	11	0.0	..
Duration of exposure (years)				
0	16	50	1.0	.
1—9	2	17	0.3	0.0—1.8
10—24	21	35	1.7	0.7—4.1
25—46	14	54	1.2	0.5—3.2
Cumulative exposure (μmol · l⁻¹ · year)				
0	16	50	1.0	.
1—6	6	16	0.9	0.2—3.6
7—17	15	38	1.2	0.4—3.1
18—70	16	52	1.4	0.6—3.7

[a] Conditional logistic regression models. The odds ratios were adjusted for smoking and vital status, in the first model also for the year of the first measurement. The highest observed values of the exposure parameters were used in the labeling of the highest category. No assumptions on latency were included in the models.

1.0 μmol · l⁻¹. The highest RR values were determined for the intermediate category (table 3).

Case-referent study

For the whole case-referent data (121 cases) the unadjusted OR value for lung cancer was 1.6 (95% CI 1.0—2.5) for the highest B-Pb of 0.8—1.9 μmol · l⁻¹ and 1.2 (95% CI 0.6—2.3) for the highest B-Pb of ≥ 2.0 μmol · l⁻¹. In the final study population (53 cases) the corresponding unadjusted estimates were 1.7 (95% CI 0.8—3.6) and 1.2 (95% CI 0.4— 4.1). The average durations of lead exposure were 22.3 and 19.3 years for the intermediate and highest B-Pb group, respectively. The average times since the first exposure were 28 and 25 years, respectively, and the average years of first exposure were 1954 and 1957.

The adjusted OR values for different lead exposure indicators are shown in table 4. When the grouping was made according to lifetime duration or cumulative exposure of total lead, a small nonsignificant excess risk was observed. Smoking seemed to be a weak negative confounder in the highest B-Pb group. A long latency seemed not to be important for the risk.

There was considerable variation in the OR for lead when information on the end of exposure was considered. The OR for the lifetime mean exposure level of ≥ 0.8 μmol · l⁻¹ was 1.2 (95% CI 0.6—2.7, adjusted for vital status and smoking). The corresponding OR for the mean exposure level of ≥ 0.8 μmol · l⁻¹ increased to 1.7 (95% CI 0.8—3.8) when the analysis focused on the period of the last 10 years before the end of the follow-up. When we assumed that it would be plausible for the risk that lead exposure had not ended earlier than a year before the end of follow-up, the corresponding OR became even higher (OR 2.3, 95% CI 1.0—5.3). However, all the exposed cases in this analysis had a rather long duration of exposure (> 10 years), and we were not able to separate the effects completely with respect to "late" periods and earlier ones.

The OR for lung cancer was 1.9 for exposure to engine exhaust and 3.3 for exposure to leaded engine exhaust at any level (table 5). The total B-Pb level seemed to modify the risk. As estimated from the logistic model, the adjusted OR for lung cancer increased exponentially by a factor of two for 10 years of combined exposure to lead and leaded exhaust (table 6). When the grouped variables were used, the risk was greatest for the duration of 25—43 years of exposure (eight cases and four referents, adjusted OR 10.8, 95% CI 2.2—52.3).

Concomitant exposure to engine exhaust and lead was classified into car service and repair, car painting, car shield work, and work in miscellaneous repair shops (repair of engines and transport facilities, road network maintenance) among forklift truck operators, car salesmen, and for a motor vehicle inspector. Exposure to

Table 5. Odds ratios (OR) for lung cancer for other occupational exposures and smoking habits. (95% CI = 95% confidence interval)

	Cases	Referents	OR[a]	95% CI[a]
Exposure				
Asbestos	11	20	1.5	0.5—3.9
Chromates	8	20	1.3	0.5—3.5
Silica	9	14	1.4	0.5—4.2
Organic solvents	18	40	1.5	0.7—3.2
Engine exhaust	12	26	1.9	0.8—4.7
Leaded engine exhaust	15	22	3.3*	1.2—9.2
Lead compounds in polyvinyl chloride production	3	4	2.0	0.3—13
Interaction of lead and engine exhaust				
B-Pb ≥ 0.8 μmol · l^{-1}/engine exhaust				
yes/yes	11	13	14.9*[b]	1.3—178[b]
yes/no	27	87	0.9	0.4—2.2
no/yes	1	13	0.3	0.0—2.6
no/no	14	43	1.0	
Interaction term alone	11	13	4.6**	1.5—14
Smoking	48	106	4.2*	1.3—13
5—14 cigarettes per day	13	32	4.6*	1.2—17
≥ 15 cigarettes per day	35	74	4.0*	1.2—13
Current smokers	44	76	4.9**	1.5—16
Ex-smokers	4	30	1.6	0.3—8.0

[a] Conditional logistic regression models. The odds ratios were adjusted for smoking, vital status, and lead exposure (vital status and lead exposure in the models for smoking). No assumptions on minimum latency were specified in the models. Pleural cancer was included in the data.
[b] Risk 14.9-fold compared with the expected OR under the assumption of multiplicative effects (which means a 4.1-fold OR compared with that of the unexposed).
* P < 0.05, ** P < 0.01.

engine exhaust was classified also for drivers of gasoline-driven vehicles. In addition, two cases and two referents were exposed to lead in other work tasks after their service as a driver. There was also one train and station man in the data who were classified as exposed only to diesel engine exhaust.

Exposure to gasoline correlated closely with exposure to engine exhaust. However, none of the cases were exposed to gasoline only without engine exhaust. When controlled simultaneously, gasoline had no independent effect. Neither the other occupational exposures nor specified lead compounds changed or modified the OR for total lead, or for the co-exposure with engine exhaust.

About 90% of the cases had been regular smokers. All of these subjects had started smoking before the age of 20 years, and the smokers had usually smoked for more than 20 years. The risk was not clearly related to the level of smoking. Duration of smoking, cumulative pack-years, or being a smoker or ex-smoker did not change the estimates for lead.

Histology

There were 19 (16%) adenocarcinomas, 49 (41%) squamous-cell carcinomas, 11 (9%) small-cell carcinomas, and 22 (18%) other or unspecified carcinomas of the lung. For 12 cases (10%) no histology was coded. The histology was missing or unknown for three cases (2%).

Table 6. Odds ratios (OR) for lung cancer for the total lead exposure among the workers exposed to leaded engine exhaust. (95% CI = 95% confidence interval, B-Pb = blood lead)

Lead exposure indicator	OR[a]	95% CI[a]
Highest B-Pb 0.8—2.6 μmol/l · l^{-1} (13 cases, 13 referents)	5.8**	1.9—18
Mean estimated level 0.8—2.0 μmol/l · l^{-1} (13 cases, 15 referents)	4.5**	1.5—14
Mean estimated level, continuous (μmol/l · l^{-1})	3.9**	1.5—9.8
Duration of exposure, continuous, per 10 years	2.0**	1.3—3.1
Cumulative exposure, continuous, per 10 x (μmol · l^{-1} · year)	2.1**	1.3—3.5
Latency, continuous, per 10 years	1.7**	1.1—2.5

[a] Conditional logistic regression models. The odds ratios were adjusted for smoking, vital status, and occupational exposure to asbestos, chromates, silica and solvents. In the last model a minimum latency of 10 years was also assumed. The highest observed values of the exposure parameters were used in the labeling of the exposure category. Pleural cancer was included in the data.
** P < 0.01.

Table 7. Odds ratios (OR) for squamous-cell carcinoma in the lung by the highest personal blood lead level (B-Pb, μmol · l^{-1}) or mean estimated lead level (μmol/l · l^{-1}). (95% CI = 95% confidence interval)

Exposure indicators	Cases	Referents	OR[a]	95% CI[a]
Highest B-Pb				
Whole population				
< 0.8	7	117	1.0	·
0.8—1.3	20	111	3.1*	1.2—8.1
1.4—1.9	14	52	4.2**	1.5—12
2.0—4.3	8	47	2.9	0.9—9.3
≥ 0.8	42	210	3.4**	1.4—8.4
Final population				
< 0.8 (model I)	5	32	1.0[+]	·
0.8—1.3 (model I)	7	31	1.9[+]	0.4—9.0
1.4—4.2 (model I)	8	20	4.7[+]	0.9—25
B-Pb (continuous) (model II)	·	·	4.1*	1.1—15
B-Pb (continuous) (model III)	·	·	3.4	0.9—13
Mean estimated lead level,[b] 0.8—2.7 μmol/l (model IV)	15	41	3.1	0.9—11.1

[a] Conditional logistic regression models. The results of the final population have been adjusted for smoking, and in models III and IV for exposure to engine exhaust and solvents. In models using B-Pb, an adjustment for the year of the first measurement was also done. Natural logarithms of continuous B-Pb were used. The highest observed values of the exposure parameters were used in the labeling of the highest category.
[b] Minimum duration of lead exposure of 10 years and time since the end of exposure less than 10 years.
* P < 0.05, ** P < 0.01, [+] P < 0.01 for the trend.

There was an increase in the OR for squamous-cell carcinoma for elevated B-Pb values even though the OR values did not change much over the different B-Pb levels (table 7). Linear estimation by fitting the natural logarithm of B-Pb values gave a slightly better fit for trend (OR 2.2, P 0.0054) than the usual exponential function. This was partly due to a small difference in the B-Pb values between the cases and referents already at very low B-Pb levels (< 0.8 μmol · l^{-1}). No clear indica-

tion of either a trend or a threshold value was seen when the dichotomous variable was included simultaneously into the model. The distribution of the industries as recorded in the monitoring data did not differ among the squamous-cell carcinoma cases from the whole data.

From among the 49 cases of squamous-cell carcinoma, 38 cases or next-of-kin were available for the mailings. The unadjusted OR for a B-Pb of ≥ 0.8 μmol · l^{-1} was 2.8 (95% CI 1.2—6.7) in this subpopulation. A complete exposure history was obtained for 20 cases (83 referents in the same strata). Eighteen cases had been regular smokers. Controlling for smoking by stratification or adjustment did not explain the risks for lead. Seven cases were assessed as exposed to solvents (OR 1.4, 95% CI 0.4—4.6) and five to engine exhaust (OR 2.7, 95% CI 0.7—10). Table 7 shows some adjusted OR values for squamous-cell carcinoma. Due to a loss of data, the risk estimates may not reflect the independent effects reliably.

OR values for all the other histological groups combined over the three B-Pb categories were 0.9 (95% CI 0.5—1.8), 1.1 (95% CI 0.5—2.3), and 0.6 (0.2—1.7). Histology-specific OR values for a B-Pb of ≥ 0.8 μmol · l^{-1} varied from 0.6 (95% CI 0.1—2.4) for small-cell carcinoma to 0.9 (95% CI 0.3—2.7) for adenocarcinoma, and 1.6 (0.5—4.6) for "other or unspecified" carcinoma. Four of the pleural cancer cases had a B-Pb value exceeding 0.7 μmol · l^{-1}. Excluding pleural cancer from the data did not change the risk estimates for lead. For example, the OR values for the three categories of cumulative lead exposure, as shown in table 4, were 0.8 (95% CI 0.2—3.5), 1.2 (95% CI 0.4—3.0), and 1.5 (95% CI 0.6—3.8) when pleural cancer was excluded. There was no clear difference in the OR for lead among the pleural cancer cases compared with the lung cancer cases, either when the analysis focused on lead exposure at the rather late periods before the end of follow-up.

The histological subtypes of the cases exposed concomitantly to lead and engine exhaust were rather similar to those of the unexposed subjects. Among the 13 exposed cases, six (46%) had squamous-cell carcinoma and three (23%) had "other or unspecified carcinoma." There were 14 (35%) and 7 (17%) observations in these categories, respectively, among the unexposed subjects. These were the two most frequent histologies also among the cases excluded from the final population. No cases of pleural cancer were found in the subcategory of concomitant exposure to lead and engine exhaust.

Discussion

In the cohort analyses, a small excess of total cancer and lung cancer was found among the workers with a B-Pb value exceeding 0.9 μmol · l^{-1}. The highest risks were seen among those whose highest B-Pb values were in the intermediate B-Pb category of 1.0—1.9 μmol · l^{-1}. A subcohort of male workers with B-Pb values of < 1.0 μmol · l^{-1} had a lower than expected incidence of all cancers, and also of lung cancer.

The decrease in the lung cancer and overall cancer incidence in the lowest B-Pb category, as well in the overall mortality category, may indicate a healthy worker effect and other biases (22, 32). For example, it has been shown in a 15-year follow-up that the lung cancer incidence for economically inactive men (including pensioners and those disabled to work) is about 1.6-fold that of working or temporarily unemployed men of the same social class (33). This fact alone would account for about a 9% increase in the expected value when the total male population is used for reference. The other potential biases in the comparison with the rates of the general population are (i) the inclusion of persons in occupations with prevalent carcinogens into the reference category, (ii) the selection of monitoring towards nondiseased workers at the workplaces, and (iii) losses of follow-up among those whose identity could not be traced. The internal comparison overcomes most of these biases.

The study used register-based information on incident cancer cases, and the follow-up focused on a rather recent period. The cancer register data are accurate and virtually complete (34—35). The data have a high sensitivity in the measure of the disease status, and the analysis by histology in the case-referent design provided an opportunity to improve the specificity. If there is any misclassification of the disease (say, a metastatic cancer classified as a primary cancer or histology unknown), it is probably nondifferential (ie, independent of exposure to lead).

The monitoring data provided objective information for the assessment of past exposure. It avoided potential bias due to the subjects' own definitions or differential recall and indicated personal variation in the uptake of lead. B-Pb is a reliable index of exposure because, in long-term exposure, the individual B-Pb levels are stable (36). In our study, the highest personal B-Pb correlated closely with the lifetime mean lead level ($r = 0.8$). A better assessment of occupational lead burden would have been obtained from regular and continuous monitoring at the workplaces. The periodic follow-up measurements were done regularly only in some industries and workplaces. Limitations in indexing tissue burden also have to be recognized. For example, differences in the particle size distribution and in the solubility of the compound can weaken the correlations between the B-Pb value and the tissue burden, particularly for the lung (37).

To reduce the possibility of differential misclassification, we made the lifetime exposure assessments

blinded. However, nondifferential misclassification could not be completely avoided since information on the work history was often crude (especially if the workplace was no longer in operation). In the assessment of potential confounders errors resulting from this situation could not be avoided either. It was thought that a differential recall could be avoided by matching the vital status. However, the risk estimates of lung cancer for coexposure to engine exhaust and lead were slightly higher if only the living referents were used (which would have been the case without matching). One cannot rule out the possibility that there was excess mortality due to some other causes among the exposed referents as well.

The study population in the case-referent study was relatively homogeneous socially and therefore selection bias was reduced in the sampling frame. In the lung cancer study, 96% of the cases and 93% of the referents were industrial workers by their main occupation, including also service and commercial sectors.

According to the personal B-Pb data, selective participation did not cause the increases in the final estimates. In the analysis of squamous-cell carcinoma of the lung, the point estimates for lead were also slightly lower in the final data. Nevertheless, the reduction of the study material widened the confidence limits. We are not able to indicate the reasons for the low response rate. One possibility is that the rate was related to the origin or nature of the disease as perceived by the respondents (21).

Lead exposure in automobile service and repair has been described in several publications (26, 28, 29). The highest lead levels in these jobs are related to car painting, welding, soldering, and shield repair. Even though the workers in this industry are often exposed also to chromates, cadmium, solvents, asbestos, and gasoline, these risk factors did not explain the increase in the risk of lung cancer in multivariate models. This was partly due to the fact that the risk was less increased in those fields in which the concentrations of the potential confounders were usually higher, for example, asbestos exposure in shipyards, plumbing and construction, and exposure to chromates and solvents in painting.

Leaded engine exhaust also contains carcinogenic substances other than lead, for example, polycyclic aromatic hydrocarbons, dichloroethane, dibromoethane, methylbromide, and organobromines or combustion derivatives of these compounds (38). It is unlikely that the components of engine exhaust as such explain the suggested risk. If the exhaust components alone had influenced the risk, then more cases would have been expected to occur independently of a later lead exposure. The rather high risk estimate for the concomitant exposure was an unexpected finding, however, and because of the possibility of nondifferential misclassification for the potential occupational confounders, correlations or synergism with other carcinogenic exposures were also possible.

Small excesses in lung cancer mortality have been reported in four of the five published cohort studies on heavily exposed lead workers (13—16, 19, 39). The results obtained in the present study suggest that the earlier studies underestimated than rather overestimated the true carcinogenic risks caused by lead exposure.

Histology-specific population-based studies have suggested that blue-collar and metal workers have an increased risk of squamous-cell carcinoma and possibly also of small-cell carcinoma of the lung (33, 40—43). A small excess of squamous-cell carcinoma of the lung has also been reported for exposure to lead compounds (44). Squamous-cell carcinoma has been reported to be the most predominant cell type in lung cancer cases with chromate exposure (45—47). An increase in this histological type of lung cancer has also been reported among gasoline-exposed workers (48). Gasoline-exposed subjects were motor transport operators, mechanics and repairmen, as well as persons with occupations in sales and commodities. An increased exposure to lead cannot be ruled out in these occupations either.

The histological pattern of lung cancer in our data suggests that the increases in the risk were not related solely to such confounders as arsenic or asbestos. For these exposures, the most dominant increase in the risk has been reported for adenocarcinoma (2, 49, 50).

There is no firm evidence on the mechanisms for the effects of lead. Interestingly, it has been reported that very low concentrations of lead (> 10 nM) can activate protein kinase C (PKC), purified from rat brain (51). This phenomenon may be of importance for the carcinogenicity of lead because the enzyme is capable of various cocarcinogenic or tumor-promoting effects (3). Several works, both in vitro and in vivo, suggest tumor-promoting effects of the PKC enzyme in human squamous-cell carcinoma (52—55). A PKC-related member of the gene family, PKC-L, has been isolated in lung tissue (56—57). PKC-L is expressed in several human cell lines, including the human squamous-cell carcinoma of the lung.

Concluding remarks

The present study suggests that lead increases the risk of lung cancer. Particularly, coexposure to lead and engine exhaust seems to increase the risk. Limited support was offered for the hypothesis that lead is associated with the risk of squamous-cell carcinoma of the lung. Experimental and cytogenetic studies also suggest carcinogenic effects for lead. The study used data sources that were as reliable as possible both for the outcome and exposure, and it also assessed the lifetime exposure indices. The main problems were concerned with the rather small study size, overall low exposure levels, and the low re-

sponse rate. The use of the monitoring data together with the blinded classification of exposure history reduced the potential biases of differential participation and response, as well as biases of both differential and nondifferential exposure misclassification. Bias or confounding did not explain the increased risks for lead. Future epidemiologic studies on lead should specify the individual exposure history adequately, as well as differentiate the histological types of lung cancer.

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