Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel

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Abstract

***Objective*—To follow up cancer incidence and mortality in a group of Swedish battery workers exposed to nickel hydroxide and cadmium oxide.**

***Methods*—869 workers, employed at least one year between the years 1940 and 1980 were followed up until 1992. Vital status and causes of death were obtained from the Swedish cause of death registry. Cancer morbidity was retrieved from the Swedish cancer registry. Regional reference rates were used to compute the expected numbers of deaths and cancers.**

***Results*—Up to 31 December, 1992, a total of 315 deaths (292 in men and 23 in women) had occurred in the cohort. For men, the overall standardised mortality ratio (SMR) was 106 (95 % confidence interval (95% CI) 93.7 to 118) and for women 83.8 (95 % CI 53.1 to 126). The SMRs for total cancer mortality were 125 (95 % CI 98.2 to 157) for men and 69.5 (95 % CI 25.5 to 151) for women. The SMR for lung cancer in men was 176 (95 % CI 101 to 287). No lung cancers were found among female workers. Up to 31 December, 1991, a total of 118 cancers had occurred in the cohort. A significantly increased standardised incidence ratio (SIR) was found for cancer of the nose and nasal sinuses in men, three cases *v* 0.36 expected, yielding an SIR of 832 (95 % CI 172 to 2430). Applying a 10 year latency period in cohort members exposed to ⩾1000 μg cadmium/m^3, the SIR was 1107 (95 % CI 134 to 4000). Similarly, for cohort members exposed to 2000 μg nickel/m^3, the SIR was 1080 (95 % CI 131 to 3900).**

***Conclusion*—There was an increased overall risk for lung cancer, but no exposure-response relation between cumulative exposure to cadmium or nickel and risk of lung cancer. There was a highly significant increased risk of cancer of the nose and nasal sinuses, which may be caused by exposure to nickel or cadmium or a combination of both exposures.**

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In the 1940s Friberg showed in his pioneering work that occupational exposure to high concentrations of cadmium oxide causes kidney damage and lung disease.[1] Since then, several epidemiological studies have found an increased mortality in workers exposed to cadmium, in particular due to lung diseases.[2–4] It is now well established that exposure to cadmium is a risk factor for diseases of the kidneys and the lungs as well as for increased mortality in lung diseases.[5 6]

The International Agency for Research on Cancer (IARC) concluded in its latest evaluation that there was sufficient evidence to classify cadmium as a human carcinogen,[7] based mainly on the results from studies of United States smelter workers,[8] although there were several constraints influencing the evaluation. The number of workers that have been studied is rather limited and historical data on cadmium exposure are sparse. Potential confounding by smoking is rarely studied and confounding by other exposures, such as nickel or arsenic, is usually not controlled for.

In previous studies of a cohort of Swedish battery workers, we have found increased mortality, mainly in respiratory disease, but also in renal disease.[4] An increased (but not significant) mortality in bladder and prostatic cancer was found in a later follow up.[9] In the most recent follow up (mortality up to 1983) the investigators found increased standardised mortality ratios (SMRs) for cancer of the lung and prostate.[10] Since then, additional employment records have been discovered and the cohort was extended with almost 400 additional workers.

No quantitative exposure information was used in the previous follow up studies and therefore a comprehensive study was designed to assess historical exposures to cadmium oxide and nickel hydroxide in detail. The exposure assessment procedure was completed in 1996 and made it possible to enhance the cohort by computing individual cumulative exposures, combining data on cadmium and nickel concentrations for different periods with employment records for each worker.

The aim of the present study was to extend the cohort to investigate mortality and cancer incidence in the extended and enhanced cohort with new detailed exposure estimates and regional reference data.

Table 1 Distribution of person-years in the Swedish battery worker cohort according to cumulative cadmium exposure and latency

	Cumulative cadmium exposure (μg/m^3×y)			
Latency	*<250*	*250– <1000*	*>1000*	*Total*
<20	6713	6258	2509	15480
⩾20	1655	3390	6538	11583
Total	8369	9648	9047	27063

Methods

The extended cohort comprised 900 (717 male and 183 female) workers employed for at least one year in the nickel-cadmium battery factory between 1931 and 1982. A total of 31 workers (3.4%) were lost to follow up, and thus 869 workers remained for the analyses. At the end of the study period (31 December 1992) the cohort had produced 27 063 person-years at risk. Vital status up to and including 1992 was obtained through computerised search in the national Swedish cause of death registry. Cancer morbidity (up to and including 1991) was assessed by computerised search in the Swedish cancer registry. All causes of death were recoded to the eighth revision of the international classification of diseases (ICD-8).

Various data on past exposure were collected by an occupational hygienist supervised by one of the authors (TB). The collection included examination of employment records and workplace measurement reports as well as interviews with key informants in the factory. A detailed description of the production history was compiled and provided the foundation for a consensus approach in which exposure concentrations were assigned to 23 generic job titles in three periods for cadmium and nickel exposure on two separate categorical scales. Quantitative estimates of breathing zone concentrations of cadmium and nickel for each category of the scales were made from personal and selected fixed point workroom monitoring data covering the period 1946–92. These estimates were linked to the combinations of generic job titles and periods to form a job-exposure matrix, which was applied to the individual work histories. The resulting individual exposure profiles for cadmium and nickel were used for the calculation of estimated cumulative exposures. Average exposure intensity was computed as the cumulative exposure divided by duration. There had been no systematic use of efficient personal respirators and no correction for such use was applied. The distribution of person-years according to cumulative exposure and latency is shown in table 1. The exposure assessment procedure will be presented in detail elsewhere (Bellander *et al*, manuscript in preparation).

In 1989, health data and smoking habits were collected by means of a postal questionnaire sent to living cohort members (n=601) and to the next of kin for deceased workers. The next of kin could be traced for 268 of the 275 dead people (97 %). Of the 869 people, 765 (88%) completed the questionnaire and qualitative smoking data (smoker *v* non-smoker) were obtained for all respondents. Quantitative smoking data were available only for 379 of the 528 smokers (72%) and were not used in the epidemiological analyses.

Standard life table analysis was performed with the OCMAP program.[11] Cause specific SMRs were computed by cumulative exposure category. Standardised incidence ratios were computed for all incident cancers. Person-years were accumulated until date of first cancer diagnosis, date of death, or the end of the study, whichever occurred first.

The previous follow up studies used reference data from the general population from all of Sweden, as regional rates were not available until recently. The battery factory is located in Kalmar county and in the present study, regional death rates as well as cancer inci-

Table 2 Observed numbers of deaths and SMRs in male battery workers (1951–92), regional reference rates, Kalmar county

Cause of death	*Observed cases (n)*	*Expected cases (n)*	*SMR*	*95% CIs*
All causes of death	292	276	106	93.7 to 118
All cancers	75	60.1	125	98.2 to 157
Cancer of the:				
Stomach	8	7.5	107	46.1 to 210
Colon	6	4.7	127	46.5 to 276
Rectum	4	3.2	125	34.1 to 321
Liver	1	1.1	93	2.3 to 516
Pancreas	6	4.0	148	54.5 to 323
Lung	16	9.1	176	101 to 287
Prostate	11	9.0	122	61.1 to 219
Bladder	3	1.7	176	36.4 to 515
Kidney	1	2.5	40	1.0 to 224
Nervous system	2	1.8	115	13.9 to 414
Lymphoma	3	2.2	134	27.5 to 390
Myeloma	2	1.3	156	18.9 to 564
Leukaemia	1	2.5	40	1.0 to 220
Diseases of the nervous system	1	2.9	35	0.9 to 195
Ischaemic heart disease	115	98.7	116	96.2 to 140
Cerebrovascular diseases	19	24.5	78	46.7 to 121
Diseases of the respiratory system	20	15.1	132	80.7 to 204
Diseases of the digestive system	10	9.3	108	51.7 to 198
Diseases of the genitourinary system	5	5.1	98	31.9 to 230
Nephritis and nephrosis	3	2.0	150	31.0 to 439
Violent deaths and poisoning	16	22.2	72	41.1 to 117
Suicide	4	8.1	50	13.5 to 127

Table 3 Observed numbers of deaths and SMRs in female battery workers (1951–92), regional reference rates, Kalmar county

Cause of death	*Observed cases (n)*	*Expected cases (n)*	*SMR*	*95% CIs*
All causes of death	23	27.4	84	53.1 to 126
All cancers	6	8.6	70	25.5 to 151
Cancer of the:				
Stomach	1	0.56	178	4.4 to 991
Pancreas	1	0.45	220	5.5 to 1230
Breast	1	1.6	63	1.6 to 352
Uterus	2	0.62	322	39 to 1160
Ovaries	1	0.76	132	3.3 to 738
Ischaemic heart disease	5	6.6	75	24.5 to 176
Cerebrovascular diseases	4	3.0	134	36.5 to 343
Diseases of the respiratory system	2	1.4	142	17.2 to 515
Diseases of the digestive system	4	0.9	444	121 to 1140
Violent deaths and poisoning	1	1.3	76.3	1.9 to 425

Table 4 Observed numbers of incident cancers and SIRs in male battery workers (1959 to 91), regional reference rates, Kalmar county, no latency period applied

Cancer diagnosis	*Observed cases (n)*	*Expected cases (n)*	*SIR*	*95% CIs*
All cancers	100	96.2	104	84.6 to 127
Cancer of the:				
Lip	1	1.57	64	1.6 to 355
Mouth	2	0.44	457	55.3 to 1650
Pharynx	2	0.62	323	39.1 to 1170
Stomach	9	7.99	113	51.5 to 214
Colon	9	7.09	127	58.0 to 241
Rectum and anus	8	5.45	147	63.4 to 289
Biliary pass and liver	4	1.62	247	67.2 to 631
Pancreas	7	3.60	194	78.1 to 400
Nose and nasal sinuses	3	0.36	832	172 to 2430
Lung	15	8.67	173	96.9 to 285
Prostate	15	19.6	77	42.9 to 127
Kidney	1	3.63	28	0.7 to 154
Urinary organs	5	6.33	79	25.6 to 184
Malignant melanoma	1	2.70	37	0.9 to 206
Skin (not melanoma)	1	3.77	26.5	0.7 to 148
Nervous system	4	3.35	119	32.5 to 306
Connective tissue, muscle	1	0.84	119	3.0 to 665
Unspecified malignancies	2	3.38	59.2	7.2 to 214
Non-Hodgkin's lymphoma	3	2.38	126	26.0 to 368
Multiple myeloma	2	1.42	141	17.0 to 509

Table 5 SMRs for lung cancer (ICD-8 162) in male battery workers in relation to cumulative cadmium exposure and latency

	Cumulative cadmium exposure (μg/m³×y)							
	<250		*250–<1000*		*>1000*		*Total*	
Latency (y)	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*
<20	2	415	1	115	1	380	4	248
⩾20	3	378	3	151	6	128	12	161
Total	5	392*	4	140	7	142	16	176*

*p<0.05.

Table 6 SMRs for non-malignant lung diseases (ICD-8 460–519) in male battery workers in relation to cumulative cadmium exposure

Cumulative cadmium exposure μg/m³×y	*Cases (n)*	*SMR (95% CI)*
<250	3	184 (38 to 536)
250–<1000	7	166 (67 to 343)
⩾1000	10	108 (52 to 198)
Total	20	132 (81 to 204)

Table 7 SMRs for lung cancer (ICD–8 162) in male battery workers in relation to duration and intensity of cadmium exposure

	Duration (y)							
	<5		*5–<10*		*>10*		*Total*	
Mean intensity (μg/m³)	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*
<50	1	518	1	359	7	275*	9	298**
50–<100	1	170	0	—	3	150	4	124
⩾100	0	—	1	389	2	85	3	106
Total	2	202	2	169	12	174	16	176*

*p<0.05; **p<0.01.

Table 8 SMRs for non-malignant lung diseases (ICD–8 460–519) in male battery workers in relation to duration and intensity of cadmium exposure

	Duration (y)							
	<5		*5–<10*		*>10*		*Total*	
Mean intensity (μg/m³)	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*
<50	2	740	0	—	2	55	4	92
50–<100	1	149	3	262	8	226	12	224*
⩾100	0	—	1	279	3	62	4	74
Total	3	261	4	206	13	108	20	132

*p<0.05.

Table 9 Rate ratios (RRs) for lung cancer (ICD–8 162) and non-malignant respiratory diseases (ICD–8 460–519) relative to cumulative cadmium exposure adjusted for age and smoking

	Lung cancer		*Respiratory diseases*	
Cumulative exposure (μg/m³×y)	*RR*	*95% CI*	*RR*	*95% CI*
<250	1.0	—	1.0	—
250–<1000	0.34	0.09 to 1.31	0.67	0.17 to 2.8
⩾1000	0.31	0.09 to 1.05	0.51	0.13 to 2.0

Table 10 SMRs for lung cancer (ICD–8 162) in relation to cumulative nickel exposure and latency

	Cumulative exposure (μg/m³ y)*							
	<250		*250–<3000*		*>3000*		*Total*	
Latency (y)	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*	*n*	*SMR*
<20	1	380	2	183	1	391	4	248
⩾20	2	392	6	201	4	101	12	161
Total	3	388	8	196	5	119	16	176*

*p<0.05.

dences from Kalmar county were used. Rate ratios (RRs) were computed for internal comparisons with Poisson regression as implemented in the EGRET computer software.[12] Person-years by sex, age (five-year intervals), calendar year (five-year intervals), cumulative exposure category, and smoking were computed and used for input to the internal analyses. The exposure category boundaries were chosen aiming at an even distribution of person-years between the categories.

Results

Up to 31 December 1992, a total of 315 deaths (292 in men and 23 in women) had occurred in the cohort. For men the overall SMR was 106 (95% confidence interval (95% CI) 93.7 to 118) and for women 83.8 (95% CI 53.1 to 126). A total of 81 malignant tumours (75 in men and six in women) were registered as the cause of death in the cohort during the follow up period. The SMR for total cancer mortality was 125 (95% CI 98.2 to 157) for men and 69.5 (95% CI 25.5 to 151) for women. The SMRs for the various causes of death are shown in tables 2 (men) and 3 (women).

A total of 118 tumours were found in the cancer registry. Two primary cancers had occurred in five people. The standardised incidence ratios (SIRs) for men are shown in table 4. Only 18 cancers were diagnosed in the women, with a total SIR=100 (95% CI 59 to 158). There were no lung cancers in the group of female workers.

In men, there was a significant increase in risk of cancer of the nose and nasal sinuses, with three cases *v* 0.36 expected, yielding an SIR=832 (95 % CI 172 to 2430). Applying a 10 year latency period for these cases, and looking at cohort members with a cumulative exposure of ⩾1000 μg cadmium/m³×years, the SIR for nose and sinus cancer (n=2) was 1110 (95 % CI 134 to 4000). Similarly, for cohort members exposed to ⩾2000 μg nickel/ m³ the SIR was 1080 (95 % CI 131 to 3900), based on the same two cases.

The subsequent analyses only include men, because of the few deaths and incident cancers that had occurred in women. The SMRs relative to level of cumulative exposure to cadmium and latency were computed for lung cancer and non-malignant respiratory diseases (tables 5 and 6).

The SMRs for lung cancer and non-malignant respiratory diseases, analysed by duration of exposure and average exposure intensity, are shown in tables 7 and 8.

The influence of smoking on the relative risks for lung cancer and non-malignant respiratory diseases was analysed with Poisson regression (table 9). When cumulative exposure and age were included in the regression equation there was a negative exposure-response relation similar to the trend shown in table 5. Adding smoking to the regression equation changed the relative risks only marginally.

Similar findings were obtained for exposure to nickel and the risk of lung cancer as shown in table 10.

Discussion

Firstly, our present findings are related to previous follow up studies of the cohort. Secondly, the results are discussed in the light of other recently published studies of similar exposures. In particular, the results on risk of lung cancer are examined. Thirdly, the impact of the present findings are discussed.

The overall SMR for men of 106 is, although not significant, higher than expected. Usually, the SMR is lower in occupational cohorts due to the healthy worker effect. The main reasons for the increased SMR are the increased risk of lung cancer (n=16, SMR=176) and the risk of ischaemic heart disease (n=115, SMR=116). The risk of lung cancer will be further explored here, whereas ischaemic heart disease will be discussed elsewhere.

No further deaths from nephritis and nephrosis have occurred since the follow up up to 1980. It should be noted, however, that these diagnoses are unusual causes of death. People with severe kidney damage may have been diagnosed with other causes of death. Another possible explanation is that the improvements in the work environment with decreasing exposure to cadmium oxide have reduced the risk of developing fatal renal diseases.

Previous studies of the cohort only included men. The present study found a lower SMR for women (SMR=84) than for men (SMR=106). Few cohorts of female workers have been studied, but one report from Iceland and a later report from the United States show similar pronounced healthy worker effects among female workers.[13 14] However, a recent Danish study of female workers exposed to cobalt does not show any healthy worker effect.[15] The United States study showed higher than expected mortality for diseases of the digestive system, especially ulcers, among service employees.[14] There was, however, only one ulcer among the four cases of digestive disease in the present study. The other three diagnoses were ulcerative colitis, pancreatitis, and cholelithiasis. The increased SMR for diseases of the digestive systems among the female workers is thus most likely to be a chance finding.

The previous follow up studies only investigated mortality. The cancer incidence findings in the present study generally confirm the results from the mortality analyses. Only one of the three cases of cancer of the nose and nasal sinuses were, however, found in the cause of death registry. The cancer incidence analyses showed remarkably high SIRs, indicating an eightfold to 10-fold increase in risk. Some previous studies in nickel refinery workers have indicated similar large relative risks,[16 17] whereas a study of workers exposed to nickel powder did not detect any increased risk of nasal sinus cancer.[18] Although there are only three cases of nasal sinus cancer in the present study, the increased risk is significant. Because of the concomitant exposure to cadmium and nickel, either or both exposures may be causal agents.

The increase in cancers of the mouth and pharynx should also be noted, although not significant. Similar increased risks have been reported in other studies of workers exposed to nickel powder[18] and solvents containing nickel.[19]

In previous studies of the cohort there was an increased relative risk of lung cancer (SMR=133; applying a 20 year latency period and >5 years of exposure SMR=175). Only workers <80 years of age were included in the analyses. The present study is not directly comparable as the cohort has been extended and no age limit was applied. However, no deaths from lung cancer occurred after the age of 80 in the present follow up. It should be noted that 16 cases of lung cancer appeared in the cause of death registry, but only 15 in the cancer registry, which is explained by the known difference (about 10%) between these registries.

In the present study there is an increased risk of lung cancer among the nickel-cadmium battery workers, but there is no increase in SMR with increasing cumulative exposure. Similar results have been reported in two recent follow up studies of the cohorts in the United Kingdom and the United States. In a recent study of workers exposed to cadmium in the United Kingdom, the relative risks were 0.85 for the middle exposure category (1600 to 4799 $\mu g/m^3 \times$years) and 0.81 for the highest exposure category ($\geq$4800 $\mu g/m^3 \times$years), when compared with the lowest exposure group.[20]

A recent reanalysis of a United States cohort included data on arsenic exposure.[21] The investigators found an exposure-response relation between cumulative exposure to cadmium and risk of lung cancer, adjusting for age, year of hire, and Hispanic ethnicity. The relative risks versus a risk of 1.0 for the reference category (<400 $mg/m^3 \times$days $\cong$ 1100 $\mu g/m^3 \times$years) were 2.30 in the second lowest exposure category (400–999 $mg/m^3 \times$days $\cong$ 1100–2700 $\mu g/m^3 \times$years), 2.83 in the second highest category (999–1999 $mg/m^3 \times$days $\cong$ 2700–5500 $\mu g/m^3 \times$years) and 3.88 in the highest exposure category ($\geq$ 2000 $mg/m^3 \times$days $\cong$ 5500 $\mu g/m^3 \times$years). In a separate analysis they examined the independent effects of cadmium exposure received in the presence of arsenic trioxide and cadmium exposure without concomitant exposure to arsenic. A significant trend for risk of lung cancer was found only for the combined exposure to arsenic and cadmium.

The highest category of cumulative exposure to cadmium in the present study was 1000 $\mu g/m^3 \times$years. Only one case was exposed to >5500 $\mu g/m^3 \times$years. Thus, the cumulative exposures were lower in the present study than in the United Kingdom and United States cohorts. It is noteworthy, however, that the increased risk found in the United States cohort seemed to be at lower cadmium exposures than in the United Kingdom cohort, in which no increased risks were found. The results in the present study are in accordance with the findings in the United Kingdom cohort.

The United Kingdom report[20] showed an exposure-response relation between exposure to cadmium fume and the mortality from non-

malignant respiratory disease, whereas the present study did not detect any such relation for exposure to cadmium oxide. On the contrary, there was an indication of a negative trend, which persisted after adjustment for smoking. There was a slight increase in the overall relative risk, however, (SMR 132 (95% CI 81 to 204)). Only four deaths due to respiratory diseases occurred between 1951 (when the cause of death registry started) and 1975, whereas the early report by Kjellström *et al*[4] reported eight deaths from respiratory diseases between 1949 and 1975, diagnosed directly from death certificates. The early heavy exposure to cadmium oxide dust may thus explain the increased relative risk found by Kjellström *et al*.

The present study includes more exposed workers than previous follow up studies of the same cohort, which would improve the study power. We also performed a detailed exposure assessment, which should decrease the misclassification that most likely occurred in the previous follow up studies. The exposure assessment procedure showed that there were no known confounders—for example, arsenic—present in the work environment of the battery plant. Furthermore, regional death rates and cancer incidences were applied instead of the national rates used in the previous follow up mortality studies.

Despite these improvements in study design, the present study shows neither positive exposure-response relations for lung cancer, nor for non-malignant respiratory diseases. The evidence for cadmium as a lung carcinogen is thus weakening, when the results from the present study are added to other recent, similar findings.[20 21]

The comparatively high relative risks for lung cancer, as well as non-malignant respiratory disease, in workers with the lowest cumulative exposures and short duration of exposure, are most likely explained by exposures to carcinogens in other industries.[22] For example, some of the battery workers worked periodically at a neighbouring shipyard, which had the same owners as the battery plant. For most workers, however, a detailed work history outside the battery plant is not known. Another explanation for the negative exposure-response relation may be the so called healthy worker survivor effect,[23] resulting from a premature selection of unhealthy workers out of the work force. A carcinogenic effect of cadmium on the lung cannot therefore be ruled out.

At an international symposium some years ago, Sir Richard Doll concluded that the possibility that cadmium may cause lung cancer by inhalation could neither be excluded nor affirmed.[24] The present findings indicate that this statement is still valid.

Conclusion

There was an overall increased risk of lung cancer, but no exposure-response relation between cumulative exposure to cadmium and risk of lung cancer. There was a highly significant increased risk of cancer of the nose and nasal sinuses, which may be caused by exposure to nickel or cadmium or a combination of both exposures.

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