Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946–92

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Abstract

Objectives—To identify and quantify any relations between occupational exposure to cadmium oxide fume and mortalities from lung cancer and from chronic non-malignant diseases of the respiratory system.

Methods—The mortality experience of 347 copper cadmium alloy workers, 624 workers employed in the vicinity of copper cadmium alloy work (vicinity workers), and 521 iron and brass foundry workers (all men) was investigated for the period 1946–92. All subjects were first employed in these types of work in the period 1922–78 and for a minimum period of one year at one of two participating factories. Two analytical approaches were used, indirect standardisation and Poisson regression.

Results—Compared with the general population of England and Wales, mortality from lung cancer among copper cadmium alloy workers was close to expectation (observed deaths 18, expected deaths 17·8, standardised mortality ratio (SMR) 101, 95% confidence interval (95% CI) 60 to 159). A significant excess was shown for lung cancer among vicinity workers but not among iron and brass foundry workers (vicinity workers: observed 55, expected 34·3, SMR 160, 95% CI 121 to 209, P < 0·01; iron and brass foundry workers: observed 19, expected 17·8, SMR 107, 95% CI 64 to 167). Increased SMRs for non-malignant diseases of the respiratory system were shown for each of the three groups (alloy workers: observed 54, expected 23·5, SMR 230, 95% CI 172 to 300, P < 0·001; vicinity workers: observed 71, expected 43·0, SMR 165, 95% CI 129 to 208, P < 0·001; iron and brass foundry workers: observed 34, expected 17·1, SMR 199, 95% CI 137 to 278, P < 0·01). Work histories of the copper cadmium alloy workers were combined with independent assessments of cadmium exposures over time to develop individual estimates of cumulative exposure to cadmium; this being a time dependent variable. Poisson regression was used to investigate risks of lung cancer and risks of chronic non-malignant diseases of the respiratory system in relation to three levels of cumulative cadmium exposure (< 1600, 1600–4799, ≥ 4800 $\mu g.m^{-3}.y$). After adjustment for age, year of starting alloy work, factory, and time from starting alloy work, there was a significant positive trend (P < 0·01) between cumulative exposure to cadmium and risks of mortality from chronic non-malignant diseases of the respiratory system. Relative to a risk of unity for the lowest exposure category, risks were 4·54 (95% CI 1·96 to 10·51) for the middle exposure category and 4·74 (95% CI 1·81 to 12·43) for the highest exposure category. There was a non-significant negative trend between cumulative cadmium exposure and risks of mortality from lung cancer. Relative to a risk of unity for the lowest exposure category, risks were 0·85 (95% CI 0·27 to 2·68) for the middle exposure category and 0·81 (95% CI 0·18 to 3·73) for the highest exposure category. Similar findings were obtained when adjustment was made for age only.

Conclusions—The findings are consistent with the hypothesis that exposure to cadmium oxide fume increases risks of mortality from chronic non-malignant diseases of the respiratory system. The findings do not support the hypothesis that exposure to cadmium oxide fume increases risks of mortality for lung cancer.

In 1953, a health survey of copper cadmium alloy workers from two factories (A and B) was carried out by Bonnell under the auspices of the Medical Research Council (MRC); findings relating to emphysema and proteinuria were reported in 1955.[1] Of the 100 alloy workers examined, nine had emphysema and proteinuria, three had emphysema without proteinuria, and seven had proteinuria without emphysema. One hundred and four employees who had never had any work contact with copper cadmium alloy had been examined as a control group; only one case of proteinuria and one case of emphysema were diagnosed. A further group of 151 vicinity workers from factory B were examined. Vicinity workers, although employed in a workshop in which copper cadmium alloys were being made, were employed in the refining of copper and the manufacture of arsenical copper, phosphor bronze, and other copper alloys. Bonnell[1] reported "there were no cases in this group in whom the findings were consistent with the diagnosis of chronic cadmium poisoning." Chronic

cadmium poisoning referred to proteinuria or emphysema induced by cadmium. In 1957, a follow up study produced diagnoses of proteinuria or emphysema in a further 24 men from the original group of 100 workers of copper cadmium alloy.[2]

Holden published two short reports, which included information on the mortality of men employed for at least 12 months as copper cadmium alloy workers at either of the two factories; follow up was to the end of 1979.[3 4] A more detailed analysis has now been carried out that includes the analysis of deaths occurring in a further 13 years of follow up. Particular emphasis is given to findings for lung cancer because of the recent evaluation by an international agency for research on cancer (IARC) Working Group that there was sufficient evidence in humans for the carcinogenicity of cadmium and cadmium compounds.[5] (This evaluation seemed to rely heavily on the significant relations between risks of lung cancer and estimated cumulative exposure to cadmium reported by Thun et al[6] and Stayner et al[7] in their analyses of mortality among a cohort of workers from a single United States cadmium recovery plant. Sorahan and Lancashire[8] have recently highlighted potentially serious problems with the data analysed by these investigators.) Emphasis is also given to findings for chronic non-malignant diseases of the respiratory system because earlier studies of health effects in this workforce found evidence of increased risks of these diseases.[1-4 9]

Materials and methods

STUDY POPULATION

The study cohort comprised 168 copper cadmium alloy workers from factory A, 179 copper cadmium alloy workers from factory B, 624 vicinity workers from factory B, and 521 iron and brass foundry workers from factory B. All of them were men. All employees worked for a minimum period of 12 months in these job categories and started the selected occupations in the period 1922–78. Ninety eight of the alloy workers who participated in the 1953 MRC survey are included in the study cohort; the remaining two workers were later judged not to have had 12 months employment as copper cadmium alloy workers. The iron and brass foundry workers were described by

Holden as a control group[4]; 16 members of Holden's original control group have now been excluded because they started employment in the foundry before 1922.

The study populations had been abstracted by Holden from much larger sets of personnel records; the selected occupations represented only a small percentage of the total workforce at the two factories (personal communication, D O'Malley). Incomplete information on job histories were available from centralised personnel records at factory A; at factory B, starter and leaver books for the relevant departments were reviewed. (These books recorded, in chronological order, names of employees with dates of starting and leaving work in a given department.) Information obtained from these sources had been augmented by information obtained from company medical records, foremen, and long serving employees to identify those workers employed directly on the manufacture of copper cadmium alloys and those workers employed in the workshop that housed the copper cadmium process but who were never employed directly on the manufacture of copper cadmium alloys (vicinity workers). The final survey cards included information on job titles and dates carried out, dates of starting work on copper cadmium alloy and duration of alloy work.

Survey cards for all members of the cohort had been sent to the Office of Population Censuses and Surveys (OPCS);[3 4] the OPCS continues to supply the principal investigator with copies of death certificates coded to the 8th revision of the international classification of disease (ICD-8) for those members of the study cohort who are dead together with embarkation details for those who have left the country. The study records have passed through several hands since the early reports[3 4] and for the purpose of this analysis all relevant information held by OPCS was double checked with the vital status as recorded in the study computer file. A few errors were identified in the computer file and these were corrected.

Table 1 shows the vital status of the study population on the closing date of the study, 31 December 1992. Vital status was unknown for only 1·7% of the total cohort although tracing was not as successful for alloy workers from factory A (6·5% untraced). It was not possible to obtain a copy of the death certificate for three of the deaths; these deaths appear only in tables of mortality from all causes.

Table 1 also shows the study population, and its four constituent subcohorts, by year of starting employment in the selected occupations. For the alloy workers and brass and iron foundry workers, this date refers to the date of starting alloy work or brass and iron foundry work, respectively. For the vicinity workers, this date refers to the date of starting employment in the vicinity of copper cadmium alloy manufacture. A study subject from factory B could, for example, have worked with arsenical copper from 1935 but only became a vicinity worker in 1940, when the manufacture of copper cadmium alloys was moved into the

Table 1 Study population by vital status at closing date of survey* and by year of start of employment

	Factory A workers	Factory B workers			
	Alloy	Alloy	Vicinity workers	Brass and iron foundry	Total
Traced alive	29	72	192	321	614
Dead	127	102	408	188	825
Emigrated	1	3	14	9	27
No trace	11	2	10	3	26
Total	168	179	624	521	1492
Year of start of employment					
1922–40†	134	39	0	56	229
1940–62‡	30	101	624	328	1083
1962–78§	4	39	0	137	180
Total	168	179	624	521	1492

*31 December 1992; †1 January 1922–31 July 1940; ‡1 August 1940–31 March 1962; §1 April 1962–31 December 1978.

same workshop (see next section). By definition, all vicinity workers started this type of employment in the period 1940–62 (see next section). Most of the copper cadmium alloy workers from factory A started alloy work in the period 1922–40; most of the copper cadmium alloy workers from factory B started alloy work in the period 1940–62.

FACTORY PROCESSES
Factory A

Production of copper cadmium alloy began on a small scale in 1922. In 1935, production was moved to another site about three miles away. The new shop was 55 m × 18 m × 9 m high and held five banks of six small coke fired pit furnaces. Eight of the 30 furnaces were used to cast copper cadmium alloys; the others were used to cast brass, bronze, phosphor bronze, and other copper alloys.

In the early years, the master alloy was made by melting cadmium in a crucible and adding copper to make a 2:1 copper cadmium mixture. After manual stirring, the mixture was cast into blocks and the final low cadmium content alloy (about 1% cadmium) was made by adding blocks of the master alloy to molten copper and stirring. The crucibles containing the final alloy were lifted by crane and their contents emptied into a large foundry ladle. The alloy was then poured into oil-dressed moulds measuring some 2·7 m × 1·8 m. There was no exhaust extraction; ventilation was supplied by side doors and by two small fans in the roof. Wartime blackout made conditions (in both factories) much worse. The mould would be filled four or five times in a working day. The casting of the master alloy was carried out by one man at the end of the shift.

Around 1952, the open furnaces were replaced by an electric rocker resistor furnace fitted with extraction equipment. The working arrangements of the improved shop were described (with accompanying diagram) by King in 1955.[10] At one end of the shop there was a series of coke fired pit furnaces, one of which was used to make the master alloy. In the middle of the shop there were induction furnaces that were used to manufacture brass and bronze, and at the other end of the shop there was the new rocker furnace used to make the final copper cadmium alloys. Some time later the mixture of the master alloy was changed to equal quantities of copper and cadmium, and the copper was melted first. Production of copper cadmium alloys ended in 1966.

Factory B

Production of copper cadmium alloys began in 1926 in room 128. The shop measured 27 m × 11 m × 4 m high and contained three 350 lb coke fired hand tilting furnaces and six 120 lb pit furnaces. Initially the shop was ventilated only by side doors and a roof louvre. In 1930, a fan was added to the gable wall. The furnaces were linked to a main flue during melting, but because the addition of cadmium and mixing were carried out manually, the extraction

hoods were often pushed aside by men standing on raised platforms to carry out these tasks. A crane to lift the crucibles containing the molten alloy was introduced around 1930. In 1936, production of the final alloy was moved to a larger room (room 278) measuring 56 m × 17 m × 8 m high, but production of the master alloy remained in room 128.

In August 1940, final alloy production was moved to the west end of the main casting bay of the copper refinery and master alloy production was moved to room 278. The copper refinery was a much larger shop measuring 134 m × 55 m × 10 m high and contained three large copper refining furnaces and two casting wheels in the main body of the building. Arsenical copper, bronze, phosphor bronze, and silver bronze were cast in the central area of this workshop. At the west end (some 60–80 m away), the workers of copper cadmium alloy operated seven oil fired hand tilting furnaces. In 1941, fans were installed in the roof and an extraction unit was placed on the furnaces in 1954. In 1957, an enclosed casting box was installed in room 278 for master alloy production.

In April 1962, production of master and final alloys was moved to room 311 (46 m × 19 m × 7 m high). This contained a single 400 lb furnace for master alloy production and 13 oil fired Morgan tilting furnaces (each 600 lb) for final alloy production; other alloys were not produced in this room. In 1969, nine Morgan furnaces were replaced with five 2000 lb electric Ajax furnaces; master alloy production continued in a Morgan furnace. More powerful extraction equipment was added in 1981 and the process remained largely unchanged until the factory ended production of copper cadmium alloys in 1989.

ESTIMATION OF CUMULATIVE CADMIUM EXPOSURES

As part of a study into inhalation of cadmium fume and emphysema among copper cadmium alloy workers at factory B, Davison *et al* reviewed 933 measurements of airborne cadmium made between 1951 and 1983 (697 with static samplers and 236 with personal samplers).[9] Cadmium exposures were estimated "by consideration of all available measurements, changes in production techniques, ventilation, and levels of production and from discussions with the occupational health physician, industrial hygienist, the management, and the work force." Table 2 shows the final exposure assessments, which have been used to estimate individual cumulative exposures to cadmium as a time dependent variable. The cumulative exposure for each man who worked with copper cadmium alloy was calculated as the sum of the estimated exposures to cadmium during each year (or proportion, if part of a year) worked with copper cadmium alloy in the period 1922–80, expressed in $\mu g.m^{-3}.y$. The exposure matrix relating to factory B (table 2) was also used to estimate cumulative exposures to cadmium for the alloy workers from factory A. Similar estimates were not available for vicinity workers, but static

Table 2 Estimated exposure to cadmium[9]

Year	Cadmium ($\mu g.m^{-3}$)
1926–30	600
1931–35	480
1936–42	360
1943–46	270
1947–54	240
1955–62	210
1963–72	156
1973	85
1974	58
1975	43
1976	44
1977	48
1978	49
1979	58
1980	56

sampling results reported by King in 1955 are consistent with vicinity workers having about 10% of the cadmium exposures received by alloy workers (alloy section: mean exposure to cadmium 69·6 μg.m^{-3}, n = 25; vicinity workers: mean cadmium exposures 6·16 μg.m^{-3}, n = 26).

EXTERNAL STANDARD

The mortality experience of this cohort was compared with that which might have been expected to occur if mortalities for the general population of England and Wales had been operating on the study cohort, with due regard to the composition of the study cohort by age (five-year age groups), sex (men only), and calendar year (five-year calendar periods).

Expectations based on person-years at risk were calculated with the PERSONYEARS computer program.[11] Men entered the person-years at risk at the end of the first year of relevant employment or 1 January 1946, whichever was the later. (For analysis of mortality among members of the 1953 MRC survey, men entered the person-years at risk on 1 January 1954.) Men left the person-years at risk on the date of death, date of embarkation, date last known alive, or the closing date of the study (31 December 1992), whichever was the earlier. Men were censored on reaching their 85th birthday—that is, they made no further contributions to expected or observed numbers past this age. The rationale for this procedure has been supplied previously.[12]

Standardised mortality ratios (SMRs) were calculated as the ratio of observed to expected numbers of deaths expressed as a percentage. In calculating P values and confidence intervals (CIs), it has been assumed that deaths occur as a Poisson process. Where significance tests have been carried out, two tailed tests were used.

INTERNAL STANDARD: POISSON REGRESSION

Five variables were considered to have the potential for influencing mortality within the cohort: age (age at follow up or age at death), year of starting alloy work, factory, time from starting alloy work, and estimated cumulative exposure to cadmium. These variables were not treated as continuous, but rather each variable was categorised into a number of levels. In constructing the models, it was necessary to ensure that there was at least one death observed at each level of each variable. Any adjustments were made before any statistical modelling was carried out. Age, time from starting alloy work, and estimated cumulative exposure to cadmium are time dependent variables and the analysis allowed, therefore, for subjects to contribute person-years at risk to contemporaneous categories.

It had been intended to use the cut off values selected by Thun et al[6] for the categories of cumulative exposure to cadmium (working lifetime (40 y) at a time weighted average (TWA) of 40 μg.m^{-3} (1600 μg.m^{-3}.y or 584·4 mg.m^{-3}.days) and working lifetime at 200 μg.m^{-3} (8000 μg.m^{-3}.y or 2922 mg.m^{-3}.days)). The use of these values would have placed a relatively small percentage (8%) of observed deaths in the highest dose category so the higher of the two cut off values was reduced to 4800 μg.m^{-3}.y (1753·2 mg.m^{-3}.days). Analyses were also carried out with exposures lagged by 10 years—that is, exposures were assumed to have no effect until 10 years had elapsed. This procedure was accomplished by adding 10 years to the dates of transition from one exposure category to another. (Thus a worker who accumulated 1600 μg.m^{-3}.y of cadmium exposure on 10 January 1951, would not accumulate this amount of lagged exposure until 10 January 1961.)

The EPICURE[13] computer program was used to provide both person-years at risk and numbers of deaths for causes of interest for all combinations of all levels of the above variables and to carry out statistical modelling by means of Poisson regression.[14] The purpose of the modelling was to establish whether the mortality experienced by the study cohort, and in particular the mortality experienced by the different cumulative exposure groups, could be described easily in terms of variables such as age and factory (covariates), or whether the inclusion of cumulative exposure to cadmium made a significant contribution to the ability of the overall model to describe the data. The significance of this contribution was assessed by the likelihood ratio test that compared deviance and degrees of freedom with and without inclusion of the cumulative cadmium exposure variable. Also, the significance of any trend in risk across the three exposure categories was assessed by repeating the analysis while treating cumulative exposure as a continuous variable coded 1, 2, or 3 for the three levels of exposure.

Table 3   Copper cadmium alloy workers (n = 347): cancer mortality and mortality from other causes, 1946–92

Cause of death	ICD-8	Obs	Exp	SMR (95% CI)
Cancer: †				
Mouth	143–145	1	0·14	724 (18 to 4033)
Oesophagus	150	0	1·31	0 (0 to 282)
Stomach	151	5	5·13	97 (32 to 227)
Large intestine	153	5	2·87	174 (57 to 407)
Rectum	154	2	2·13	94 (11 to 339)
Pancreas	157	4	1·84	218 (59 to 558)
Lung	162–163	18	17·84	101 (60 to 159)
Prostate	185	2	2·83	71 (9 to 255)
Bladder	188	3	1·80	167 (34 to 487)
Other urinary	189	2	0·74	272 (33 to 983)
Brain	191–192	1	0·82	121 (3 to 677)
Lymphoma	200, 202	2	0·68	293 (35 to 1058)
Hodgkin's	201	1	0·28	362 (9 to 2018)
Leukaemia	204–207	2	0·96	209 (25 to 756)
All neoplasms	140–239	52	44·94	116 (86 to 152)
Non-cancers:				
Circulatory system	398–458	88	85·31	103 (83 to 127)
Respiratory system	460–519,866‡	54	23·52	230*** (172 to 300)
Digestive system	520–577	9	4·81	187 (86 to 355)
Genitourinary system	580–629	3	2·74	110 (23 to 320)
Accidents	800–949§	2	3·69	54 (7 to 196)
Suicide	950–959	1	1·70	59 (1 to 328)
All causes	1–999	217	175·64	124** (108 to 141)

** P < 0·01; ***P < 0·001; †Sites of cancer for which there were no observed deaths and for which the expectation was less than 1·0 are not shown in the table. ICD-8 codes (and expectations) were as follows: 140–141 (0·19), 142 (0·06), 146–149 (0·30), 152 (0·08), 155 (0·03), 158–159 (0·18), 160 (0·09), 161 (0·45), 172–173 (0·33), 174 (0·06), 186 (0·09),193 (0·08), 203 (0·44); ‡ see text; § excluding 866 (see text).

Results

EXTERNAL STANDARD

Table 3 shows observed and expected numbers of deaths both for cancer by site and for broad groupings of non-cancers; results relate to

Table 4 Mortality of occupational groups from lung cancer and non-malignant diseases of the respiratory system, by time from starting employment, 1946-92

Time from starting employment (y)	Alloy workers			Vicinity workers			Brass and iron foundry workers		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
Cancer of lung†:									
1-9	1	0·6	182	5	2·2	230	2	1·0	210
10-19	4	2·4	167	5	6·2	80	1	2·8	35
20-29	4	4·5	90	21	10·4	202**	5	5·1	99
30-39	4	5·4	74	19	10·4	183*	6	4·9	122
≥40	5	5·1	99	5	5·1	97	5	4·1	122
Total	18	17·8	101	55	34·3	160**	19	17·8	107
Diseases of respiratory system (non-malignant)‡:									
1-9	2	0·7	282	4	3·0	133	1	1·1	93
10-19	7	3·2	218	13	7·7	168	5	2·5	203
20-29	17	5·6	301**	25	12·7	196**	7	4·6	152
30-39	13	3·6	206**	16	12·7	126	16	4·7	339***
≥40	15	7·7	196**	13	6·8	191*	5	4·3	118
Total	54	23·5	230***	71	43·0	165***	34	17·1	199**

* P < 0·05; ** P < 0·01; *** P < 0·001; † ICD 8th: 162-163; ‡ ICD 8th: 460-519 and 866.

Table 5 Mortality of occupational groups from all causes, lung cancer, and non-malignant diseases of the respiratory system by entry cohort, 1946-92

Subgroup	Factory	1922-40†			1940-62‡			1962-78§		
		Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
All causes:										
Copper cadmium alloy	A	97	84·8	114	20	18·5	108	1	0·7	142
Copper cadmium alloy	B	31	22·5	138	62	45·2	137*	6	4·0	150
Vicinity workers	B	—	—	—	391	328·9	119***	—	—	—
Brass and iron foundry	B	36	36·1	100	129	110·9	116	22	16·8	131
Cancer of lung¶:										
Copper cadmium alloy	A	2	8·3	24(*)	1	1·9	52	0	0·1	0
Copper cadmium alloy	B	4	2·2	181	9	5·0	181	2	0·4	490
Vicinity workers	B	—	—	—	55	34·3	160**	—	—	—
Brass and iron foundry	B	3	3·8	78	13	12·2	106	3	1·8	169
Diseases of respiratory system (non-malignant)‖:										
Copper cadmium alloy	A	26	12·4	210**	4	2·4	167	0	0·1	0
Copper cadmium alloy	B	9	3·2	283*	13	5·3	247**	2	0·2	826
Vicinity workers	B	—	—	—	71	43·0	165***	—	—	—
Brass and iron foundry	B	8	4·6	173	24	11·3	213**	2	1·2	163
All causes other than lung cancer and non-malignant diseases of respiratory system:										
Copper cadmium alloy	A	69	64·1	108	15	14·2	106	1	0·6	179
Copper cadmium alloy	B	18	17·1	105	40	34·9	115	2	3·4	59
Vicinity workers	B	—	—	—	265	251·6	105	—	—	—
Brass and iron foundry	B	25	27·7	90	92	87·4	105	17	13·8	123

* P < 0·05; ** P < 0·01; *** P < 0·001; ( ) indicates deficit; †1 January 1922-31 July 1940; ‡1 August 1940-31 March 1962; §1 April 1962-31 December 1978; ¶ICD 8th: 162-163; ‖ICD 8th: 460-519, and 866.

copper cadmium alloy workers from the two factories combined. Compared with the general population of England and Wales, there were significant excesses of non-malignant diseases of the respiratory system (observed deaths 54, expected 23·52, SMR 230, 95% CI 172 to 300, P < 0·001) and for mortality from all causes (observed 217, expected 175·64, SMR 124, 95% CI 108 to 141, P < 0·01). There was no significant excess for all causes excluding non-malignant diseases of the respiratory system (observed 163, expected 152·12, SMR 107, 95% CI 93 to 126). Observed and expected numbers of deaths from non-malignant diseases of the respiratory system included findings for ICD-8 E866 (accidental poisoning by heavy metals and their fumes). A total of 20 deaths were classified under this rubric; 17 of these death certificates indicated that death was due to chronic non-malignant disease of the respiratory system caused by chronic cadmium poisoning. Findings for cancer of the lung (observed 18, expected 17·84, SMR 101, 95% CI 60 to 159) and cancer of

the prostate (observed two, expected 2·83, SMR 71, 95% CI nine to 255) were unexceptional.

Table 4 shows observed and expected numbers of deaths from lung cancer and non-malignant diseases of the respiratory system by successive 10-year periods from first employment in the selected occupations; results are shown for copper cadmium alloy workers, vicinity workers, and brass and iron foundry workers. For lung cancer, a significant overall excess is shown for vicinity workers only. There are notable excesses in later periods of follow up, 20-39 years from starting local work. For non-malignant diseases of the respiratory system, significant overall excesses are shown for all three sub-cohorts. For earlier (< 20 years) and later (≥ 20 years) periods of follow up the SMRs were similar.

Table 5 shows observed and expected numbers of deaths for all causes, lung cancer, non-malignant diseases of the respiratory system and a large remainder category (all causes other than lung cancer and non-malignant dis-

Table 6   Mortality in participants of the 1953 MRC study into men casting copper cadmium alloys, 1954–92

Group in 1953 survey†		Factory	Obs	Exp	SMR (95%CI)
All causes:					
1A	alloy workers	A	48	38·4	125 (92 to 166)
1B	alloy workers	B	31	20·0	153* (105 to 220)
II	vicinity workers	B	167	143·8	116 (99 to 135)
CB	control group	B	21	28·1	75 (46 to 114)
Cancer of lung‡:					
1A	alloy workers	A	1	4·0	25 (1 to 141)
1B	alloy workers	B	3	2·2	135 (28 to 396)
II	vicinity workers	B	21	15·3	137 (85 to 210)
CB	control group	B	0	2·9	0 (0 to 126)
Diseases of the respiratory system (non-malignant)§:					
1A	alloy workers	A	14	5·7	245** (134 to 411)
1B	alloy workers	B	9	2·4	368** (168 to 699)
II	vicinity workers	B	32	19·5	164* (112 to 231)
CB	control group	B	2	3·7	54 (6 to 194)
All causes other than lung cancer and non-malignant disease of respiratory system:					
1A	alloy workers	A	33	28·7	115 (79 to 161)
1B	alloy workers	B	19	15·4	123 (74 to 193)
II	vicinity workers	B	114	109·0	105 (86 to 126)
CB	control group	B	19	21·5	88 (53 to 138)

* P < 0·05, ** P < 0·01; †See reference[1] for description of groups 1A, 1B, etc. All 58 members of the original group 1A were identified, all 42 members of the original group 1B were identified, and 42 members of the original group CB were identified. Membership of the original group II was "over identified" (see text); ‡ICD 8th: 162–163; §ICD 8th: 460–519, and 866.

eases of the respiratory system) by year of starting employment for each of the four subcohorts. Alloy workers from factories A and B have, overall, similarly increased SMRs for non- malignant diseases of the respiratory system (factory A: observed 30, expected 14·8, SMR 202, 95% CI 136 to 289, P < 0·001; factory B: observed 24, expected 8·7, SMR 276, 95% CI 177 to 410, P < 0·001) and similarly unincreased SMRs for the category all causes other than lung cancer and non-malignant diseases of the respiratory system (factory A: observed 85, expected 78·9, SMR 108, 95% CI 86 to 133; factory B: observed 60, expected 55·4, SMR 108, 95% CI 83 to 139). A similar pattern is shown for each of the three entry cohorts, albeit these comparisons are based on relatively small numbers. The alloy workers from factories A and B have, however, very different overall SMRs for lung cancer (factory A: observed three, expected 10·3, SMR 29, 95% CI 6 to 86, P<0·05; factory B: observed 15, expected 7·6, SMR 198, 95% CI 111 to 325, P < 0·05). A similar pattern is also shown for each of the three entry cohorts. The SMRs for lung cancer among alloy workers from factory A for the calendar year periods 1946–80 and 1981–92 were 25 (based on two deaths) and 42 (based on one death), respectively (not shown in table).

Table 6 shows observed and expected numbers of deaths for four different cause groups of the participants of the 1953 MRC survey. It was not possible to identify the members of the control group from factory A in the 1953 survey. The 1955 paper by Bonnell indicated that 151 vicinity workers were examined in the 1953 survey.[1] The record cards for the mortality study, however, indicated that 237 employees were members of the original group of vicinity workers, and it is this group that is described in table 6. The alloy workers (both factories combined) have a notable excess mortality from non-malignant diseases of the respiratory system (observed 23, expected 8·1, SMR 284, 95% CI 180 to 426, P<0·001) but

no excess mortality from lung cancer (observed 4, expected 6·2, SMR 65, 95% CI 18 to 165).

INTERNAL STANDARD

At the outset of this updated analysis, cancer of the lung (ICD-8 162–163) and chronic non-malignant diseases of the respiratory system (ICD-8 490–519) were selected for further study. Cases were selected as those deaths for which any part of the death certificate (1a, 1b, 1c, or II) would be coded to the above categories. Occupational exposure to cadmium was not expected to have a discernible influence on many causes of death. Consequently, mortality from all causes excluding lung cancer, non-malignant chronic diseases of the respiratory system, and nephritis and nephrosis was also studied to assess the usefulness of the explanatory variables used in the statistical models.

Table 7 provides relative risks (12 separate analyses) by levels of estimated cumulative exposures to cadmium (three levels: < 1600, 1600–4799, ≥ 4800 μg.m^{-3}.y) and based solely on the experience of the 347 copper cadmium alloy workers. Table 7 also includes summaries of 12 further analyses that assessed the significance of any trends of risk across the three exposure levels. Cumulative exposure to cadmium is analysed simultaneously either with (left hand side of table) age (seven levels: 45–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84) or with (right hand side of table) age, year of starting alloy work (four levels: 1922–39, 1940–49, 1950–59, 1960–78), factory (two levels: A, B), and time since starting alloy work (five levels: 1–9, 10–19, 20–29, 30–39, ≥ 40 y). The top half of the table relates to unlagged exposures; the bottom half of the table relates to exposures lagged by 10 years. The inclusion of the variable cumulative exposure to cadmium made a highly significant improvement to the models for chronic non-malignant diseases of the respiratory system; there were notably increased relative risks for this cause of death. The inclusion of the variable cumulative exposure to cadmium did not approach a significant improvement to the models for lung cancer; relative risks for this cause of death were close to (or below) unity.

Findings were not materially changed when the analysis was restricted to copper cadmium alloy workers from factory B. For example, the corresponding relative risks for the point estimates of 0·50 and 0·46 (table 7) for cancer of the lung were 1·34 (95% CI 0·44 to 4·05) and 0·54 (95% CI 0·12 to 2·56). Corresponding relative risks for the point estimates of 3·46 and 3·32 shown for chronic non-malignant diseases of the respiratory system were 5·47 (95% CI 2·11 to 14·19) and 3·19 (95% CI 1·06 to 9·61). When the analysis was restricted to copper cadmium alloy workers from factory A, corresponding relative risks for chronic non-malignant diseases of the respiratory system were 3·00 (95% CI 0·68 to 13·30) and 4·30 (95% CI 0·99 to 18·66). Findings were not obtained for cancer of the lung because there were only three deaths available for analysis.

It was possible to gain an independent

Table 7 Relative risks† for cancer of the lung and chronic diseases of the respiratory system (non-malignant) by level of cumulative exposure

Cumulative exposure to cadmium ($\mu g.m^{-3}.y$)	Deaths n	RR‡ (95% CI)	Likelihood ratio test§ P value	RR¶ (95% CI)	Likelihood ratio test§ P value
Unlagged:					
Cancer of lung:‖					
<1600	10	1·0		1·0	
1600-	5	0·50 (0·17 to 1·46)		0·85 (0·27 to 2·68)	
≥4800	4	0·46 (0·14 to 1·49)	0·289	0·81 (0·18 to 3·73)	0·947
Evaluation of trend††		0·65 (0·36 to 1·18)	0·144	0·89 (0·43 to 1·84)	0·753
Chronic diseases of respiratory system (non-malignant)‡‡:					
<1600	8	1·0		1·0	
1600-	28	3·46** (1·58 to 7·59)		4·54*** (1·96 to 10·51)	
≥4800	24	3·32** (1·48 to 7·42)	0·001	4·74** (1·81 to 12·43)	< 0·001
Evaluation of trend		1·61** (1·15 to 2·23)	0·004	1·96** (1·27 to 3·02)	0·002
All other deaths (with exclusion)§§:					
<1600	38	1·0		1·0	
1600-	51	1·29 (0·85 to 1·96)		1·39 (0·88 to 2·21)	
≥4800	47	1·29 (0·84 to 1·99)	0·404	1·43 (0·85 to 2·42)	0·300
Evaluation of trend		1·13 (0·92 to 1·40)	0·249	1·19 (0·92 to 1·54)	0·187
Lagged by 10 years:					
Cancer of lung:					
<1600	11	1·0		1·0	
1600-	4	0·41 (0·13 to 1·28)		0·78 (0·23 to 2·72)	
≥4800	4	0·60 (0·19 to 1·95)	0·257	1·17 (0·24 to 5·83)	0·865
Evaluation of trend		0·70 (0·37 to 1·30)	0·243	1·01 (0·47 to 2·19)	0·974
Chronic diseases of respiratory system (non-malignant)††:					
<1600	14	1·0		1·0	
1600-	24	1·91 (0·98 to 3·70)		2·57* (1·20 to 5·49)	
≥4800	22	2·47* (1·24 to 4·93)	0·025	4·21** (1·67 to 10·58)	0·005
Evaluation of trend		1·55** (1·11 to 2·16)	0·009	2·02** (1·29 to 3·17)	0·002
All other deaths (with exclusion):§§					
<1600	41	1·0		1·0	
1600-	53	1·38 (0·91 to 2·07)		1·52 (0·96 to 2·39)	
≥4800	42	1·45 (0·93 to 2·25)	0·178	1·71 (0·99 to 2·96)	0·108
Evaluation of trend		1·21 (0·97 to 1·49)	0·089	1·31 (0·99 to 1·71)	0·051

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
†Based on the mortality experience of the 347 copper cadmium alloy workers.
‡Adjustment for age (see text for levels).
§Difference between the deviance for a model that includes the variable cumulative exposure to cadmium and the deviance for a model that excludes this variable. This difference is interpreted as a χ^2 value with degrees of freedom equal to the number of terms added to the fuller model[14] (three terms for the analyses by level of exposure, or one term for the analyses which evaluated trends).
¶Adjustment for age, year of start of alloy work, factory, and time since starting alloy work (see text for levels).
‖ICD-8, 162–163, underlying or contributory cause.
††Relative risk for change in exposure of one level.
‡‡ICD-8, 490–519, underlying or contributory cause.
§§Excludes any death certificate with underlying or contributory cause coded to 162–163, 490–519, or 580–584.

assessment of the likely reliability of the estimates of cumulative exposure to cadmium used in this report by comparing individual estimates with in vivo measurements of cadmium in liver. These measurements were obtained from neutron activation analysis and were included in the findings reported by Davison et al.[9] In vivo data were available for 68 copper cadmium alloy workers in the cohort reported here; the spearman rank correlation coefficient between the in vivo measurements of cadmium in liver and the estimated cumulative exposures to cadmium (based on job histories and the job exposure matrix shown in table 2) was 0·55 (n = 68, P < 0·001).

Discussion

This analysis has provided very different findings for non-malignant diseases of the respiratory system and lung cancer among copper cadmium alloy workers. For non-malignant diseases of the respiratory system there were significantly increased SMRs for alloy workers from each of the two factories. Also, the Poisson regression analysis, which used an

internal standard, found that mortality risks increased with estimated cumulative exposure to cadmium. For lung cancer, there was a significantly depressed SMR for copper cadmium alloy workers from factory A and a significantly increased SMR for copper cadmium alloy workers from factory B. The Poisson regression analysis did not find cumulative exposure to cadmium to be an important risk factor for lung cancer, even when the analysis was restricted to alloy workers from factory B.

The unusually low SMR for lung cancer among copper cadmium alloy workers from factory A was unexpected and possible reasons for this deficit were examined in some detail. The possibility of a major artifact (such as a group of lung cancer cases being inadvertently excluded from the study) was investigated. Such an exclusion could not have taken place after the cohort was traced by the OPCS because all data supplied by the OPCS in the lifetime of the study have been checked with the current computer files. It does not seem to have taken place at the time the cohort was defined—for example, if records for lung cancer cases known to the company had been filed

separately from the source data used for this study—because the relevant SMR was low both for the period after the date of data collection (1981–92) and for the earlier period. Moreover, in 1980, health concerns for workers exposed to cadmium centred on cancer of the prostate, renal damage, and non-malignant diseases of the respiratory system; no survey was in progress at factory A on the topic of lung cancer. The findings for mortality among the participants of the 1953 MRC survey also add weight to the view that the deficit is not the result of an artifact in data collection, because data for the MRC survey were collected more than 20 years before this study was initiated. Some of the deficit may be due to regional differences; factory A was situated in a rural setting whereas factory B was in an urban setting. The lifestyles of alloy workers from the two factories may well have been similar; findings for all other causes of death combined would support this view. Many SMRs were calculated; it is not particularly surprising, therefore, that one of them should describe a significant deficit. It was not possible to assess the role of cigarette smoking in this deficit.

It was also important to gain some independent evidence of whether the individual cumulative estimates of exposure to cadmium used in the Poisson regression analyses provided reliable estimates of true exposures. Some supporting evidence was provided by the comparison of cumulative exposure estimates to cadmium with in vivo measurements of cadmium in liver; liver cadmium concentration has been found to be "proportional to duration and intensity of cadmium exposure in workers without as well as with renal dysfunction."[15] Further reassurance was provided by the positive Poisson regression findings for chronic non-malignant diseases of the respiratory system. These findings were not unexpected given what is already known about emphysema in copper cadmium alloy workers from these factories.[1-4 9]

These data have limitations. Data on smoking histories were not available, although there is no reason to think that they would be correlated with the employment histories analysed in this study. More importantly, perhaps, quantitative data on occupational exposures other than cadmium were also not available. The subcohort of iron and brass foundry workers had been referred to by Holden[4] as a control group, on the grounds that such employees were not exposed to cadmium but probably had similar social characteristics. They were working, however, in an extremely dirty environment and were exposed to considerable amounts of other chemicals, including polycylic aromatic hydrocarbons. It is these other exposures that were probably responsible, at least in part, for the increased SMRs for non-malignant diseases of the respiratory system found in this group of workers. Likewise, the vicinity workers were exposed to a different mixture of chemicals and this mixture included arsenic. Arsenic exposure may be responsible, at least in part, for the increased SMRs obtained for lung cancer in this group of work-

ers.[16] Exposure to cadmium would seem an unlikely explanation given that Bonnell[1] found "no cases in this group in whom the findings were consistent with the diagnosis of chronic cadmium poisoning" and given that King found relatively low levels of cadmium oxide fume in those parts of the workshop distant from the cadmium operations.[10] Arsenic exposure may also be responsible, at least in part, for the increased SMR found for copper cadmium alloy workers from factory B. These workers could have been exposed to arsenic in the general workshop environment or from unrecorded job rotations in the workshop. It is not inconceivable that a common exposure (which by definition could not be cadmium) was responsible for the similarly increased SMRs found for non-malignant diseases of the respiratory system among the copper cadmium alloy workers, the vicinity workers, and the iron and brass foundry workers, even though there was a positive association between risks of mortality and estimated cumulative exposure to cadmium among the copper cadmium alloy workers.

The study is also limited in that an independent historical assessment of cadmium exposures was only available for factory B. Its use for the copper cadmium alloy workers at factory A must have led to some errors in individual annual exposure estimates; misclassification relating to placement in one or more of the three levels of cumulative exposure used in the Poisson regression analysis, however, was probably modest given that processes were broadly similar and that improvements were made over time at both factories. Because the classification of work histories involved the help of former employees, it follows that the subcohorts could not now be accurately reabstracted from factory records. This is an unattractive but unavoidable feature of this study. Finally, if non-malignant diseases of the respiratory system and lung cancer are, in fact, long term sequelae of exposure to cadmium oxide fume, then the toll of mortality from non-malignant disease may have acted as a cause of death competing with the lung cancer mortality in this study. Even taken together, however, the above limitations do not explain why the findings for lung cancer were so different from those for non-malignant diseases of the respiratory system.

In conclusion, the copper cadmium alloy workers studied in this cohort had excess risks of non-malignant diseases of the respiratory system rather than excess risks of lung cancer. Findings in relation to estimated cumulative exposures to cadmium were consistent with the hypothesis that exposure to cadmium oxide fume increases risks of mortality for chronic non-malignant diseases of the respiratory system.

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