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Cancer Risks in Aluminum Reduction Plant Workers

A Review

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Objective and Methods: This review examines epidemiological evidence relating to cancers in the primary aluminum industry where most of what is known relates to Söderberg operations or to mixed Söderberg/prebake operations. **Results and Conclusions:** Increased lung and bladder cancer risks have been reported in Söderberg workers from several countries, but not in all. After adjustment for smoking, these cancer risks still increase with cumulative exposure to benzo(a)pyrene, used as an index of coal tar pitch volatiles exposure. Limited evidence has been gathered in several cohorts for an increased risk of tumors at other sites, including stomach, pancreas, rectum/rectosigmoid junction, larynx, buccal cavity/pharynx, kidney, brain/nervous system, prostate, and lymphatic/hematopoietic tissues (in particular non-Hodgkin lymphoma, Hodgkin disease, and leukemia). Nevertheless, for most of these tumor sites, the relationship with specific exposures has not been demonstrated clearly and further follow-up of workers is warranted.

Alumina is extracted from the bauxite ore, and the metal aluminum is produced by the electrolysis of the alumina dissolved in a bath of mainly molten aluminum fluoride and cryolite. Electrolysis takes place in "pots," of which there are basically two types (Fig. 1). These are housed in a potroom. Variants of the "prebake anode type" are center break and side break (VS), and variants of the "Söderberg anode type" are vertical stud and horizontal stud (HS).

In the prebake type, several prebaked carbon blocks are set in two rows. These carbon anodes are fabricated outside the potroom in the "carbon plant." The anodes are made from pure carbon, which is usually finely ground petroleum coke. This is heated and mixed with a binder of hot pitch and pressure molded into blocks, which are baked at about 1100°C in an oven. These blocks are then fixed on conductive hangers ("rodded") so that they can be placed in the pots. Anodes consumed during the electrolytic process are replaced when almost burnt up. In the center break type, alumina is added to the molten cryolite in the middle, between the two rows of anodes, after breaking a crust of residue that floats on the molten bath. The alumina is fed continuously or at intervals, and this can be done without opening the hood placed over the pot. In the side break cell, crust-breaking is done between the anodes and the wall of the cell; hoods must be opened to do this, which lowers the fume collection efficiency. The hoods in both types are designed to extract gases and fumes released during electrolysis.

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In Söderberg pots, the paste of the pitch and petroleum coke is dropped into a steel casting hanging above the pot. The anodes are thus continuously produced from this anode paste, which is baked in place by the heat from the electrolytic process. In the vertical stud type, the current enters the cell through vertical steel pins (studs) that hold the anode in place. The fumes are collected at the sides of the pot from the lower part of cast iron structure around the anode (the skirt). Ravier[1] estimated that in the 1970s, between 5% and 40% of the fumes escaped into the potroom air. With this type of cell, there is only one large anode. In the horizontal stud, the studs enter the anode from the side, so the whole pot is covered by a hood to collect the released gases and fumes. The cathode in all types of pots is insulated steel lined with carbon. With the prebake type of anode, the main exposure to polycyclic aromatic hydrocarbons (PAHs) occurs during manufacture of the anode, whereas in a Söderberg plant, all workers can be exposed to PAHs during operation of the cell. As the anodes used in prebake cells are baked before they are placed in the pots, they are likely to release low levels of PAHs, if any, during the electrolytic process.

Workers in both types of potrooms have the potential for exposure to heat, alumina, carbon and cryolite dust, carbon monoxide and dioxide, coal tar pitch volatiles (CTPVs), hydrogen fluoride and other fluorides, sulfur dioxide, and high static magnetic fields. Depending on ancillary operations at the plant, workers may have the potential for exposure to a wide range of other agents, including chlorides, metals (eg, beryllium, cadmium, chromium, copper, mercury, nickel, and vanadium), caustic soda, and crystalline silica. Workers involved in pot lining can also be exposed to tars and fluorides, and in some cases, asbestos used as pot insulation.

The pots and the evolution of working conditions in potrooms have been described by several authors.[1–4] Typical airborne contaminants and physical stresses encountered in the aluminum industry have also been previously reviewed in some detail.[5]

CTPVs AND PAHs

Coal tar pitch volatiles have been prominent agents for investigation in potrooms and carbon plants. More than 100 PAHs have been identified in primary aluminum smelters, and most derive from the coal tar used as a binder in the carbon anodes.[6] The composition of the anodes varies, with 25% to 30% pitch mixed with calcined petroleum coke, with proportions depending on raw material properties. The pitch contains as much as 20% PAHs, and 19 PAHs have been commonly found in the air of aluminum smelters, which included one established human carcinogen, one probable carcinogen, and seven PAHs classified as possible human carcinogens (as of April 2013 according to the International Agency for Cancer Research [IARC]). It was found that the concentration of benzo(a)pyrene (B(a)P) did not correlate the best with the concentrations of certain more volatile PAHs, but it did correlate extremely well with the particulate phase of known carcinogenic substances. The authors of this study concluded that B(a)P was an excellent index of total PAH exposures and also of 18 other PAHs emitted in the Söderberg smelter studied.[6] They also found that the ratios of the concentrations of various PAHs to the concentration of B(a)P showed remarkable stability with worksite, day, and season as long as no major changes were made to electrolytic process conditions or

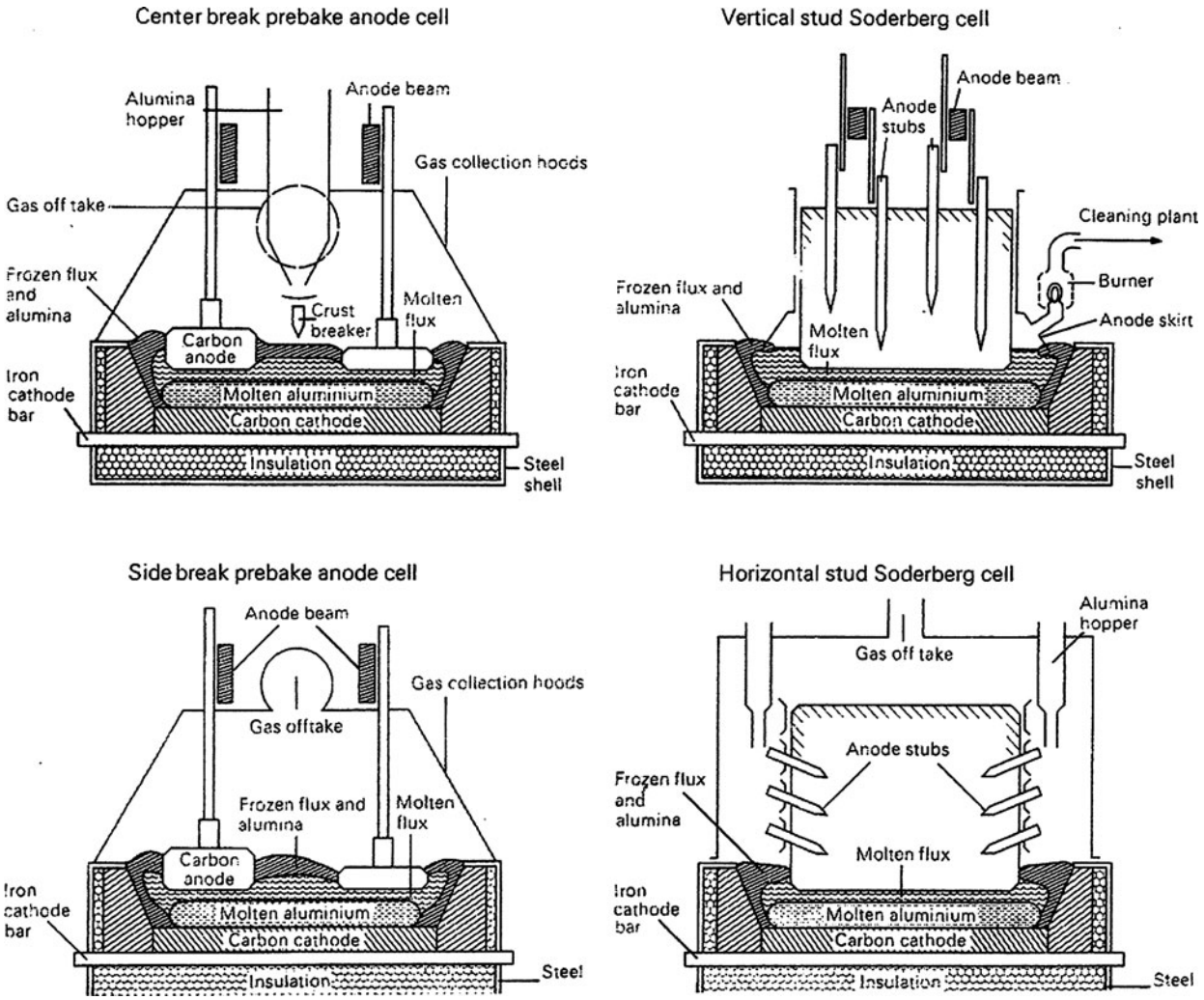

FIGURE 1. Various types of aluminum reduction cells (pots).[1]

the coal tar pitch used to fabricate the process electrodes.[6] Typical levels of B(a)P measured in the aluminum industry vary with the process, with the lowest levels measured in prebake plants (0.02 to 0.05 $\mu g/m^3$ in a Norwegian prebake plant in the mid-1970s) and the highest levels around workers handling electrodes (geometric means close to 37 $\mu g/m^3$ in the 1990s reported in one country) (see Table 1).

Kreyberg[13] seems to be the first to suggest that exposure to B(a)P from coal tar pitches in electrodes used in the aluminum industry might pose a risk of lung cancer for their workers. Since then, there have been several reviews of the risks associated with exposure to PAHs in the aluminum primary production industry[2,3,14] and in a wider range of industries where PAHs are encountered.[15,16]

The risk of lung cancer from residential PAH exposure has been assessed using B(a)P as an index of exposure.[17–19] These estimates have been based on occupational studies involving CTPV exposures that have included the primary aluminum reduction industry. Armstrong et al[19] translated the lifetime lung cancer risks calculated by Gibbs[17] on the basis of studies from eight industries involving PAH exposures, into the same unit risk ratios that they used in a meta-analysis of some 39 studies. The resulting risk ratios for these industries ranged from 1.02 to 1.58, which were similar to their own meta-estimate of 1.20 (1.11 to 1.29). The estimated means for coke oven and aluminum smelters in the analysis by Armstrong et al[19] were also very similar (1.17 and 1.16), which on the basis of the Gibbs analysis would have been 1.27.[17] A more recent analysis involving 677 lung cancer deaths and using a linear model on the basis of the Quebec aluminum smelter study follow-up to 1999 gave a relative risk (RR) of 1.35 (95% confidence interval [CI] = 1.22 to 1.51) at 100 $\mu g/m^3$ B(a)P-years, which was slightly higher than in the meta-analysis, and earlier Gibbs values.[20] The best fitting models were a two-knot cubic spline and a power curve ($RR = (1 + bx)^p$), the latter giving an RR of 2.68 at 100 $\mu g/m^3$ B(a)P-years. On the basis of 147 lung cancer deaths in aluminum workers in British Columbia,[21] it was found that a log-log dose–response model best described the lung cancer risk and a log-linear B(a)P model gave the best fit for bladder cancer. No other B(a)P-associated cancer risks seem to have been modeled with exposure to CTPVs in the aluminum industry.

OTHER EXPOSURES

Both CTPVs and PAHs arise mainly from the electrodes, but potroom emissions also derive from the cryolite baths (which contain aluminum salts with fluorides), from the alumina (aluminum oxide and various elements), and from other operations during the smelting process. Reported exposures are varied: aluminum fluorides, fibrous sodium aluminum tetrafluoride particles, calcium fluoride, sulfur dioxide, carbon monoxide and dioxide, chlorine gas, trace metals (eg, beryllium, cadmium, chromium, copper, vanadium, mercury,

TABLE 1. Typical Measured Exposure Levels of Benzo(a)pyrene in Aluminum Reduction Plants

References	Plant Country (Province/State)	Department/Job/Task	Concentrations	Comments
Bjørseth et al[7]	Norway	Anode plant	ND–0.3 $\mu g/m^3$	Stationary samples ($n = 21$)
		Prebake plant	ND–0.05 $\mu g/m^3$	Mid-1970s
		Söderberg potroom	ND–9.0 $\mu g/m^3$	
Lindstedt and Sollenberg[8]	Sweden	Söderberg plant	1.8–5.3 $\mu g/m^3$	Stationary samples ($n =$ not specified)
				1968–1978
Tjoe Ny et al[9]	Suriname	Söderberg plant	Geometric mean:	Personal samples ($n = 16$)
		Potmen	2.2 $\mu g/m^3$	July to August 1990
		Electrode men	37 $\mu g/m^3$	
Petry et al[10]	Switzerland	Anode plant	8-h time-weighted averages: 0.16–4.88 $\mu g/m^3$	Personal samples, 5-d full-shift samples ($n = 6$)
				Early 1990s
Carstensen et al[11]	Sweden	Söderberg potrooms	Time-weighted average median concentrations of particulates:	Personal, full-shift samples ($n = 93$)
			0.97 $\mu g/m^3$ (range: 0.02–23.5)	End of the 1990s
Sanderson et al[12]	Canada (Quebec and British Columbia)	Söderberg plant	Geometric mean concentrations:	Personal samples ($n = 19$)
		Stud maintenance, crust breaker	1998: 1.68 $\mu g/m^3$/2002: 1.14 $\mu g/m^3$	Horizontal stud
		Anode operator, rack raiser	1998: 5.72 $\mu g/m^3$/2002: 1.80 $\mu g/m^3$	
		Potroom control operator	1998: 1.15 $\mu g/m^3$/2002: 0.26 $\mu g/m^3$	
Lavoué et al[4]	Canada (Quebec)	Söderberg potrooms	Median geometric mean: 0.46 $\mu g/m^3$	One plant with the largest number of measurements ($n = 2937$) performed between 1975 and 1999 (86% between 1975 and 1989)
			Maximum geometric mean: 134.28 $\mu g/m^3$	

ND, Not Detected.

and nickel), silica, and phenols.[5,22] Respirable and thoracic particles measured in a Norwegian aluminum smelter showed a higher abundance of large particles (diameter of ≥500 nm) in the Söderberg potroom air compared with the prebake one. The largest proportion of particles found in both types of potrooms was aluminum oxide–cryolite mixtures (65% of particles in the prebake potroom and 45% in the Söderberg one). The proportion of all particles that were aluminum oxides, soot, and silicates in the Söderberg potroom was at least twice that of the prebake potroom. Brass and iron/titanium oxides were also found in small amounts.[23] Beryllium levels (around a hundredth to a tenth of the threshold limit value of 2 $\mu g/m^3$) were also measured in aluminum smelters in Norway[24] and in the United States.[25] The highest concentrations were in a prebake potroom where Jamaican alumina was used.[24]

Two other exposures have been reported regularly, but rarely studied in relation to cancer in the aluminum industry: heat and static and alternating magnetic fields.[5,26] Extreme heat is a well-known hazard in metal smelting and is not considered carcinogenic as such; however, it can cause dehydration, which prevents diluting and flushing of carcinogens, and could increase their retention and an imbalance of myoglobin in organs such as the bladder and colon; dehydration also predisposes to constipation and urinary tract infections, as well as cancers of the bladder[27] and perhaps colon.[28] Extremely low frequency static magnetic fields between 0.1 and 10 mT have also been reported in potrooms.[29]

PREVIOUS REVIEWS

There have been several reviews of cancer risks as part of publications on the aluminum primary production industry since the early 1970s, but the number of systematic reviews has been small.

In 1981, Simonato[30] carried out a fairly thorough epidemiological overview of cancer risks in this industry and reported on studies in Russia, the United States, Canada, and Italy conducted before that time. He concluded that the data were consistent with an association between aluminum production in Söderberg plants and lung cancer but found that data suggesting associations with skin cancer and lymphomas were inconclusive and that these required further investigation.

This was followed shortly by the IARC review in 1984 of cancer risks related to the aluminum process.[2] They considered the data to provide limited evidence that certain exposures in the aluminum industry were carcinogenic to humans, giving rise to cancer of the lung and bladder.[2] They considered a possible causative agent to be "pitch fume." They also concluded that at that time, there was inadequate evidence for hematopoietic and pancreatic cancer but mentioned leukemia and lymphosarcoma/reticulosarcoma as occurring in isolated studies. In 1987, this was updated to "occupational exposures during aluminum production are carcinogenic to humans" (group 1).[31] In 2010, the IARC working group on PAHs classified "occupational exposures during carbon electrode manufacture" as probably carcinogenic to humans (group 2A).[32]

The available evidence was reviewed as of 1991 by Norwegian authors who concluded that the Söderberg process was associated with bladder cancer and that tar exposure in the aluminum industry was associated with lung cancer; they also indicated that there might be an increased risk of leukemia and pancreatic cancer among potroom workers and of kidney and brain cancer in aluminum production in general.[3]

Another review of mortality studies in aluminum reduction plants published in 1993 concluded that there was " . . . no currently

convincing evidence in support of a carcinogenic effect in workers employed in the industrial production of aluminum."[33] A valid criticism at that time was that studies had not considered smoking effect in evaluating lung cancer. Nevertheless, this has now been taken into account in various studies. In 1997, as part of a review of occupational and environmental exposure to PAHs, risks were reviewed in several industries including the aluminum reduction industry.[34] In the latter they made an effort to distinguish Söderberg and prebake plants. They listed the following cancers as occurring in association with prebake operations: respiratory, bladder, kidney, and lung; and in Söderberg plants, cancers of the lung, larynx, bladder, and kidney. In 1998, another review of cancer risks specifically in the primary aluminum industry was carried out.[14] Cancers of the lung, trachea and bronchus, and bladder were considered to be associated with employment in the industry, with cancers of the pancreas, kidney, stomach, brain, Hodgkin disease, non-Hodgkin lymphomas (NHL), and leukemia deserving further investigation. Ten years later, available studies in 2005 were reviewed[16] and a meta-analysis was produced for respiratory and urinary tract cancers. This listed 15 publications on the aluminum industry, which they indicated included nine cohorts, but combined the results of eight cohorts. The authors however did not differentiate results between Söderberg and prebake processes and pooled mortality and incidence results. For example, they treated the US[35] study as one cohort instead of several cohorts from different types of plants as described by the original authors, and they only partially interpreted the Norwegian studies,[36] not mentioning that there were Söderberg plants with excess lung cancer compared with local rates. They concluded that there was no excess risk of lung/respiratory cancers in aluminum workers on the basis of 688 cases from nine studies (meta-RR = 1.03; 95% CI = 0.96 to 1.11); the test for heterogeneity between these studies was however statistically significant. The authors noted a significant excess for bladder cancer in primary aluminum production (meta-RR = 1.29; 95% CI = 1.12 to 1.49), from eight studies that were not heterogeneous. Further, it is well recognized that in large populations, the excess may be small overall, but subsets can carry a significant risk. The high exposure categories of workers in these various studies were not combined to determine if they showed any excess, so very little, if any weight, can be given to these pooled results.

WORLD EXPERIENCE

While the processes used in various countries are essentially the same, raw material sources and the operating conditions in the various plants are likely to differ. In view of this, it was considered useful to examine what is known about cancer risks in various countries and then to combine the experience to better understand what risks exist overall in the primary aluminum production industry. Table 2 summarizes the published cohort studies available, by country or continent of origin of the study, and Table 3 presents a summary of the associations found for selected types of cancer.

Australia

Fritschi and colleagues[62,63] reported on mortality and cancer incidence in bauxite miners and workers in an alumina refinery in Australia that has 40% of the world's bauxite reserves. The cohort included 5828 men employed for more than 3 months since 1983 and followed through 2000. There was a significant increased mortality from malignant pleural mesothelioma and a higher risk of melanoma, but the latter was not related to duration of employment in production or maintenance. Although the follow-up period in this study is relatively short (less than 20 years), the study is important because it examined one of the raw materials used in the aluminum production process. The cohort had a lower risk of incident lymphohematopoietic cancers.

A study by Sim and colleagues[37] at two Australian prebake aluminum smelters reported mesothelioma as the only significantly increased cause of death. Deaths from prostate cancer were significantly elevated in those who had worked for more than 20 years in production (standardized mortality ratio [SMR] = 239) or maintenance (SMR = 367). There was a statistically significant excess incidence of stomach cancer (standardized incidence ratio [SIR] = 195) in all smelter employees and ever-office workers, of mesothelioma overall (SIR = 241) and in ever-production workers (SIR = 298); of kidney cancer overall (SIR = 199) and in ever-production (SIR = 239) and ever-office workers (SIR = 287) and urinary cancer in overall workers (SIR = 145) and in ever-production workers (SIR = 168). They found no trend with duration of employment for stomach cancer or urinary cancer and no pancreatic cancer. This cohort was young with almost 25% of person-years of observation since 1998. Both prebake plants had separate anode producing plants, but it is not clear whether workers from these plants were included in the study population.[37]

The smoking-adjusted relationship between mortality and cancer incidence in these same two prebake plants and benzene-soluble fraction (called benzene-soluble materials [BSM] in other studies), B(a)P, fluoride, and inhalable dust showed monotonic relationships between respiratory cancer and cumulative inhalable dust, cumulative fluoride exposure and cumulative B(a)P exposure, none statistically significant.[38] They also reported a monotonic nonstatistically significant trend for stomach cancer, but bladder cancer was not associated with either B(a)P or benzene-soluble fraction. No other outcomes were associated with exposure. The trend values found in this study are not very convincing of any strong relationships. As the cohort is still young and the follow-up, short, useful information will need to await further follow-up. The Australian cohort is interesting because it represents one of the few pure prebake operations in the world that has been studied epidemiologically.

Canada

Gibbs and colleagues published several studies of a few cohorts of aluminum smelter workers in Quebec.[41,64] Their first publication reported that mortality from lung cancer increased from 101.5 in men with 0 tar-years of exposure to 271.2 for those with 21 tar-years or more of exposure, without adjustment for cigarette smoking. Nevertheless, in a later study, Armstrong and colleagues[65] showed that the excess was not due to smoking and exposure–response relationships were demonstrated using BSM and B(a)P as indices of exposure to CTPVs. That case-cohort study resulted in a rate ratio of 1.25 and a lifelong risk of 2.2% after 40 years of exposure at 2 mg/m^3 BSM, although the predicted risks (rate ratio and lifelong) were 1.4% and 3.8% using a curvilinear model. This study was the basis for the possible application of a probability of causation model in compensating workers exposed to CTPVs in the aluminum industry.[66] In a further follow-up study to 1977, Gibbs and colleagues[42,67] found that all cancers, cancer of the stomach and esophagus, lung and other malignancies combined were statistically significantly increased in workers ever exposed to tars, and that cancers of the esophagus and stomach, urinary organs, and bladder were shown to increase with increasing tar-years of exposure. In the late 1970s and early 1980s, other Canadian researchers suspected an increased risk of bladder cancer incidence,[68,69] and in 1984, Thériault and colleagues[70] reported a case-control study on 488 cases of bladder cancer occurring between 1970 and 1979 in hospitals surrounding aluminum smelters in Quebec. Of 96 bladder cancer cases identified as employees, 85 were selected for study as they had worked for more than 12 months. The mean latency between first employment and diagnosis was 23.9 years. A higher proportion of cases than controls were smokers, and the odds ratio (OR) for workers in the Söderberg potrooms was significantly increased with an unadjusted OR of 2.7 (95% CI = 1.64 to 4.43). The OR for workers exposed to 20 BSM-years or more was 7.22 and for 20 B(a)P-years or more was 12.38.[70] In a later quantitative exposure analysis,[71] the RR for

TABLE 2. Brief Description of Published Cohort Studies on Workers in Aluminum Reduction Plants

References, Country (Province/State) Study Design	Department/Job/Task	Comparison Group	Follow-Up Period	Comments	Person-Years of Observation (Total Cancer Deaths or Cases)
Australia					
Sim et al,[37] Friesen et al[38] Australia Mortality and cancer incidence cohort	• 2 aluminum reduction plants, started in 1962 and 1986 (prebake process) • 4396 men (565 women not described)	General Australian population	1983–2002	• "Young" cohort and short period of follow-up (31% of p-y before 1991 and 24% after 1998) • Some smoking data • Number lost to follow-up not specified • >88% of cause of death determined	68,752 p-y (78 cancer deaths/233 new cases)
Canada					
Spinelli et al[39,40] Canada (BC) Mortality and cancer incidence cohort	• 1 aluminum reduction plant (Söderberg process) • 6423 workers with ≥3 yrs of employment between 1954 and 1997	General British Columbia population	Mortality: 1957–1999 Incidence: 1970–1999	• Little smoking data • 13.6% lost to follow-up • >98% of cause of death determined	151,057 p-y (336 cancer deaths/662 new cases)
Gibbs et al[41 4243–44] Canada (QC) Mortality and cancer incidence cohort	• 4 aluminum reduction plants (A: old prebake + Söderberg; B and C: Söderberg; D: prebake) • Plant A—pre-1950 (started in 1920): 5285 men working on January 1, 1950 • Plant B—pre-1951 (started in 1916): 529 men working on January 1, 1951 • Plant C—pre-1950 (started in 1937): 163 men working on January 1, 1950 • Plant A—post-1950: 6697 men hired after January 1, 1950 • Plant B—post-1951: 1082 men hired after January 1, 1951 • Plant C—post-1950: 1379 men hired after January 1, 1950 • Plant D (started in 1978): 568 men hired since 1978	General Quebec population	Mortality: A: 1950–1999 B: 1951–1999 C: 1950–1999 D: 1978–1999 Incidence: 1980–1999	• Large study with several cohorts • Some smoking data • Number lost to follow-up not specified but mentioned that vital status was ascertained for virtually all workers • 97%–100% of cause of death determined	p-y A pre: 188,263.4 B pre: 19,980.1 C pre: 5779.8 A post: 172,798.5 B post: 24,324.6 C post: 41,552.6 D: 8476 (5474 cancer deaths/>1878 new cases)
China					
Liu et al[45] China Mortality cohort	• 6 carbon plants and 1 potroom and carbon department of an aluminum reduction plant (process not specified) • 6635 men working since January 1, 1971 (unspecified number of workers in the aluminum reduction plant)	11,470 males in steel rolling mills	1971–1985	• Most workers from carbon plants • Individual data on smoking • 1.34% lost to follow-up • 100% of cause of death determined	95,847 p-y (149 cancer deaths)
France					
Mur et al[46] France Mortality cohort	• 11 aluminum reduction plants (3 prebake, 2 Söderberg, others mixed processes) • 6455 men employed for ≥1 yr between 1950 and 1976	General French population	1950–1976	• Large study with several cohorts • Some smoking data • Approximately 2% lost to follow-up • Only 71.3% of cause of death determined	113,671 p-y (199 cancer deaths)

(*continued*)

TABLE 2. (*Continued*)

References, Country (Province/State) Study Design	Department/Job/Task	Comparison Group	Follow-Up Period	Comments	Person-Years of Observation (Total Cancer Deaths or Cases)
Moulin et al[47] France Mortality cohort	• 1 aluminum reduction plant (both prebake and Söderberg processes) (originally studied in Mur et al[46]) • 2133 men employed for ≥1 yr between 1950 and 1994	Regional population	1968–1994	• Some smoking data • Exclusion of workers born outside France • 9.5% lost to follow-up • 94% of cause of death determined	35,145 p-y (101 cancer deaths)
Italy					
Giovanazzi and D'Andrea[48] Italy Mortality cohort	• 1 aluminum reduction plant (mainly Söderberg) • 494 men employed (212 potroom workers and a "control" group of 282 workers from other departments)	General Italian population and Trento province population	1965–1979	• Statistically significant excess of deaths from liver cirrhosis among potroom workers • Small numbers • No smoking data • Number lost to follow-up not specified • Unspecified percentage of cause of death determined	All plant: 5306 p-y (56 cancer deaths) Potroom: 2115 (40 cancer deaths)
Carta et al[49–50] Italy (Sardinia) Mortality cohort Nested pancreatic cancer case-control study	• 1 aluminum reduction plant (prebake) • 1152 men employed for ≥1 yr between 1972 and 1980 • Nested case-control study: 6 cases, 72 controls	Regional population	1972–2001	• Some smoking data • No loss to follow-up • 100% of cause of death determined	29,010.8 p-y (51 cancer deaths; 6 deaths from pancreatic cancer)
Norway					
Andersen et al[51] Norway Mortality and cancer incidence cohort	• 4 aluminum reduction plants (both prebake and Söderberg processes) • 7410 men alive in 1953 and employed before 1970 for ≥18 mo	Specific county population	Mortality and incidence: 1953–1979	• Large study with several cohorts • No smoking data • Number lost to follow-up not specified • No analysis of cancer mortality	Person-years of observation not specified (unspecified number of cancer deaths, 428 new cases)
Rönneberg et al[52] Norway Mortality and cancer incidence cohort	• 1 aluminum reduction plant (prebake process) (originally studied in Andersen et al[51]) • 1137 men employed for ≥6 mo between 1922 and 1975 (plant closure)	General Norwegian population	1953–1991	• Little smoking data • 3.9% lost to follow-up • No analysis of cancer mortality	32,816 p-y 552 cancer deaths, 210 new cases)
Rönneberg et al[53] Norway Cancer incidence cohort	• 1 aluminum reduction plant (Söderberg process) (originally studied in Andersen et al[51]) • Men employed for ≥6 mo • 2647 short-term workers (employed for <4 yrs) • 2888 production workers (≥4 yrs) • 373 maintenance workers (≥4 yrs)	General Norwegian population	1953–1993	• No smoking data • 0.8% lost to follow-up	Short term: 65,976 p-y (226 new cases) Production: 71,219 p-y (339 new cases) Maintenance: 9950 p-y (41 new cases)

(*continued*)

TABLE 2. (*Continued*)

References, Country (Province/State) Study Design	Department/Job/Task	Comparison Group	Follow-Up Period	Comments	Person-Years of Observation (Total Cancer Deaths or Cases)
Romundstad et al[54] Norway Cancer incidence cohort	• 6 aluminum reduction plants (both prebake and Söderberg processes) (5 of which were originally studied in Andersen et al[51]) • 11,103 men employed for >3 yrs	General Norwegian population	1953–1996	• Large study with several cohorts • Smoking data available for three plants/six • Number lost to follow-up not specified	272,554 p-y (1503 new cases)
Romundstad et al[36] Norway Mortality and cancer incidence cohort	• 2 aluminum reduction plants (mainly Söderberg process) (1 of them originally studied in Andersen et al[51] and in Romundstad et al[36]) • 5627 men employed for >6 mo	General Norwegian population	Mortality: 1962–1995 Incidence: start of employment—1995	• Smoking data available for 80% of workers for >3 yrs • Number lost to follow-up not specified • Unspecified percentage of cause of death determined	Mortality: 128,020 p-y (226 cancer deaths) Incidence: 139,554 p-y (425 new cases)
Romundstad et al[55] Norway Cancer incidence cohort	• 1 aluminum reduction plant (originally Prebake, changed to the Söderberg process in 1939) (also reported in Romundstad et al[36]) • 1790 men employed for >5 yrs	General Norwegian population	1953–1995	• Some smoking data available for 75% of workers for >5 yrs • Approximately 2% lost to follow-up	36,587 p-y (286 new cases)
Russia Konstantinov[56,57] Russia Mortality cohort	• As reported in Simonato[30] • No information on size of cohort, duration of follow-up, or process	Not specified	1956–1966	• No information on size of cohort, duration of follow-up, or losses to follow-up, smoking data	Not specified
Sweden Björ et al[58] Sweden (Västernorrland) Cancer incidence cohort	• 1 aluminum reduction plant (started in 1942, Söderberg process) • 2264 men (excluding office workers) employed for >6 mo between 1942 and 2000	Three for mortality: general Swedish, Northern Swedish, and county populations Incidence: the fourth one: seven largest municipalities in Northern Sweden	Mortality: 1952–2004 Incidence:1958–2005	• No smoking data • Number lost to follow-up not specified, but probably very low	70,856 p-y (170 cancer deaths, 323 new cases)
USA Milham[59] USA (WA) Mortality cohort	• 1 aluminum reduction plant (started in 1946, prebake process) • 2103 men who worked for ≥3 yrs at the plant and at least 1 yr between 1946 and 1962 and were still alive in 1962	General US population	1962–1976	• No smoking data • Number lost to follow-up not specified • 95.5% of cause of death determined • No information on workers who left or died before 1962	44,307 p-y (98 cancer deaths)
Rockette and Arena[35] USA Mortality cohort	• 14 aluminum reduction plants (both prebake and Söderberg processes) • 21,829 men who worked for ≥5 yrs at one of the plants between 1946 and 1977	General US population	1946–1977	• Very large study with several cohorts • No smoking data • 1.2% lost to follow-up except for two plants with six and 16% missing files • 97.6% of cause of death determined	Person-years of observation not specified (796 cancer deaths)

BC, British Columbia; p-y, person-years of observation; QC, Quebec; WA, Washington State.

bladder cancer was shown to increase with cumulative exposure to BSM and B(a)P and was significant for B(a)P ($P < 0.001$). The RR was estimated to be 3.3 for a cumulative exposure of 100 $\mu g/m^3$ B(a)P-years. The same researchers found the ORs for bladder cancer to be increased for men employed more than 1 year in the carbon plant but no exposure–response trend after adjusting for smoking and employment in Söderberg plants. The same result was observed for the period of employment in prebake operations.[72]

Gibbs and colleagues[43,44,60] published the most recent studies on the Quebec cohorts, covering the years 1950 to 1999 for mortality, and 1980 to 1999 for cancer incidence. Among workers hired before 1950/1951, there was a highly statistically significant excess of all cancers, digestive system cancers, bladder cancer, lung cancer, and stomach cancer, and deaths by cancers of rectum and rectosigmoid junction, pancreas, and larynx were statistically significantly in excess at one plant. There was a highly significant trend in SMRs with a B(a)P index of exposure for lung cancer ($P < 0.001$) and bladder cancer ($P < 0.001$). The trend for rectum and rectosigmoid junction was almost significant ($P = 0.06$). The newer cohorts comprised 9158 men and 686 women hired in Söderberg plants and 588 men and 42 women in a prebake plant with more than 1 year of seniority. Among workers hired after 1950/1951 in the Söderberg plants, there were nonstatistically significant increases in mortality from cancers of the esophagus, rectum and rectosigmoid junction, pancreas (at one plant only), respiratory cancer, larynx, lung, trachea and bronchus, brain, and NHL, but not stomach. The relatively high risk of pancreatic cancer at one plant did not seem to be related to B(a)P exposure levels. The numbers of deaths in women and men from the prebake plant were too small to reach any conclusions.[60] The cancer incidence through 1999 for workers in the pooled Söderberg cohorts (cohorts hired before 1950/1951 and after 1950/1951 described earlier) showed that the number of cases was above expectation for stomach cancer (SIR = 122.8), buccal cavity and pharyngeal cancer (SIR = 116.5), cancer of the small intestine (SIR = 125.0) and cancer of the rectum and rectosigmoid junction (SIR = 121.6), gallbladder (SIR = 112.2), pancreas (SIR = 115.8), peritoneum (SIR = 206.9), larynx (SIR = 132.2), lung bronchus and trachea (SIR = 120.0), pleura (SIR = 137.0), bladder (SIR = 181.7), brain and nervous system (SIR = 123.2), bone (SIR = 136.4), and Hodgkin disease (SIR = 110.1). Lung and bladder cancer increased with increasing cumulative exposure to B(a)P and so did laryngeal cancer and buccal cavity cancer. The SIRs for the lymphatic and hematopoietic system, including NHL, were increased for all post-1950 cohorts but not for men hired before 1950. This suggests that either this cancer has appeared because of competing risks or this is a "new cancer" deserving attention. Lymphatic and myeloid leukemia, which was below expected levels in the pre-1950 cohorts, was now above expected levels in the post-1950 cohorts (SIR = 115).[44] There was only one prebake plant with a very small number of cases, but there were more brain cancers than expected (SIR = 419.7, on the basis of two cases only). A follow-up of the same cohorts and other cohorts through 2004 has now been carried out, but results are not yet published. Nevertheless, this latest follow-up has not revealed any additional brain cancers in this cohort. Spinelli and colleagues[39] studied the mortality and cancer incidence of male workers with more than 5 years of employment at a vertical Söderberg aluminum reduction plant in British Columbia. That study identified 338 deaths and 158 incident cancers. There were significantly elevated rates of bladder cancer incidence and brain cancer mortality. The risk of bladder cancer was related to CTPV cumulative exposure, as was the risk of lung cancer (with a trend of borderline significance), although the rate of lung cancer was similar to that of the British Columbia population. The risks for lung cancer and bladder cancer were unchanged when smoking was taken into account. The risk of NHL and kidney cancer also increased with CTPV exposure although the overall rates were the same as the general population, but the numbers were small.

In 2006, Spinelli and colleagues[40] published a 14-year update of their earlier historical cohort (Table 2). Mortality and cancer incidence was compared with that of the British Columbia population, and Poisson regression was used to examine risk by cumulative exposure to BSM and B(a)P as the indices of exposure. The overall mortality from all causes was lower than that of the province, and the mortality from all cancers was similar to that of the general population of British Columbia. There was no significant excess mortality from any cause. For cancers with more than one observed death, nonsignificant excess mortality was reported for cancers of the oropharynx (SMR = 2.38), pancreas (SMR = 1.22), pleura (SMR = 1.98), brain (SMR = 1.54), stomach (SMR = 1.4), and bladder (SMR = 1.39), and NHL (SMR = 1.1).

For cancer incidence, there was a statistically significant excess of bladder (SIR = 1.8) and stomach (SIR = 1.46) cancer. Nonsignificant excess cancer incidence was reported for the following sites: lip (SIR = 1.58), nasopharynx (SIR = 1.80), pancreas (SIR = 1.25), pleura (SIR = 2.22), male breast (SIR = 2.11), testis (SIR = 1.12), brain (SMR = 1.48), and lung (1.10). Spinelli and colleagues[73] also reported that stomach, lung, bladder and kidney cancers, and NHL showed a statistically significant increasing trend with increasing cumulative B(a)P and BSM exposures. Validated estimates of BSM and B(a)P were used to examine the relationships between lung and bladder cancers and BSM and B(a)P; as expected, BSM and B(a)P were highly correlated ($r = 0.94$), but the precision increase by using B(a)P as opposed to BSM was 14% for bladder cancer and 5% for lung cancer.[21]

China

In 1997, Liu and collaborators[45] reported on the mortality of men employed for more than 15 years in carbon plants and the potroom of one aluminum reduction plant in China. Causes of death were obtained from the pension department and diagnosis was verified at the hospital. A reference population of 11,470 men working in steel rolling mills and considered nonexposed was used. Follow-up period was from 1971 through 1985 although some workers had been observed for more than 30 years since first hire. Workers were categorized as having high, moderate, low, and no exposure to carbon compounds. Overall, there were statistically significant excesses of mortality from all cancers, esophageal cancers, and lung cancer. In addition to these cancer sites, the authors reported statistically significant excesses of deaths from digestive cancer (SMR = 197), and liver (SMR = 225) in the highly exposed category. The SMR for esophageal cancer was 546 in the moderately exposed workers and 141 in the nonexposed workers. The SMR for lung cancer increased from 149 in the nonexposed workers to 430 in the highest exposed workers. Standardized mortality ratios also nonsignificantly increased for stomach cancer (SMR = 180) and other cancers (SMR = 182) in the highly exposed category. The SMR for esophageal cancer was statistically significant more than 10 years after the first employment, and for lung cancer after more than 20 years. Although the choice of the reference group might be criticized because of its likely exposure to occupational carcinogens, the findings are quite in line with those from other studies. It may be of importance that bladder cancers were not mentioned, although there were 17 cancers listed as "other cancers."

France

In France, Mur and colleagues[46] undertook a study of 6455 men employed for more than 1 year in 11 aluminum plants. Because of the difficulties in obtaining death certificate information in that country, causes of death were known for only 71% of workers. Assuming the same mortality patterns for workers with and

TABLE 3. Cohort Studies* That Have Reported Significant and Nonsignificant Excesses (Risk Estimate of 110 or More) of Malignant Tumors in Aluminum Workers in Various Countries

	Mortality		Incidence	
Malignant Tumor Site	**Statistically Significant Excess**	**Nonstatistically Significant Excess**	**Statistically Significant Excess**	**Nonstatistically Significant Excess**
Buccal cavity and pharynx		Spinelli et al[40] [S] (oropharynx)		Spinelli et al[40] [S]
		Gibbs et al[43] [S]		Gibbs and Sévigny[44] [S]
Lip				Romundstad et al[54] [P+S]
				Spinelli et al[40] [S]
Esophagus	Liu et al[45] [U]	Gibbs and Sévigny[60] [S]	Björ et al[58] [S+P]	Gibbs and Sévigny[44] [S]
Stomach	Konstantinov et al[57] [S]	Giovanazzi and D'Andrea[48] [S]†	Spinelli et al[40] [S]	Romundstad et al[36] [S]
	Gibbs et al[43] [S]	Rockette and Arena[35] [P]	Gibbs and Sévigny[44] [S]	
		Liu et al[45] [U]	Sim et al[37] [P]	
		Spinelli et al[40] [S]		
		Gibbs and Sévigny[60] [S]		
Small intestine				Gibbs and Sévigny[44] [S]
Colon				Romundstad et al [36,54,55] [P+S]
Rectum and rectosigmoid junction or rectum	Gibbs et al[43] [S]	Gibbs and Sévigny[60] [S]		Romundstad et al[54,55] [P+S] (rectum)
				Gibbs and Sévigny[44] [S]
Peritoneum				Gibbs and Sévigny[44] [S]
Liver	Liu et al[45] [U]	Milham[59] [P]		Rommunstad et al[55] [S+P]
		Mur et al[46] [S+P] (liver and gallbladder)		Gibbs and Sévigny[44] [S]
Pancreas	Rockette and Arena[35] [P+S]	Milham[59] [P]	Romundstad et al[36,54] [S+P]	Spinelli et al[40] [S]
	Carta et al[50] [P]	Rockette and Arena[35] [S and P]	Gibbs and Sévigny[44] [S]	
	Gibbs et al[43] [S]	Mur et al[46] [S+P]		
		Moulin et al[47] [S+P]		
		Spinelli et al[40] [S]		
		Gibbs and Sévigny[60] [S]		
Nose and sinuses		Spinelli et al[40] [S]		Romundstad et al[55] [S+P]
Larynx	Gibbs et al[43] [S]	Gibbs and Sévigny[60] [S]	Gibbs and Sévigny[44] [S]	Romundstad[36,54] [S+P]
		Moulin et al[47] [S+P]		Sim et al[37] [P]†
Lung/bronchus, trachea, and lung	Konstantinov et al[56,57] [S]	Giovanazzi and D'Andrea[48] [S]†	Gibbs and Sévigny[44] [S]	Romundstad[36] [S]
	Liu et al[45] [U]	Rockette and Arena[35] [S and P+S] (≥25 yrs)	Björ et al[58] [S+P]	Spinelli et al[40] [S]
	Gibbs et al[43] [S]	Mur et al[46] [S+P]†		Sim et al[37] [P]
	Gibbs and Sévigny[60] [S]	Sim et al[37] [P]‡		
Pleura		Spinelli et al[40] [S]		Spinelli et al[40] [S]
				Gibbs and Sévigny[44] [S]
Pleural mesothelioma	Sim et al[37] [P]		Sim et al[37] [P]	
Respiratory tract		Milham[59] [P]		Sim et al[37] [P]
Bone		Mur et al[46] [S+P] (bone, connective tissue, skin, and breast)		Gibbs and Sévigny[44] [S]
Skin	Konstantinov et al[56,57] [S]	Mur et al[46] [S+P] (bone, connective tissue, skin, and breast)		
Breast in males		Mur et al[46] [S+P] (bone, connective tissue, skin, and breast)		Spinelli et al[40] [S]
Prostate	Sim et al[37] [P]†	Milham[59] [P]		Romundstad et al[54,55] [P+S]
		Gibbs et al[43] [S]		Gibbs and Sévigny[44] [S]
		Gibbs and Sévigny[60] [S]		

(*continued*)

TABLE 3. (*Continued*)

Malignant Tumor Site	Mortality		Incidence	
	Statistically Significant Excess	Nonstatistically Significant Excess	Statistically Significant Excess	Nonstatistically Significant Excess
Testis		Milham[59] [P]		Romundstad et al[36] [S] Spinelli et al[40] [S] Sim et al[37] [P]
Penis				Rommundstad et al[55] [S+P]
Bladder	Gibbs et al[43] [S]	Rockette and Arena[35] [S] Mur et al[46] [S+P] Moulin et al[47] [S+P] Spinelli et al[40] [S] Gibbs and Sévigny[60] [S] Sim et al[37] [P]†	Romundstad et al[36,54] [S+P] Spinelli et al[40] [S] Gibbs and Sévigny[44] [S]	Romundstad et al[55] [P+S] Sim et al[37] [P]
Kidney		Milham[59] [P] Rockette and Arena[35] [P and P+S] Gibbs et al[43] [S] Sim et al[37] [P]	Rommundstad et al[54] [S+P] Sim et al[37] [P]	Romundstad et al[55] [P+S] Gibbs and Sévigny[44]
Urinary tract			Sim et al[37] [P]	Björ et al[58] [P+S]
Brain/central nervous system (malignant tumors)		Milham[58] [P] Mur et al[46] [S+P] Spinelli et al[40] [S]	Björ et al[58] [S+P] (central nervous system)	Spinelli et al[40] [S] Gibbs and Sévigny[44] [S]
Pituitary adenomas				Cullen et al[61] [P]
Thyroid				Romundstad et al[54,55] [S+P]
Head and neck				Björ et al[58] [P+S]
Lymphosarcoma and reticulosarcoma	Milham[59] [P]	Rockette and Arena[35] [P and S] Mur et al[46] [S+P] (lymphosarcoma, reticulosarcoma, multiple myeloma, and other lymphoid tissues)		
Hodgkin disease		Milham[59] [P] Gibbs et al[43] [S]		Romundstad et al[36,54] [S+P] Gibbs and Sévigny[44] [S]
Non-Hodgkin lymphoma		Spinelli et al[40] [S] Gibbs et al[43] [S] Gibbs and Sévigny[60] [S]		Gibbs and Sévigny[44] [S]
Multiple myeloma		Mur et al[46] [S+P] (lymphosarcoma, reticulosarcoma, multiple myeloma, and other lymphoid tissues) Gibbs et al[43] [S] Gibbs and Sévigny[60] [S]		Romundstad et al[36,54] [P+S] Gibbs and Sévigny[44] [S]
Other lymphatic cancers		Rockette and Arena[35] [S] Gibbs et al[43] [S]		
Leukemia		Milham[59] [P] Rockette and Arena[35] [P and S and P+S] Mur et al[46] [S+P] Gibbs et al[43] [S] Gibbs and Sévigny[60] [S]		Romundstad et al[36] [S+P] Gibbs and Sévigny[44] [P+S] (lymphatic and myeloid)
Lymphatic and hemopoietic cancers	Milham[59] [P] Carta et al[50] [S+P] (lymphomas and leukemias)	Rockette and Arena[35] [S]		Gibbs and Sévigny[44] [S]

*Not all authors are reported as later articles incorporated the same cohorts. Some of the excesses in this table did not show relationships with employment duration or exposure levels.

†Production, potroom, or maintenance workers.

‡Maintenance only, not production.

[P], prebake; [S], Söderberg process; [S+P], both Söderberg and prebake processes; [U], unspecified reduction process.

without ascertained causes of death, there were more deaths than expected from cancers of lung (SMR = 114), bladder (SMR = 209), pancreas (SMR = 145), liver, gallbladder, and hepatic bile ducts (SMR = 245), brain (SMR = 213), and leukemia (SMR 156). For lung cancer, the SMR was larger for workers from the Söderberg process (SMR = 136), but also for workers with less than 10 years of work duration (SMR 194). There were only 144 deaths and two thirds of the workers had worked less than 20 years.

In 2000, a follow-up mortality study in one of the above-mentioned Söderberg plants was undertaken by Moulin and colleagues.[47] The average follow-up duration until 1994 was 16.5 years. There was a marked healthy worker effect, no increased risk of lung cancer deaths, and a nonstatistically significant increase in bladder cancer (SMR = 177), an increase that was larger among men who were more likely to be exposed to PAHs for more than 10 years (SMR = 2.54).

Italy

Giovanazzi and D'Andrea[48] reported on the mortality of workers in a plant that started up in 1929 and mainly used the Söderberg process. There was a statistically significant excess of cancer deaths (SMR = 1.8), and only four lung cancer deaths with 1.9 expected.

Another group of researchers, led by Carta et al,[49] in 1992 reported a statistically significant excess of pancreatic cancer (three deaths, 0.8 expected; SMR = 388) in a small study of 1148 workers hired between 1971 and 1980 in a prebake primary aluminum production plant in Sardinia and followed through December 31, 1990. In the anode plant, there were two deaths with an expected 0.1 death. There were only 48 deaths overall and in view of the young cohort, the authors were not convinced that the excess could be linked to work in the industry. In 2004, Carta and colleagues[50] published a follow-up study of the same workers until the end of 2001, and there was still a statistically significant increase in pancreatic cancer (six deaths; SMR = 2.4) as well as in leukemias and lymphomas (eight deaths; SMR = 2.03). The authors separated the workers in three groups of increasing PAH exposure on the basis of the department, and showed that the risk was further increased among workers in the anode plant for both cancers, statistically significant for pancreatic cancer (SMR = 5.0) and almost significant for leukemias/lymphomas (SMR = 2.88; 95% CI = 0.98 to 8.50). A case-control analysis of the pancreatic cancer cases showed that employment in the anode factory, previous job as a farmer, and hyperglycemia were all three factors independently associated with an increased risk. There were no increases in lung cancer or bladder cancer deaths.[50]

Norway

The first study of cancer in the Norwegian aluminum industry was reported in 1982 by Andersen and colleagues.[51] Cancer cases were obtained from the Norwegian Cancer Registry and the expected rates were based on county rates. The two old plants had been using unhooded prebake cells since 1915, but one was converted to Söderberg in 1953. The new plants started in 1950 and used Söderberg cells in seven out of eight potrooms until 1968.[3] It was not possible to distinguish workers who had been employed in Söderberg and prebake, although one plant involved only prebake operations. Both cohorts of the old plants and the prebake only plant showed an excess of lung cancer incidence. The lung cancer excess overall was statistically significant (Observed = 57; Expected = 35.9) and seemed to be larger in the processing departments. The observed number of incident cases of leukemia and of bladder, kidney, and larynx cancers exceeded expectation but were not statistically significant in excess.[51] Nevertheless, it was noted that using the whole Norwegian population as reference did not make a difference for the old plants, but the new plant would have shown a deficit for lung cancer and bladder cancer if national rates had been used instead of the county rates.[3]

In 1995, Rönneberg and Andersen[52] published a report on a prebake aluminum plant previously included in the original Andersen study. The authors reported a statistically significant increase in incidence of bladder cancer with exposure to CTPVs 40 years or more before diagnosis, and in incidence of lung cancer for exposure 35 to 50 years before diagnosis. They also mentioned an association between incidence of kidney cancer and exposure to heat 20 to 35 years before diagnosis.[52]

In 1999, the same group of authors described the experience at an aluminum smelter, in Western Norway.[53] This smelter started production with HS Söderberg cells between 1948 and 1950, then a carbon plant producing anode paste from petroleum coke and coal-tar pitch was added in 1949, and Söderberg VS potrooms between 1959 and 1962. Prebake cells were introduced between 1959 and 1970. Cancer incidence was determined between 1953 and 1993 using the Norwegian Cancer Registry. The study found a statistically significant increased incidence of lung cancer in short-term workers (SIR = 152) and in maintenance workers (SIR = 211), and a nonsignificant increase of cancers of the lip (SIR = 204; 95% CI = 93 to 387) and of the rectum (SIR = 141; 95% CI = 92 to 209) among production workers, and of lymphatic and hematopoietic cancers among maintenance workers (SIR = 239; 95% CI = 96 to 492). Dose–response analysis with cumulative PAH exposure showed a statistically significant trend with cancers of the bladder and the lip among production workers 30 years or more after the first exposure. There was no association between cumulative exposure to PAHs and lung cancer, heat and kidney cancer, or magnetic fields and lymphatic and hematopoietic cancer. A potentially important observation was the statistically significant excess of lymphatic and hematopoietic cancer in maintenance electricians, and the authors suggested that electrical discharges might be a useful avenue for future investigation.[53]

In 2000, the same group of authors published a study of cancer incidence in another aluminum plant in Western Norway.[55] This plant started production in 1920 with unhooded prebaked anodes, then in 1939 changed to Horizontal Söderberg technology, which was used until 1978. In 1958, the plant added VS potrooms, and in 1981, a potline using hooded center prebake pots. There were no statistically increased SIRs for any cancer site. Nevertheless, there were more than expected cancer incidences of several sites with a lower CI limit above 90, namely cancers of the colon (SIR = 140), rectum (SIR = 140), prostate (SIR = 110) and thyroid (SIR = 310). The SIR for lung cancer was less than 100 and the SIR for bladder cancer was 130 (95% CI = 80 to 190), and there was no relationship between lung or bladder cancer and increasing cumulative exposure to PAHs. There were no cancers of the bladder or lung in nonsmokers. The authors did note the small size of their study.[55]

In the same year, the same group of authors, led by Romundstad,[54] published a report on cancer incidence in the aluminum industry. These six plants had been previously studied.[51–55] Three of these plants began before 1920 and the others between 1948 and 1958, and the population involved mixed prebake and Söderberg workers. That study did show an overall statistically significant excess of bladder cancer (SIR = 130), which increased with increasing cumulative PAH exposure, reaching a rate ratio around 2 for the upper level of exposure after a lag of 20 years or more. There was no association with lung cancer, or between lung cancer and cumulative PAH exposure. Although there was a significant excess of lung cancer when local rates were used (SIR = 140), national rates were preferred as the reference because they are more robust than local rates. There was a borderline significant trend of increased kidney cancer risk with increasing cumulative exposure to PAHs. There were also higher rates of pancreatic cancer in PAH-exposed workers than those in nonexposed workers but no clear exposure–response

relationship. In this study, the cancers for which the SIR exceeded 110 with a lower CI limit of 90 or more were colon (110), rectum (110), prostate (110), and multiple myeloma (140), all nonsignificant.[54]

The same authors also produced an analysis of two of these plants that started operating in the mid-1950s.[36] They reported findings similar to those of the six-plant study—a significant excess risk of bladder cancer among workers exposed to PAH, but no clear dose–response relationship. The data also suggested an association between exposure to PAH and pancreatic cancer, but no association with lung cancer. An elevated multiple myeloma risk was also observed among workers employed for more than 3 years (SIR = 197; 95% CI = 98 to 352).

Russia

As reported by Simonato[30] and later by Enterline,[74] studies were done by Konstantinov and colleagues in two Söderberg and one prebake aluminum smelters in the then Union of Soviet Socialist Republics in 1971 and 1974.[56,57] Those reviewers noted that there was no information on the size of the study populations.[30,74] The first study reported statistically significant excess mortality for lung and skin cancers among workers 18 to 39 years old in a Söderberg plant, whereas there were no cancer deaths in the prebake plant. The second study reported no overall cancer excess in a prebake operation but SMRs of 360 and 170 from respiratory cancer in Söderberg plants and an overall RR of 2.3 from stomach cancer in one Söderberg plant but not the other. An almost 40-fold excess of skin cancer morbidity was also reported in persons aged 18 to 39 years in one of the Söderberg plants but not in the prebake operations. There seems to have been no more recent studies reported in the English language from Russia.

Sweden

In 2008, Björ and collaborators published an incidence cohort study conducted at an aluminum reduction plant.[58] Four reference populations were used, with rates from Sweden, Northern Sweden, the county, and seven municipalities that had socioeconomics similar to that of Sundsvall where the plant was located. Compared with Northern Swedish rates, there were statistically significantly increased incidence of cancers of the lung (SIR = 162), central nervous system (SIR = 183), and esophagus (SIR = 258), and the rates from these causes were elevated in comparison to rates in Sweden and in the seven municipalities. Workers with more than 10 years of employment had an SIR for lung cancer of 199 (95% CI = 121 to 307), which had increased from 139 (95% CI = 67 to 256) among workers employed for less than 2 years, with no significant trend; however, the authors noted the absence of smoking data. There was also no significant trend for increasing years of employment for central nervous system cancers or from cancers of the urinary organs, but SIRs were elevated for the latter compared with Sweden (SIR = 129) and Northern Sweden (SIR = 111), although not when the seven municipalities rates were used (SIR = 102) and risk did not increase with increasing years of employment. The lack of bladder cancer excess is noteworthy as this study had a very long follow-up period.[58]

USA

In 1974, Milham completed an occupational mortality study on more than 300,000 men who died between 1950 and 1971 in Washington State.[75] Using a proportional mortality ratio analysis, excess mortality from cancer of the lung, pancreas, and malignant lymphoma was found in the state aluminum industry. Although proportional mortality ratio analyses have some serious limitations, these findings have been corroborated elsewhere in the literature since that time.

Five years later, Milham[59] investigated the mortality of workers in a prebake plant in Washington State. He defined exposure as working in the carbon plant, rodding, potlining, potrooms and quality control. He found a statistically significant increased mortality from lymphocytic and hematopoietic cancers (SMR = 184), including lymphosarcoma and reticulosarcoma with a statistically significant SMR of 316 in all workers (643 in "exposed" workers). Several sites presented nonsignificant excesses overall that were larger among exposed workers: leukemia (SMR = 109 and 131), and cancers of the respiratory system (SMR = 117 and 129), prostate (SMR = 162 and 211), and liver (SMR = 164 and 273). Pancreatic cancer (SMR = 238), Hodgkin disease (SMR = 397), and benign tumors (SMR = 679) were significantly higher in nonexposed workers, and respiratory cancer and lymphatic and hematopoietic cancer mortality did increase somewhat with latency. The author concluded that some of the lymphatic and hematopoietic and lung cancers might be of occupational origin. He also mentioned a statistically significant excess of benign tumors of the brain (SMR = 391; five deaths).[59]

A few years later, Rockette and Arena[35] carried out a large study in 14 plants that included horizontal Söderberg, VS, prebake (P), and mixed prebake and Söderberg operations (M). Cause-specific mortality was compared with that of the US population. There was a statistically significant increased SMR for benign and unspecified tumors in the prebake plants (SMR = 200). There were nonstatistically significant elevated SMRs from cancers of the stomach (SMR-P = 113.3), pancreas (SMR-P = 132.9; SMR-M = 125.5), kidney (SMR-P = 151.3), bladder (SMR-S = 161.8), lymphosarcoma and reticulosarcoma (SMR-P = 132.2; SMR-S = 116.7), and leukemia and aleukemia (SMR-P = 127.6; SMR-S = 130.8; SMR-M = 123.5). Strangely, the statistically significant excess of leukemia and aleukemia in Söderberg workers was found among workers employed for less than 15 years, whereas the excess in prebake workers was found among workers employed for more than 15 years. There was no excess of bladder cancer deaths in workers ever employed in the potrooms or carbon plant in the US studies.[35]

When the SMRs for pancreatic cancer were examined in relation to cumulative employment, there appeared to be an increasing risk with increasing employment in prebake and Söderberg potroom workers but not in carbon plant workers. The pattern of SMRs for lung cancer was not very clear: for the prebake workers, the SMRs were elevated with cumulative employment of less than 10 years and between 20 and 25 years, whereas for the Söderberg workers, they were elevated with 10 to 15 years and with more than 25 years of employment.[35]

A cluster of four cases of pituitary adenomas was reported in aluminum workers between 1990 and 1994.[61] The epidemiological investigation on 25 cases of pituitary adenomas diagnosed in 17 plants across the United States reported an OR of 1.12 for ever working in a reduction plant, but the OR decreased when the analysis was restricted to 5 years and more of working at a reduction plant. The authors concluded that there was "no strong evidence" to suggest an occupational origin for the adenomas.

GRAPHITE ELECTRODE FABRICATION

Seven articles presented studies on cancer incidence or mortality among workers in carbon electrode manufacturing plants. One of the articles also included aluminum reduction workers.[45] Most studies were rather small, with fewer than 50 deaths or cases of lung cancer and smaller numbers of other cancers, which in most studies precluded meaningful exposure–response analyses. Most studies reported on single plants with workforces varying from 332[76] to 2219 workers with follow-up as short as 10 or 10 years,[77,78] and ranging up to 47 years.[79]

The mortality of 2219 white employees in US carbon electrode and carbon specialty plants was studied for the period 1974 to 1983.[77] The plants opened in 1937 or earlier, and the study

population was employed at one of the 11 active locations on January 1, 1974, and had at least 10 years of prior service. The total number of cancer deaths was not large ($n = 78$). There was a statistically significant excess of lung cancer in one plant that did not involve CTPV exposures but did use "asbestos." The only excess (not statistically significant) was from lymphopoietic cancer deaths that occurred mostly in salaried employees. This study is relatively small, cohort definition is cross-sectional, and the follow-up is only 10 years. As cancers such as lung cancer and bladder cancer have latencies of 20 and 30 years or more, this study might not have detected an excess even if there had been one.

Two Asian studies reported a statistically significant increase in lung cancer mortality,[45,76] and a Swedish study mentioned a nonsignificant increase on the basis of two deaths.[79] The other studies did not find an increased risk for lung cancer. Bladder cancer mortality was elevated in one French plant with a follow-up of 25 years on the basis of three deaths[78] and an Italian one with a 40-year follow-up on the basis of seven deaths.[80] An Italian study reported a fourfold increase in liver cancer mortality, and the authors mentioned specific exposures to phenolic and furfuryl resins used in the plant but also pointed out they could not adjust for lifestyle factors and hepatic viral infections.[81]

Thus, the available evidence from graphite electrode workers is limited in its usefulness for the interpretation of risks to aluminum reduction workers.

AVAILABLE EVIDENCE BY CANCER SITE

Decisions concerning causality are usually based on criteria such as the following which include those proposed by Sir Bradford-Hill[82]: strength of association (RR and OR), consistency (of results between different studies), specificity (association limited to specific workers and types of disease), temporal relationship (cause to precede consequence), biological gradient (dose–response or exposure–response relationships), biological plausibility (according to actual knowledge), coherence (considering the natural history of the disease), experimental evidence (whether preventive actions reduce the association), and analogy (consideration of evidence from similar exposures). Of course, the studies considered must also provide some evidence that the increased risk is not caused by bias or confounding. On the basis of most of these criteria, the IARC has classified occupational exposures during aluminum production as a causal factor, with sufficient evidence in humans, for cancers of the lung and the bladder.[83]

The cancers reported in various studies are summarized in Table 4, with an evaluation of several of the Bradford-Hill criteria. It should be noted that several indicators have been used in these different studies, from job title and departments to cumulative exposure to (B(a)P); the latter has been a useful index of exposure, but is probably highly correlated with all contaminants and physical agents in the potrooms and the carbon plants, so associations do not mean that a specific agent is the causal factor unless there is additional mechanistic or experimental evidence for expecting that agent to cause the disease. When the cancer does not seem to be related to the B(a)P or BSM index of exposure, it is only possible, with rare exceptions (eg heat and electromagnetic field), to examine the strength of association with employment in the industry. In the following section, chemicals potentially encountered in the smelting industry have been taken from the historical review undertaken by Benke and colleagues in 1998.[5] The IARC has been taken as a reference source for carcinogenic classification. This should not be interpreted that the current authors fully endorse the classification for all substances. The authors' interpretation of the currently available evidence is presented next under the categories "no convincing evidence," "little evidence," "some evidence," "consistent evidence," and "reasonably strong evidence." These interpretations were based on the following criteria, which are also shown as footnotes to Table 4:

Insufficient data: There were few reports concerning these cancer sites that were also rare.
No convincing evidence: Most studies did not show an increased or decreased risk, were studies with a small increased risk that was not statistically significant, were without adjustment for major potential confounders, and/or were studies with some evidence that there was no exposure–response relationship.
Little evidence: The evidence was deemed insufficient to conclude that there was a possible association (eg no more than one study) with a statistically significant increase in the risk or with a risk of more than 1.5, and some inconsistent borderline evidence of exposure–response relationship.
Some evidence: There were a few positive studies showing a possible association with more than one study with a statistically significant increase in the risk and more than one study with a risk of more than 1.5, and at least borderline evidence of exposure–response in 2 studies or more.
Consistent evidence: The evidence suggested a probable association as most studies showed increased risks with some evidence of exposure–response and at least one study with a risk of more than 2.0.
Reasonably strong evidence: Most studies showed an increased risk with evidence of exposure–response in several studies and more than one study with a risk of more than 2.0.
Buccal cavity and pharynx: No convincing evidence (exposure unclear).

Studies in Quebec have shown a slightly elevated but nonsignificant increased incidence of this cancer in four of the six cohorts observed. Furthermore, there is an exposure–response relationship between the incidence of this cancer and B(a)P cumulative exposure for workers hired before 1950 but not for the workers hired after 1950.[44] Mortality from this cause was below expectation in the Quebec cohorts, but was elevated for pharyngeal cancer in British Columbia, Canada. Nevertheless, in Australia (prebake only), France and the United States (prebake and Söderberg), there was no excess incidence or mortality for this cancer site and this site was not mentioned in the Norwegian studies. The inconsistency in findings needs to be further investigated before this cancer can be considered to be related to an occupational exposure in this industry. According to the IARC, pharynx cancer is linked, with limited human evidence, to exposure to asbestos.[84]

Esophageal cancer: no convincing evidence (exposure unclear). Esophageal cancer was reported as statistically significantly increased in two studies: a Chinese mortality study[46] and a Swedish incidence study.[75] Increased mortality and incidence have also been reported in Quebec, but mostly in one plant.[44,60] Nevertheless, when a latency of 20 years was applied, there was a nonsignificant increased mortality from this cause in all years of hire categories for cohort members. The main risk factors associated with esophageal cancer are alcohol intake, smoking, gastroesophageal reflux disease, and drinking very hot liquids, which were not adjusted for in the available studies. Exposure to tetrachloroethylene, which may be found in some metal smelting industries, has been classified by the IARC as carcinogenic for the esophagus, but with limited human evidence.[85]
Stomach cancer: some evidence (exposure unclear). Stomach cancer remains an enigma. It has been reported in several cohorts, but does not have a clear relationship with increasing exposure using B(a)P as the index. Stomach cancer has been reported in Australian prebake operations with a monotonic trend with B(a)P exposure, but also there was an increased risk among office workers. This was not found in the Quebec studies of Söderberg plant workers where

TABLE 4. Summary of the Available Evidence* of a Causal Relationship Between Work in Aluminum Production and Selected Cancer Sites

Cancer Sites	Strength of Association	Strength (More Than 100,000 Person-Years)	Any SS Increase‡	Consistency§	Exposure Gradient	Comments§	Force of Evidence‖
Buccal cavity and pharynx	M: 0.13–2.38; I: 0.79–3.16	M: 0.66–2.38; I: 0.0.79–3.16	No	Decreased risk found in most studies	Little evidence (in one study, among smokers)	Mostly decreased risk, little evidence of exposure–response, but the effect of potential confounders cannot be ruled out	–
Esophagus	M: 0.54–5.46; I: 0.6–2.58	M: 0.54–1.32; I: 0.6–2.56	Yes: I(1), M(1)	No (increased in China and Sweden)	No evidence (no: one study)	Mostly decreased risk, no evidence of exposure–response, and the effect of potential confounders cannot be ruled out	–
Stomach	M: 0.74–2.3; I: 0.65–4.04	M: 1.0–1.48; I: 1.0–4.04	Yes: I(3), M(2); EG with B(a)P(2)	No (variable results)	Some evidence (yes: two mortalities, one incidence; no: one mortality, one incidence)	Moderate increase in risk, inconsistent results, some evidence of exposure– response after adjustment for smoking, but the effect of potential confounders cannot totally be ruled out	+
Rectum and rectosigmoid junction or rectum	M: 0.46–1.30; I: 0.65–1.452	M: 0.74–1.304; I: 0.97–1.452	No	No increased risk in most studies	Little evidence (yes: one study)	Mostly no increase in risk, little evidence of exposure–response, but the effect of potential confounders cannot be ruled out. Few reports	–
Pancreas	M: 0.92–1.49; I: 0.9–2.59	M: 1.08–1.49; I: 0.9–2.59	Yes: I(2), M(2); EG with PAHs(2)	Increased risk in most studies	Some evidence (yes: three to four studies; no: one study)	Moderate to high increase in risk, some consistency between studies, some evidence of exposure–response in a few plants, but the effect of potential confounders cannot be ruled out	++
Larynx	M: 0.907–1.57; I: 0.79–5.67	M: 0.907–1.57; I: 0.79–5.67	Yes: I(1)	No increased risk in most studies	No evidence (no: one study)	Moderate to high increase in risk, studies generally negative, no evidence of exposure–response, but the effect of potential confounders cannot be ruled out	–

(*continued*)

TABLE 4. (*Continued*)

Cancer Sites	Strength of Association	Strength (More Than 100,000 Person-Years)	Any SS Increase‡	Consistency§	Exposure Gradient	Comments§	Force of Evidence‖
Lung/bronchus, trachea, and lung	M: 0.63–4.3; I: 1.0–2.65	M: 1.07–1.36; I: 1.0–2.12	Yes: I(2), M(2); EG with B(a)P(2)	Increased risk found in all but two studies	Very good evidence (yes, several studies; also for smoking-adjusted risks)	Moderate increase in risk, studies generally positive, very good evidence of exposure–response, after adjustment for smoking	+++¶
Pleura, including mesothelioma	M: 1.98–4.36; I: 1.37–3.02	M: 1.98; I: 1.37–3.02	Yes: I(1), M(1)	Risk not reported in most studies	Insufficient evidence	Rare cancer. Risk appears to be probably associated with use of asbestos. Few reports	–
Bone	M: 2.04; I: 1.36	M: NA; I: 1.36	No	Insufficient reports	Insufficient evidence	Very rare cancer. Small increase, no evidence of exposure–response. Very few reports	?
Skin melanoma	M: NA; I: 0.35–1.66	M: NA; I: 0.5–0.80	No	Decreased risk found in most studies	No evidence	Mostly decreased risk, no evidence of exposure–response, no adjustment for potential confounders	–
Skin nonmelanoma	M: NA; I: 0.8–1.05	M: NA; I: 0.8	No	Decreased risk found in most studies	No evidence	Mostly decreased risk, no evidence of exposure–response, no adjustment for potential confounders	–
Prostate	M: 0.63–2.11; I: 0.48–1.55	M: 0.70–0.93; I: 0.96–1.45	Yes: I(1), M(1)	Decreased risk found in most mortality studies. Increased risk in many incidence studies	Little evidence (yes: one mortality study; no: two incidence studies	Some increased incidence risks, decreased risk in most mortality studies, little evidence of exposure–response	–
Testis	M: 0.76–7.07; I: 0.74–1.57	M: NA; I: 0.8–1.12	No	No (variable results)	No evidence (no: one study)	Small increase in risk, no evidence of exposure–response, no adjustment for potential confounders. Very few reports	–
Bladder	M: 0.65–2.24; I: 0.78–4.9	M: 0.85–2.24; I: 1.3–4.9	Yes: I(3), M(1); EG with B(a)P(4)	Increased risk in most studies	Very good evidence (yes: three to four studies; no: two studies)	Small to high increased risk, studies generally positive, very good evidence of exposure–response, after adjustment for smoking	+++¶

(*continued*)

TABLE 4. (*Continued*)

Cancer Sites	Strength of Association	Strength (More Than 100,000 Person-Years)	Any SS Increase‡	Consistency§	Exposure Gradient	Comments§	Force of Evidence‖
Kidney	M: 0.49–2.09; I: 0.74–1.99	M: 0.49–1.06; I: 0.96–1.96	Yes: I(2); EG with B(a)P(2)	Increased risk in several studies	Some evidence (yes: three studies; no: two studies)	Small to moderate increase in risk (incidence), several positive studies, some evidence of exposure–response	+
Brain/central nervous system	M: 0.54–2.13; I: 0.62–1.90	M: 0.967–2.13; I: 0.90–1.48	Yes: I(1)	Increased risk in several studies	Little evidence (borderline yes: one study; no: one study)	Small to high increase in risk, several positive studies, little evidence of exposure–response	±
Lymphosarcoma and reticulosarcoma	M: 1.16–1.75; I: NA	M: NA; I: NA	Yes: M(1)	Insufficient reports (two mortality studies)	Insufficient evidence	Small to moderate increase in risk. Very few reports	?
Hodgkin disease	M: 0.24–3.97; I: 0.36–1.96	M: 0.3–1.16; I: 0.49–1.93	No	Increased risk in a few studies	Insufficient evidence	Small to moderate increase in risk, no clear evidence of exposure–response, no adjustment for potential confounders	−
Non-Hodgkin lymphomas	M: 0.24–1.42; I: 0.36–1.96	M: 0.24–1.42; I: 0.90–1.55	Yes: I(1); EG with B(a)P(1)	Increased risk in a few studies	Little evidence (yes in study); borderline (no in one study)	Small to moderate increase in risk, little evidence of exposure–response, no adjustment for potential confounders	±
Multiple myeloma	M: 0.84; I: 0.84–1.97	M: 0.84; I: 1.50	No	Increased risk in a few studies	Insufficient evidence	Small increase in risk, no evidence of exposure–response, no adjustment for potential confounders	−
Leukemia	M: 0.57–1.56; I :0.28–2.00	M: 0.84–1.56; I: 0.89–2.00	Yes: M(1)	Increased risk in a few studies	Insufficient evidence	Small to moderate increase in risk, no evidence of exposure–response, no adjustment for potential confounders	±
Lymphatic and hemopoietic cancers	M: 0.84–2.30; I: 0.85–1.14	M: 1.01–1.16; I: 0.85–1.13	Yes: M(2)	Increased risk in a few studies	Insufficient evidence	Small increase in risk, little evidence of exposure–response, no adjustment for potential confounders	±

* Bradford-Hill's criteria of specificity and of analogy have not been retained here.

†Studies that have accumulated 100,000 person-years of observation or more are those of Mur et al[47] (mortality); Romundstad et al[74] (incidence); Spinelli et al[40] (incidence and mortality); Gibbs et al[43,44,60] (incidence and mortality).

‡Number of studies between parentheses.

§Risk qualification: decreased, less than 1.0; small, 1.1 to 1.5; moderate, 1.6 to 2.0; high, 2.1 or more.

‖Force of evidence categories and criteria: ? (insufficient data), there were few reports concerning these cancer sites that were also rare; − (no convincing evidence), most studies did not show an increased or decreased risk or were studies with a small increased risk that was not statistically significant or were without adjustment for major potential confounders, and/or were studies with some evidence that there was no exposure–response relationship; ± (little evidence), the evidence was deemed insufficient to conclude that there was a possible association, for example, no more than one study with a statistically significant increase in risk or with a risk of more than 1.5, and some inconsistent borderline evidence of exposure–response relationship; + (some evidence), there were a few positive studies showing a possible association with more than one study with a statistically significant increase in risk and more than one study with risk of more than 1.5, and at least borderline evidence of exposure–response in two studies or more; ++ (consistent evidence), the evidence suggested a probable association as most studies showed increased risks with some evidence of exposure–response and at least one study with risk of more than 2.0; +++ (reasonably strong evidence), most studies showed an increased risk with evidence of exposure–response in several studies and more than one study with a risk of more than 2.0.

¶Evidence classified sufficient for humans according to the IARC for this cancer site.

B(a)P, benzo(a)pyrene; EG, exposure gradient; I, incidence; M, mortality; NA, not available; PAHs, polycyclic aromatic hydrocarbons; SS, statistically significant.

there was no relationship with B(a)P exposure, whereas in British Columbia there was a statistically significant trend with exposure when a 20-year lag was included and after adjustment for smoking. In conclusion, stomach cancer risk seems to be associated in some way with employment in the aluminum smelter industry, but the etiology is unknown.

Among agents reported to be present in some potrooms, lead and asbestos have been classified by the IARC as carcinogenic for the stomach, but with limited human evidence.[85]

Rectum and rectosigmoid junction: no convincing evidence (exposure unclear). Cancer of the rectum and cancer of the rectum and rectosigmoid junction have been found in statistically significant excess only in Quebec cohorts and slightly above expectation in Norway. There is also an indication that the risk might be exposure-related although the strength of the association is still weak. Among potroom exposures, only asbestos has been classified by the IARC as carcinogenic for the colon and rectum, but with limited human evidence.[85] In Australia, where increased incidence and mortality for mesothelioma have been found among prebake workers, no increase in colorectal cancer was reported.[37]

Pancreatic cancer: consistent evidence (exposure unclear). Although pancreatic cancer has now been reported in cohorts in several countries, there is no clear consistency in results. It is interesting to note that in the US study, there was a clear excess of pancreatic cancer mortality in workers ever working in the potrooms (SMR = 138) and carbon plant (SMR = 142.1).[35] The excess was significant for workers spending more than 5 years in the potrooms, and the highest risk was in prebake operations. In Italy also, the excess was larger in carbon plant workers and it was also reported that previous work as a farmer and hyperglycemia were associated with the increased risk.[51] In Norway, the increased risk was found in mixed prebake and Söderberg plants (with higher risks with a 20-year lag), whereas in Quebec, the highest risk was found in one small plant with risks being essentially at background in much larger plants. This cancer needs further investigation in several countries and also in prebake operations, especially with adequate control of known risk factors. So far, this cancer site has not been associated with sufficient evidence to conclude that it is related to a specific exposure found in potrooms.

Larynx: no convincing evidence (exposure unclear). Increased risks of laryngeal cancer have been reported in Quebec (especially in one plant, without an exposure–response trend), France, and Norway, but the number of cases is generally small (from 7 to 60) and the adjustment for potential confounding factors, in particular smoking and alcohol consumption, has not been adequately done in any study. Among potroom exposures, strong inorganic acid mists and asbestos have been classified by the IARC as carcinogenic for the larynx with sufficient human evidence.[85]

Lung cancer: reasonably strong evidence (PAHs and possibly other exposures). Lung cancer, as noted previously, meets most of the criteria as far as Söderberg operations are concerned. Smoking as a confounder has been considered and eliminated. In the Canadian studies, the associations are strong and there are clear exposure–response relationships. The findings are also compatible with the findings in coke oven and other PAH-exposed populations, and PAHs are known to induce tumors. There are indications that as the level of exposure to CTPVs has decreased, so has the risk of lung cancer. It must be recognized that smoking rates have also decreased and the smoking data in all studies are imperfect.

On the basis of the levels of exposure associated with the increased risks in Söderberg operations, one would not predict high risks in prebake operations. The fact that some have been reported in prebake operations requires that this continue to be monitored and that potential confounders be fully taken into account. The absence of lung cancer in some Söderberg operations is most likely related to the levels of exposure, sizes of cohorts, and/or follow-up period, although differences in the operating conditions, pitches, and PAH mixtures cannot be totally excluded. It should be also noted that lung cancer excesses have been well described in other industries involving PAH exposures.

Other agents than PAHs, which have been associated with sufficient human evidence to lung cancer, encountered in the aluminum reduction industry are soot, asbestos, beryllium, cadmium, chromium, nickel, and silica for example.[85] Nevertheless, the most probable etiological agents are PAHs. Coal tar pitches from which PAHs originate have been classified by the IARC as having sufficient evidence for carcinogenicity in humans.[85]

Skin cancers: no convincing evidence (coal tar pitch, arsenic). Only three studies reported increased risks of skin cancer: a Norwegian study reported increased incidence of malignant melanoma among workers with 3 years or less of cumulative employment in one prebake aluminum plant (workers with more than 3 years had a nonsignificant deficit); a Russian study reported statistically significant increases of deaths from unspecified skin cancer ranging from 6.6 among workers aged 40 years or more to 38.8 among younger workers; and finally a French study reported a twofold increase of death from cancers of the skin and other sites (breast, bone, and connective tissue). All the other studies mentioned deficits or did not report a result for skin cancers. None of these studies adjusted for sun exposure.

Coal tar pitch and arsenic and inorganic arsenic compounds (a potential potroom exposure) have been classified by the IARC as carcinogenic for nonmelanotic skin cancer with sufficient human evidence.[85]

Prostate and testicular cancer: no convincing evidence (exposure unclear). Prostate cancer was reported to be increased after 20 years of work in an aluminum smelter in Australia, and the increase was statistically significant for mortality but not for incidence.[37] Nonsignificant increases were also reported in Quebec and Norway, but no exposure–response trend could be found, and four other studies did not report increased risks. The proportion of the population screened for prostate cancer varies a lot between countries, which makes incidence difficult to compare from one study to another, and the long survival associated with that cancer makes mortality a less than adequate risk estimate to follow. Three studies reported figures on testicular cancer, two of which with a nonsignificant increase[37,40] and one with no increase.[54]

Among potential potroom exposures, arsenic and cadmium have been classified by the IARC as carcinogenic for the prostate, but with limited human evidence; no occupational exposures have yet been linked to testicular cancer.[85]

Bladder cancer: reasonably strong evidence (aluminum production) and limited evidence (CTPVs). There seems to be little doubt that when studies in Söderberg plants allow adequate follow-up time and workers have had adequate exposure in the potrooms, they are at an increased risk of bladder cancer. Indeed, there is evidence that bladder cancer is strongly associated with Söderberg potrooms in Canada and Norway, detected at statistically nonsignificant levels in the United States and France. Studies have shown that this risk increases with increasing exposure using the B(a)P index or BSM indices of exposure. In Quebec, the studies have also shown, in parallel with reducing B(a)P exposure, mortality and incidence of this cancer have reduced. These reductions may be related to earlier detection, better treatment, and reductions in exposure to B(a)P or agents correlated with this index, but the specific etiological factor remains unknown. Workers in the carbon plant were reported not to have an increased risk of bladder cancer,[71] and in spite of long follow-up, there is no clear increase in bladder cancer incidence among Söderberg workers in Sweden. Comparison of raw materials and operating conditions may be useful. As bladder cancers are often associated with amines or nitroso compounds,

these have been proposed as etiological factors, but studies have shown the potential for exposure to any significant quantity of these to be small, although plausible.[86] Another possible explanation is an indirect dehydrating effect of heat on urine concentration. There is evidence that persons who drink large quantities of fluid are at a reduced risk of bladder cancer,[87] and this has been linked to frequency of urination.[88] Potroom work in the past involved considerable exposure to heat, a hazard that has reduced in parallel with B(a)P concentrations. Smoking has also been linked to bladder cancer risk, but while contributing to the risk, it does not totally explain the excess risk in CTPV-exposed workers. The jury on the specific etiological factor in bladder cancer is still out.

Soot and coal tar pitch have been associated with limited human evidence to bladder cancer.[85] This evidence comes in large part from the aluminum industry studies.

Kidney cancer: some evidence (exposure unclear). Although the evidence is weaker than for bladder cancer, there are reports of an increased risk of kidney cancer in aluminum production workers in many countries. Several of the reported increases are in prebake facilities with significant excesses being reported in Australia.[37] A possible association is credible because an exposure that increases bladder cancer risk might be anticipated to increase to some extent the risk in other urinary organs; it is however noteworthy that a bladder cancer excess was not reported in the Australian prebake operations. Although some exposure–response relationships examined have not been convincing, the cancer incidence in Söderberg plants in Quebec[44] and British Columbia[40] does suggest the possibility of an association. Heat has been suggested as a factor in kidney cancer in aluminum smelters,[55] but recent studies have failed to find associations between total fluid intake and renal cancer.[7,89]

Among potroom exposures, only cadmium has been classified by the IARC as carcinogenic for the kidney, but with limited human evidence.[85]

Brain and central nervous system cancers: little evidence (exposure unclear). Nonstatistically significant increased risks of brain and central nervous system malignant tumors have been reported in the Canadian cohorts, in one French study, in a Norwegian plant and in the United States, whereas the increase was statistically significant in the Swedish Söderberg cohort. No exposure–response trend was reported however, and the increase does not appear to be associated with a particular process. After investigating a cluster of four cases in a US prebake aluminum plant, "no strong evidence ... that the rate of pituitary adenomas is increased in aluminum workers generally" was found.[76] There do not appear to have been other reports of these adenomas. One study mentioned an increased risk of benign brain tumors in an American aluminum reduction plant, but no other authors reported such increased risks.

Lymphatic and hematopoietic cancers: no convincing to little evidence (exposure unclear). There is no consistent evidence that leukemias, lymphomas, or any other hematopoietic cancers are associated with work in potrooms. Nevertheless, several studies in different countries reported increases in mortality or in incidence, for only one disease (eg, lymphosarcoma in the United States, Hodgkin disease in Norway, or NHLs in Canada) or for all hematopoietic diseases grouped (in Italy). Non-Hodgkin lymphomas have been reported to occur more frequently than expected in Quebec but no trend with B(a)P cumulative exposures although a significant trend was noted with B(a)P in British Columbia but observed rates were below British Columbia rates. No chemical potroom exposure has been so far classified by the IARC as carcinogenic to the hematopoietic system. Nevertheless, extremely low frequency magnetic fields have been linked with limited human evidence to childhood leukemia.[85]

CONCLUSION

It is now clear that cancers of the lung and the bladder are associated with work in most Söderberg potrooms, and there are indications that prebake plants should be further investigated for these cancers taking into account smoking and excluding carbon plants. Cancer incidence studies are preferable as some causes such as bladder cancer do not always result in death and other outcomes may not be detected using mortality only. Furthermore, it is preferable to find any cancer excess as early as possible so that preventive actions might reduce future risks. The risk and ability to detect the risks in the different studies are probably limited by the long latencies, misclassification in levels of exposure, and less than adequate control of smoking. Differences in sources of pitches and other sources of PAHs may also be explanatory factors. Advances in methods of determining exposure should be an integral part of epidemiological follow-up to improve exposure and consequently risk estimates. Certain types of cancer, such as cancers of the stomach, kidney, and pancreas, whose risks do not seem to increase in relation to B(a)P exposure in the large Quebec cohorts, nevertheless do appear to consistently occur more frequently in certain cohorts including prebake and Söderberg operations. It is possible that these diseases are related to other professional exposures than CTPVs, and it is also possible that they do not have an occupational origin. The fact that they are now reported in several countries, with both the prebake and Söderberg processes, and appear to be more frequent in the newer cohorts suggests that they need to be examined in greater depth. Brain cancer and certain hematopoietic and lymphatic cancers also warrant further study as they appear to follow an exposure–response distribution with CTPVs although their risks have not been reported frequently as increased.

It should be noted that in epidemiological studies, such as those reported here, the number of statistical tests was large and many of the observations may well have occurred by chance. This is also the case for the many tests carried out in other mortality and cancer incidence studies. Furthermore, only in few cases did the studies test a specific hypothesis that a given agent was related to a specific cancer outcome. Nevertheless, the causes are noted so that one can observe whether the same causes appear in independent studies as consistency in results can indicate a problem. Although the evidence for causality is limited by inadequate information on specific exposures to examine exposure–response, or on biological plausibility, those cancers that fulfill several of the criteria for potential causality should certainly continue to be monitored in this industry. Longitudinal studies should also continue, especially for the newer processes, but incorporate improved exposure assessments and multiple chemical and physical exposure indices as well as B(a)P, in order to explore the etiology of cancers identified in excess in the Söderberg plants and carbon plants. This may be pertinent to preventing risks from future exposures in plants using newer technology where firm information on risks may not exist for many years because of latency considerations. Mortality is clearly a late measure of outcome, and incidence studies are to be preferred whenever possible. As exposure levels decrease, incidence and the risks of cancer will also decrease. In this regard, attention should to be paid to increasing the populations for investigation by carefully planned interindustry cooperative studies with well-defined goals and methodologies, possibly using some studies to identify hypotheses and others to test them.

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