conjunctivitis, frequently with hemorrhage, were found in the anterior segments of the eyes. After engineering controls were introduced to lower worker exposure to aerosols and vapors, eye damage decreased from 6.2 to 2.6 cases/100 workers.

The extent of eye damage in workers exposed to aerosols from nickel electrolysis tanks cannot be adequately assessed on the basis of this study [67], since the extent of exposure to aerosols, the procedures and criteria used to determine the extent of eye damage, and the number of workers studied were not reported. In addition, the eye damage may have resulted from an allergic conjunctivitis rather than from exposure to nickel. The study does suggest, however, that damage to the nose and eyes may occur in workers exposed to aerosols from nickel electrolysis tanks, even though the role of nickel sulfate in producing these effects is not clear.

Epidemiologic Studies

Comparisons of mortality in the discussions of epidemiologic data that follow are expressed as ratios of observed (O) to expected (E) deaths. Probabilities have been calculated from the cumulative Poisson distribution when E was less than 5 and from the chi-square test when E was 5 or more. These ratios are considered significant at $P<0.05$.

(a) Wales

The nickel refinery at Clydach, Wales, where nickel is purified by the Mond (carbonyl) process, began operations in 1902 [36]. The refining process at Clydach was originally divided into six stages: crushing and grinding of nickel-copper matte*; calcining* of the crushed matte at 800 C [41] to produce mixed oxides of copper and nickel; extraction of copper by leaching with sulfuric acid; reduction* of nickel oxide to impure nickel powder; revolatilization of impure nickel powder in the presence of carbon monoxide to form nickel carbonyl; and decomposition of nickel carbonyl gas in the presence of heat to form pure nickel and carbon monoxide [36].

The refinery receives nickel-copper matte from a nickel smelter in Canada. Thus, the composition of the matte has changed as the smelting processes used in Canada have improved. Before 1933, the matte contained 40-45% nickel, 35-40% copper, and 17% sulfur [23]. In 1933, the matte was changed to 74% nickel, 2.3% copper, and 23% sulfur, and in 1936, the sulfur content of the matte was reduced to 6.5% [23]. In 1945, nickel oxide was substituted as the feed material at Clydach [36], eliminating potential worker exposure to nickel sulfides*. Between 1945 and 1961, the nickel oxide from Canada, formed by sintering* impure nickel matte, was ground and calcined at Clydach to remove impurities before entering the carbonyl refining process [23]. Grinding and calcining were discontinued at Clydach in 1961, since the nickel oxide formed in fluid bed roasters in Canada was pure enough to be refined directly by the carbonyl process [23].

The first epidemiologic study of deaths of workers at the Clydach nickel refinery was conducted by Hill in 1939. Hill's findings, reviewed and updated by Morgan in an unpublished report [35], were submitted to NIOSH by International Nickel (U.S.), Inc. (Inco). From company insurance and employment records, Hill determined the total number of deaths and the number of deaths from lung cancer and nasal cancer in refinery workers and pensioners between June 1929 and January 1938. The expected number of deaths for the group was estimated from age- and cause-specific death rates for men in England and Wales, which were available for 1931-1935.

Hill found that the O/E ratios of deaths were 16:1 for lung cancer (16 observed, 1 expected, $P<0.05$) and about 22:1 for nasal cancer (11 observed, 0-1 expected, $P<0.05$) [35]. Since the numbers of observed and expected deaths for all other causes were nearly the same (67 observed, 72 expected), Hill concluded that the increase in the number of deaths in these nickel refinery workers (105 observed, 84 expected) was due almost entirely to the increase in deaths from nasal and lung cancers.

For futher analysis, pensioners were excluded and workers were divided by occupation into process and nonprocess workers [35]. Process workers included calciner, reverberatory, and cupola* furnace workers; repairmen, electricians, and superintendents; special order, traffic, and yard workers; and those involved in the extraction of copper, the concentration of nickel sulfate, or the leaching of nickel matte. The occupations of nonprocess workers were not described. The study included about 438 process workers and 389 nonprocess workers. Since the process-worker group was slightly larger and older, a few more deaths would normally be expected in this group. The number of deaths in process workers from causes other than lung or nasal cancer was nearly equal to the number in nonprocess workers (35 in process workers, 34 in nonprocess workers). In contrast, 15 deaths from lung cancer and 11 deaths from nasal cancer occurred in process workers, but only one death from lung cancer and no deaths from nasal cancer occurred in nonprocess workers. Based on these findings, Hill concluded that workers at the Clydach nickel refinery had a very high incidence of deaths from nasal and lung cancer between 1929 and 1938, and that nearly all of these deaths occurred in process workers.

Hill indicated that the number of deaths recorded for the nickel refinery workers was probably underestimated, since deaths of former workers not eligible for pensions were not listed in the company records [35]. In addition, he found inconsistencies in the recording of deaths by the company. The summary report [35] apparently quoting Hill, stated that "certain names on the list of cases of lung cancer appear on the list [of deaths] as due to other causes and some do not appear on the list of deaths at all." Since all of the deaths may not have been identified, Hill stressed that emphasis should be placed on the O/E ratio of deaths in the worker-pensioner group, rather than on the actual number of recorded deaths.

In the update of Hill's findings, Morgan reviewed data on deaths in workers and pensioners at the Clydach nickel refinery between 1938 and 1946 [35]. He found that the O/E ratios of deaths were 13.3:1 for lung cancer (40 observed, 3 expected, $P<0.05$) and about 40.0:1 for nasal cancer (20 observed, 0-1 expected, $P<0.05$). Morgan's findings indicated that the death rate from lung and nasal cancer had remained elevated in workers who died through 1946.

In a 1958 report, Morgan [36] compared changes in the number of deaths from lung cancer and nasal cancer in workers and pensioners at the Clydach nickel refinery with changes in the processes used to refine nickel. In addition, Morgan determined the departments or processes in which most of the workers who died from lung or nasal cancer had been employed and attempted to identify the cancer-causing agents to which these workers may have been exposed. Morgan [36] also summarized Hill's [35] unpublished epidemiologic study [35] on the risks of death from lung and nasal cancer in workers at this refinery.

From company employment and insurance records, Morgan [36] identified 131 deaths from lung cancer and 61 deaths from nasal cancer in 9,340 workers and pensioners who were first employed at the nickel refinery between 1900 and 1957. Morgan [36] observed that most of these deaths occurred in workers first employed at the refinery before 1925. This finding is not reviewed in detail here, since the variations in the risk of death from lung and nasal cancer according to the year of first employment in workers at the Clydach nickel refinery were also assessed in epidemiologic studies by Doll et al in 1970 [39] and in 1976 [40].

From occupational histories of workers who had died, Morgan [36] identified 507 who had been employed for 15-25 years in only one department. He then determined the percentage of workers who died from lung or nasal cancer for each department. As shown in Table III-1, deaths from both lung cancer and nasal cancer were most frequent in calciner furnace workers and copper sulfate workers, followed by other furnace workers, crushing and grinding department workers (concentrators), and workers transporting matte to the nickel sheds where nickel carbonyl was formed as an intermediate in the Mond (carbonyl) process for refining nickel. The author also reported that deaths from nasal cancer occurred most frequently in workers who cleaned the underground flues of the calciner furnaces.

TABLE III-1

LUNG AND NASAL CANCERS IN WORKERS EMPLOYED AT A NICKEL REFINERY IN CLYDACH, WALES*

Process or Department	Average Annual Population		Lung Cancer Cases		Nasal Cancer Cases	
	No.	%	No.	%	No.	%
Gas production	-	-	1	2	-	-
Calcination	58	12	14	25	14	42
Copper sulfate	87	17	20	35	8	25
Nickel sulfate	57	11	4	7	3	9
Furnace	36	7	2	3	5	15
Crushing and grinding	26	5	2	3	1	3
Nickel sheds	163	32	5	9	1	3
Fitters	80	16	9	16	1	3
Total	507	100	57	100	33	100

*Employed in one department 15-25 years between 1900 and 1957

Adapted from Morgan [36]

Morgan [36] observed that the decline in the numbers of deaths from lung cancer and nasal cancer paralleled improvements in both work practices and refinery processes. Changes that contributed to a decrease in worker exposure to dust and fume included: improvements in calciner furnaces, the use of arsenic-free sulfuric acid beginning in 1922, and the issuance of nose and mouth respirator pads also beginning about 1922 [36]. Calciner furnaces that released less dust than those used previously were installed in 1910 and improved in 1924. Until 1936, however, calciner flues were cleaned manually. By 1936, the calciner furnaces, each with its own grinding mill, had been replaced by a central grinding plant with an air-swept ball mill and 12 rotary-hearth calciners equipped with dust collectors and electrostatic precipitators [36]. The calciner sheds were considered by Inco to be the dirtiest part of the refinery [41]. Dust was generated by crushing and grinding nickel-copper matte, by handling finely divided residues returned from the Mond process, and by operating calciner furnaces with insufficient draft and dust collecting equipment [41].

Estimates of the concentrations of airborne nickel and total airborne dust at the Clydach nickel refinery were provided in 1976 by Inco [41]. The concentration of total airborne dust was measured in two calciner sheds in 1932 by determining the difference in tare and final weights of a plug of wool in a tube, through which 100 liters of air were drawn at a height of about 5 feet in each shed. In one shed, 14 and 8 mg/cu m of airborne dust were measured; in another, in which older calcining equipment was used, dust concentrations of 42, 13, and 12 mg/cu m were found. No information on the collection efficiency of this sampler is available, but it was probably quite low. Concentrations of sulfur dioxide were measured by absorption in an oxidizing solution, followed by acidimetric analysis. In a calciner shed with newer equipment, an average of 1.5 ppm sulfur dioxide (range 0.2-3.8) was found in 4 samples; in an older shed, 12 samples contained an average of 25.4 ppm sulfur dioxide (range 3.8-54). Apparently the use of newer equipment reduced sulfur dioxide concentrations but did not greatly affect total dust levels. Moreover, in 1932, the plant was operating at reduced capacity because of economic events [41] and the concentrations of airborne dust probably would have been much greater under full operating conditions. The concentration of total airborne dust was measured at the refinery in millions of particles per cubic foot (mppcf) in 1945 and in 1949 [41]. In 1945, four locations in the central grinding plant were sampled, and ranges of 1.8-13.7, 2.6-19.1, 1.4-7.5, and 1.9-16.8 mppcf were reported for particles less than 10 μm in diameter. In 1949, eight samples in the grinding plant averaged 5 mppcf (SD=3.7, range 1.7-8.1), four samples in the calciner buildings averaged 10.5 mppcf (SD=2.2, range 9.5-11.8), and 17 samples in the carbonyl sheds averaged 6 mppcf (SD=5.2, range 3.1-10.6). Based on analyses of the process material, it was estimated that the dusts may have contained about 70% nickel [41].

Inco provided the data they used to convert the dust-counting data from the grinding plant, calciner buildings, and carbonyl sheds to concentrations expressed as mg/cu m [41]. Based primarily on particle sizing of the dusts from a currently operating fluid-bed roaster and density data from a 1915-1917 study in a nickel plant in New Jersey that is no longer operating, conversion factors of 5 for grinding dusts, 3 for calciner dusts, and 1 for carbonyl process dusts were assigned. Applying these factors, the grinding plant total dust concentration ranged from 7 to 95.5 mg/cu m in 1945 and averaged 25 mg/cu m in 1949. Calciner dusts averaged 31.5 mg/cu m and carbonyl process dusts averaged 6 mg/cu m in 1949. The data were probably broad estimates, since information from which the validity of these conversion factors may be determined is not available.

Inco has recently tested the efficiency of the gauze masks that were issued to workers about 1923 [41]. Dust generated in the modern fluid-bed roasting processes was used to test the efficiency of double gauze masks (workers wore two masks at a time), which was reported as ranging from 85-95%. Concentrations of dust from fluid bed roasting that were swept through the mask ranged from 1.43 to 8.39 mg/cu m, and the average particle size of this dust was about 6 μm. Inco also reported that the double gauze masks were 70-90% efficient in filtering fine dust from both the new and old carbonyl plants at Clydach, although the size distribution of the dust was not given. Data on the dust generated in the years of greatest cancer hazard are not available, but it seems reasonable to assume that the dust exposure of workers was greatly reduced by the introduction of gauze masks in 1923.

Based on estimates of environmental concentrations of airborne nickel and estimates of the efficiency of the gauze masks, it appears that workers who did not wear gauze masks, ie, workers first employed before 1923, were exposed to concentrations of airborne nickel refinery dust about ten times greater than those to which workers near new calciner furnaces who wore double-gauze masks, ie, workers first employed after 1936, were exposed. Inco has recently concluded that the use of double gauze respirator masks was the most significant factor in reducing worker exposure to dust and fumes at the Clydach nickel refinery [41].

Morgan [36] attempted to identify the agents associated with the development of lung or nasal cancer in workers by comparing the pattern of deaths from lung cancer and nasal cancer with possible exposure to radiation, nickel carbonyl, and arsenic. He indicated that there was no evidence of radioactivity in nickel matte at any stage in the refining process, although supporting data were not reported. In addition, Morgan

[36] concluded that deaths from lung and nasal cancer in the Clydach nickel refinery workers were not associated with exposure to nickel carbonyl, for three reasons: first, these deaths were not limited to workers in the nickel sheds where nickel carbonyl was formed; second, workers in the nickel sheds were also exposed to dust from nickel matte; and third, the number of deaths from lung and nasal cancer declined substantially with the year of first employment, particularly in the years after 1924, although the carbonyl refining process was not changed during the study period. Morgan also concluded that these deaths in nickel refinery workers were probably associated with exposure to dusty operations, to drying and powdering copper sulfate, to arsenic present in the sulfuric acid used for copper extraction, or to a combination of these factors. Morgan reported that the arsenic content of the sulfuric acid used for copper extraction was highest between 1917 and 1919 and then declined rapidly, so that sulfuric acid was nearly arsenic-free by 1926. Since the decline of the arsenic content in the sulfuric acid paralleled the decline in the number of deaths in workers from lung and nasal cancer by year of first employment at the refinery, Morgan concluded that arsenic was probably the carcinogenic agent associated with the development of lung and nasal cancer in Clydach nickel refinery workers.

As previously stated, Morgan's report [36] indicates that many of the deaths of workers from lung cancer and nasal cancer could not be linked to nickel carbonyl exposure. However, Morgan's study is insufficient either to substantiate or to refute the suggestion that exposure to nickel carbonyl is associated with the development of cancer of the respiratory organs. Morgan's [36] theory that deaths from lung or nasal cancer were probably associated with exposure to arsenic in heated calcined dusts is not well supported by his study, because the use of arsenic-free sulfuric acid coincided with the introduction of double gauze masks which reduced worker exposure to airborne nickel as well as to airborne arsenic. Thus, agents associated with the development of lung and nasal cancer in workers at the Clydach nickel refinery have not been conclusively identified in Morgan's study. It appears, however, that improvements in equipment and engineering controls and the use of double-gauze masks by workers contributed to decreased exposures to cancer-causing agents and to subsequent decreases in the risk of death from lung and nasal cancer in workers at this plant.

In 1937, a plant was built at Clydach to produce nickel sulfate, and, in 1939, a department, which currently (1976) produces nickel chloride and nickel carbonate, was opened to produce other nickel salts [41]. Each plant employed about 80 people. No cases of nasal cancer and 2 cases of lung cancer were identified in nickel sulfate plant workers who had not been employed in any other areas of the refinery before 1925. Likewise, no cases of nasal cancer and two cases of lung cancer were identified in chemical salt department workers first employed after 1925. Although the methods used to identify nasal and lung cancer cases and the risk of developing these cancers were not reported, the number of cases of lung cancer found in these workers does not appear to be excessive.

In a 1958 epidemiologic study, Doll [37] estimated the risks of death from lung cancer and from nasal cancer in Clydach nickel refinery workers. He reviewed death certificates for all men who died between 1938 and 1956 in health districts where nickel refinery workers lived; death certificates were obtained from two health districts between 1938 and 1956 and from two additional health districts between 1948 and 1956. Information from death certificates was used to classify each death according to the occupation of the worker at the time of death or when last employed. Deaths were then classified by cause within each occupational group. Information on residents dying outside the district was included in the local health records, and Doll concluded that nearly all of the deaths in workers employed at the nickel refinery at the time of death and a large proportion of the deaths of workers last employed at the refinery were identified.

The ratio of deaths from lung cancer to deaths from all causes except lung and nasal cancer was determined for men other than those who were last employed in aluminum, copper, spelter (zinc), or patent fuel works, in nickel or oil refineries, in steel industries, or in coal mines. These ratios were determined for each 10-year age group and were used to estimate the expected number of deaths from lung cancer in nickel refinery workers based on the number of deaths from all causes other than cancers of the nose and lung in these workers.

Although Doll [37] indicated that nasal cancer is quite rare in the general population, 16 deaths from nasal cancer were identified in men who were not listed as nickel refinery workers on their death certificates. Doll contacted the relatives of most of these men and found that at least seven of them had worked in the nickel refinery at some time. Since the death rate from nasal cancer in the four health districts was elevated by the inclusion of former nickel refinery workers, Doll estimated the expected number of deaths from nasal cancer in Clydach nickel refinery workers from national rather than from local mortality statistics. The expected number of deaths from nasal cancer between 1938 and 1956 in workers last employed at the nickel refinery was derived from the age-specific death rates from nasal cancer in England and Wales, first available in 1950. Doll indicated that the estimate was unlikely to be greatly in error since the crude death rate for nasal cancer in England and Wales had remained nearly constant from 1938 to 1956.

In nickel refinery workers, the O/E ratio of deaths from lung cancer was 13.8:1 between 1938 and 1947 in two health districts (36 observed, 2.6 expected, $P<0.05$) [37]. Between 1948 and 1956, the ratio decreased to 6.7:1 in the same two health districts (39 observed, 5.86 expected, $P<0.05$) and it was 4.9:1 in all four health districts (48 observed, 9.88 expected, $P<0.05$) for the same period. The O/E ratio of deaths from nasal cancer was 242:1 in two health districts between 1938 and 1947 (16 observed, 0.066 expected, $P<0.05$) and decreased to 159:1 in all four health districts between 1948 and 1956 (13 observed, 0.082 expected, $P<0.05$). Doll indicated, however, that the apparent decline in the risk of death from lung cancer in nickel workers could not be regarded as evidence of an actual decrease, since the death rate from lung cancer had increased substantially in England and Wales between 1938 and 1956. In fact, the data indicated that the actual number of excess deaths from lung cancer in Clydach nickel refinery workers was about the same in 1938-47 and 1948-56.

To evaluate the influence of occupation within the refinery on the risk of death from lung or nasal cancer, the O/E ratios of deaths from these causes were compared in process workers and nonprocess workers [37]. Doll's findings, shown in Table III-2, suggest that although process workers were more likely to die from lung or nasal cancer than nonprocess workers, the number of deaths from these causes was significantly greater in both groups of nickel workers than in the general population.

TABLE III-2

DEATHS FROM CANCERS OF THE NOSE AND LUNG IN PROCESS AND NONPROCESS WORKERS AT A NICKEL REFINERY IN CLYDACH, WALES*

Work Category	Nasal Cancer			Lung Cancer		
	O	E	O/E**	O	E	O/E
Process workers	19	0.064	<u>297</u>	28	3.93	<u>7.1</u>
Nonprocess workers	10	0.084	<u>119</u>	20	5.95	<u>3.4</u>
Total	29	0.148	<u>196</u>	48	9.88	<u>4.9</u>

*Nasal cancer deaths recorded in two health districts from 1938 to 1947 and four health districts from 1948 to 1956; lung cancer deaths recorded in four health districts from 1948 to 1956

**O = observed deaths; E = expected deaths; O/E = ratio of observed to expected deaths; underscored values are statistically significant at the 0.05 level ($P<0.05$).

Adapted from Doll [37]

Since the procedures and criteria used to identify process and nonprocess workers were not reported, the study suggests, but does not clearly indicate, that both process and nonprocess workers at the Clydach nickel refinery had increased risks of death from lung and nasal cancer.

In 1958, Williams [38] reported the results of a microscopic examination of the lungs of five men who had been employed at the Clydach nickel refinery. The occupational histories and the date at death (where applicable) were given for each worker. In addition, the concentrations of nickel and arsenic in the lungs of 2 of the 5 workers were measured, and these values were compared with the average concentrations of nickel found in the lungs of 25 coal miners and 25 nonminers who had no known workplace exposure to nickel, and with the average concentrations of arsenic found in the lungs of 10 coal miners and 10 nonminers. Four of the 5 men with workplace exposure to nickel had worked in areas where they could have been exposed to nickel carbonyl, and 3 of the 4 had recently experienced "one mild, transitory attack of acute nickel carbonyl poisoning." One man who had an attack had been employed for 17 years and had worked only in the nickel sheds where nickel carbonyl was formed. The other 3 had worked in the wet-treatment plant, in the copper sheds, as gas producers, or as general laborers, but they had never been employed as furnace workers. The fifth person had not worked in the nickel sheds, but had been a furnace worker for 33 years.

Williams [38] found that the concentrations of nickel in the lungs from the two nickel workers were 90 and 120 ppm of dry tissue and that the average concentration of nickel in the lungs of 25 coal miners and 25 nonminers was below the limit of detectability of 5 ppm for nickel. In contrast, the average concentrations of arsenic in the lungs of the two nickel workers, the 10 coal miners, and 10 nonminers were all below the limit of detectability of 0.2 ppm for arsenic. Williams indicated that lung cancers were found in 4 of the 5 workers. Diffuse interstitial fibrosis was seen in the lungs of all five nickel workers. Squamous-cell metaplasia was found in the lungs of two workers who also had squamous-cell carcinoma, and alveolar-cell metaplasia was found in the lung of one worker. The author concluded that bronchial squamous-cell metaplasia should not necessarily be considered a premalignant condition and that there were no pathologic changes observed that could be specifically associated with exposure to nickel.

In a book published in 1956, Goldblatt and Goldblatt [68] concluded that it was unlikely that exposure to arsenic was associated with the development of lung cancer and nasal cancer in nickel workers. The authors indicated that extensive exposure to arsenic dusts caused perforations of the nasal septum but was not associated with the development of cancers of the nose and ethmoid sinuses. Goldblatt and Goldblatt also indicated that there was no reported evidence of an increase in lung and nasal cancer in workers in other industries using sulfuric acid, although sulfuric acid containing oxides of arsenic had been used for many years in industries where exposure to dusts and fumes was prevalent. The authors did not indicate, however, if adequate epidemiologic studies of workers using arsenic-containing sulfuric acid had been conducted.

In a 1966 review of cancers of the respiratory system, Hueper [69] concluded that nickel, not arsenic, was the principal agent associated with lung cancer and nasal cancer in workers at the Clydach nickel refinery. Citing studies available at that time, he emphasized that not all nickel workers were exposed to arsenic, but that all were exposed to vapors (probably carbonyl), dusts, and fumes of nickel. Hueper also indicated that, according to available records, symptoms of arsenic poisoning and arsenic-related cancers at nonrespiratory sites were not evident in nickel workers.

In 1970, Doll et al [39] reported an additional epidemiologic study designed to assess the risk of death from lung cancer and nasal cancer in Clydach nickel refinery workers. From company paysheets, workers employed at the refinery for at least 5 years between 1934 and 1949 were identified and included in the study; all but 27 (3.2%) of the 845 workers in the study were traced from their year of first employment until death or until January 1, 1967. Death certificates were obtained for all workers who died and the cause of death was classified according to the seventh revision of the World Health Organization (WHO) classification [70].

The workers were divided into six groups according to year of first employment and the number of years at risk from 1939 to 1966 was determined for each group. The expected number of deaths was estimated from the number of years at risk and the corresponding annual age-specific death rate for England and Wales. The observed and expected numbers of deaths were determined for nasal cancer, lung cancer, other cancers, all other causes, and all causes. Since age-specific death rates for nasal cancer were not available before 1950, the age-specific death rate for nasal cancer for 1950-1954 was used to estimate the expected number of nasal cancer deaths in nickel refinery workers between 1939 and 1950.

Doll et al [39] found that 482 (57%) of the 845 workers in the study had died before the beginning of 1967, 39 of them from nasal cancer and 113 from lung cancer. The number of workers, the number of years at risk, the numbers of observed and expected deaths, and the O/E ratios of deaths from several causes by year of first employment are shown in Table III-3. In workers first employed before 1925 the O/E ratio of deaths from nasal cancer averaged 364:1. In contrast, no deaths from nasal cancer were identified in the 282 workers first employed between 1925 and 1944. The O/E ratio of deaths from lung cancer averaged 7.5:1 in workers first employed before 1925, decreased to 1.8:1 in workers first employed between 1925 and 1929, and to 1.1:1 in workers first employed between 1930 and 1944. The O/E ratio of deaths from causes other than cancer was 1.2:1 and did not vary appreciably with year of first employment at the nickel refinery. Doll et al indicated, however, that this ratio was probably not excessive since the death rate in the part of Wales where the nickel refinery was located was usually greater than that for all of England and Wales.

TABLE III-3

DEATHS IN WORKERS AT A NICKEL REFINERY IN CLYDACH, WALES, AS OF JANUARY 1, 1967*

Year of First Employment	Number of Workers	Years at Risk	Cause of Death														
			Nasal Cancer			Lung Cancer			Other Cancers			Other Causes			All Causes		
			O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Before 1910	96	955.5	8	0.026	308	20	2.11	9.5	9	8.43	1.1	49	50.86	0.96	86	61.43	1.4
1910–1914	130	1,060.5	20	0.023	870	29	2.75	10.5	10	7.18	1.4	48	40.98	1.2	107	50.94	2.1
1915–1919	87	915.0	6	0.015	400	13	2.29	5.7	9	4.32	2.1	31	23.33	1.3	59	29.94	2.0
1920–1924	250	2,923.0	5	0.043	116	43	6.79	6.3	21	11.57	1.8	86	62.01	1.4	155	80.41	1.9
1925–1929	77	1,136.0	0	0.014	-	4	2.27	1.8	3	3.67	0.8	20	20.06	1.0	27	26.01	1.0
1930–1944	205	2,945.0	0	0.022	-	4	3.79	1.1	6	5.49	1.1	38	28.43	1.3	48	37.73	1.3
Before 1925	563	5,854.0	39	0.107	364	105	13.94	7.5	49	31.5	1.6	214	177.18	1.2	407	222.72	1.8
1925–1944	282	4,081.0	0	0.036	-	8	6.06	1.3	9	9.16	0.98	58	48.49	1.2	75	63.74	1.2
Total	845	9,935.0	39	0.143	273	113	20.00	5.7	58	40.66	1.4	272	225.67	1.2	482	286.46	1.7

*845 workers employed for at least 5 years, first employed on or before April 1944 and traced until January 1, 1967

Adapted from Doll et al [39]

Doll et al [39] also determined that the risk of death from nasal cancer but not from lung cancer increased with the age at which the worker was first employed at the nickel refinery. In addition, the authors reported that the risk of death from lung cancer but not nasal cancer decreased as the length of time since 1925 increased. Doll et al reasoned that the risk of death from lung cancer appeared to decrease with time, since nickel refinery workers who smoked cigarettes may have died from lung cancer at an earlier age than cigarette smokers in the general population. Since smoking histories were not available for these workers, the hypothesis cannot be confirmed from this study.

The study by Doll et al [39] supports earlier findings [22,36] that suggested that the number of deaths from lung and nasal cancers had decreased substantially with the year of first employment at the Clydach nickel refinery, particularly for workers first employed after 1925. Doll et al did not attempt to identify the cancer-causing agents to which nickel refinery workers were exposed. In addition, the influence of occupation within the refinery on the increased risk of death from lung or nasal cancer was not determined, since it was considered impractical to obtain detailed occupational histories from all 845 men in the study. Since the decline in the risk of death from lung and nasal cancer had been both rapid and substantial, Doll et al concluded that the "results confirm the previous suggestion that the cancer hazard had been effectively eliminated by the beginning of 1925." As noted below, Doll et al [40] later revised their conclusions.

In 1976, Doll et al [40] updated the 1970 study [39] of deaths of workers at the Clydach nickel refinery. In the 1970 study, the authors determined the number of deaths that occurred before January 1, 1967, in 845 workers employed for at least 5 years between 1934 and 1949. In the 1976 study [40], they determined the number of deaths that occurred before January 1, 1972, in 967 workers employed for at least 5 years between 1929 and 1949. The same methodology was used in both studies. Of the 967 workers in the 1976 study, all but 37 (3.8%) were traced until death or until the beginning of 1972. Doll et al reported that 689 of the workers in the study (71%) had died before the end of 1972, including 56 from nasal cancer and 145 from lung cancer. In addition, nasal cancer was listed as an associated cause of death on the death certificates of two workers; one worker was first employed at the refinery between 1920 and 1924 and the other between 1925 and 1929. The number of workers, the number of observed and expected deaths, and the O/E ratios of deaths from several causes by year of first employment at the refinery are shown in Table III-4.

Both studies by Doll and his coworkers [39,40] showed that the risks of death from nasal cancer and lung cancer have decreased substantially in Clydach nickel workers with year of first employment at the refinery. As shown in Tables III-3 and III-4, the number of deaths from nasal cancer increased from 39 in the 1970 study [39] to 56 in the 1976 study [40], but the O/E ratios of deaths from nasal cancer, 273:1 in the 1970 study and 252:1 in the 1976 study, were nearly the same. The number of deaths from lung cancer increased from 113 in the earlier study to 145 in the update. The O/E ratio of deaths from lung cancer for workers first employed before 1925 decreased slightly, from 7.5:1 in the 1970 study to 7.0:1 in the 1976 study. For workers first employed between 1925 and 1944, however, the O/E ratio of deaths from lung cancer was greater in the 1976 study. For

TABLE III-4

DEATHS IN WORKERS AT A NICKEL REFINERY IN CLYDACH, WALES, AS OF JANUARY 1, 1972*

Year of First Employment	Number of Workers	Cause of Death														
		Nasal Cancer			Lung Cancer			Other Cancers			Other Causes			All Causes		
		O**	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Before 1910	119	14	0.036	389	24	2.389	10.0	10	14.637	0.68	69	84.95	0.81	117	102.01	1.2
1910-1914	150	24	0.037	649	34	3.267	10.4	10	13.549	0.74	69	75.95	0.91	137	92.84	1.5
1915-1919	105	11	0.025	440	20	3.070	6.5	10	8.064	1.24	48	44.28	1.08	89	55.44	1.6
1920-1924	285	7(1)	0.071	99	50	9.642	5.2	27	20.902	1.29	125	115.63	1.08	209	146.25	1.4
1925-1929	103	0(1)	0.026	-	9	3.615	2.5	7	7.247	0.97	44	41.02	1.07	60	51.91	1.2
1930-1944	205	0	0.034	-	8	5.463	1.5	11	8.786	1.25	58	46.14	1.26	77	60.42	1.3
Before 1925	659	56(1)	0.170	329	128	18.367	7.0	57	57.152	1.00	311	320.85	0.97	552	396.54	1.4
1925-1944	308	0(1)	0.060	-	17	9.078	1.9	18	16.033	1.12	102	87.16	1.17	137	112.33	1.2
Total	967	56(2)	0.230	252	145	27.445	5.3	75	73.185	1.02	413	408.01	1.01	689	508.87	1.4

*967 workers employed for at least 5 years between 1929 and 1949 and traced until January 1, 1972
**Nasal cancer was given as "associated cause" of death in 2 additional cases, 1 for 1920-24 and 1 for 1925-29.

Adapted from Doll et al [40]

workers first employed between 1925 and 1929, the O/E ratio of deaths from lung cancer was 1.8:1 in the 1970 study and 2.5:1 in the 1976 study; the ratio was statistically significant in the 1976 study. In workers first employed between 1930 and 1944, the O/E ratio of deaths from lung cancer was 1.5:1 in the 1976 study compared to 1.1:1 in the 1970 study; this increase was not statistically significant. The O/E ratio of deaths from lung cancer for workers first employed between 1925 and 1944 was 1.3:1 in the 1970 study and 1.9:1 in the 1976 study; the ratio was statistically significant in the 1976 study.

By increasing the number of workers included in the study and by increasing the followup period by 6 years, Doll et al [40] found that the risk of death from lung cancer in workers first employed after 1925, although greatly decreased, was still greater than that of the general population of England and Wales. Nasal cancer was not listed as the cause of death of any for the 308 workers first employed at the refinery between 1925 and 1944, although, for one worker, nasal cancer was listed as a contributing cause of death, with heart failure considered the primary cause.

Doll et al [40] concluded that the 1976 study "provides strong evidence that some element of risk persisted in this period," ie, that the risk of death from lung cancer was elevated in workers first employed at the Clydach nickel refinery after 1925.

(b) Norway

In 1950, Loken [42] reported on three cases of lung cancer in workers employed at a nickel refinery in Kristiansand, Norway, where matte from nickel sulfide ore, originally from a Norwegian smelter and later from Canada, was processed [10]. The first case was that of a a 58-year-old man who had been employed at the refinery for 36 years and had worked in a roasting-kiln area. The second case was that of a 59-year-old man employed at the refinery for 22 years, first in shearing nickel metal and later as a shop foreman. Squamous-cell carcinomas of the lung without any associated pathologic lesions of significance were found on microscopic examinations of the lungs of both workers. The third case of lung cancer was reported in a 46-year-old man who had worked in the roasting-kiln area of the refinery for 10 years. The employee had left the nickel refinery after developing extensive nickel dermatitis and had worked at various jobs, usually in mechanical workshops, for 10 years prior to the diagnosis of lung cancer. Microscopic examination of his lungs revealed three conditions: fibrous nodule and isolated asbestos bodies indicating pneumoconiosis, changes reportedly typical of Boeck's sarcoid, and squamous-cell carcinoma. Loken reported that the silica content in the lungs of this patient, 2.7 mg/g of dry tissue, was within normal limits, but the nickel content, 2.8 mg/g of dry tissue, was quite high, even though the patient had not been employed at the nickel refinery for 10 years. Since nickel was refined electrolytically at this plant, Loken's 1950 report was the first to suggest that respiratory cancer in nickel workers was not confined to workers employed in the Mond (carbonyl) process.

In 1973, Pedersen et al [43] conducted an epidemiologic study designed to assess the incidence of cancer of the respiratory organs in workers employed at the Kristiansand nickel refinery. They indicated that, particularly since 1950, major process changes have tended to reduce worker exposure to dusts and fumes, but these changes were not described. From company records, 1,916 male workers who were first employed at the refinery before 1961 and had been employed there for at least 3 years were identified. The date of birth, the dates on which employment began and terminated, and the length of employment in each department were listed in each worker's employment record. Workers employed in more than one department were classified by the department in which the longest time was spent, except that workers who had been employed for shorter periods in a process department were classified as process workers when their longest employment had been in departments that clearly entailed minimal exposure to nickel. The four work categories used by the authors were: roasting and smelting; electrolysis; other processes; and other. The "other" work group included office workers, general laborers, fitters, etc. The 1,916 workers were traced in the Norwegian Cancer Registry and through national mortality statistics between 1953 and 1971. The observed number of deaths from all causes and the number of cases of cancer in the nose, larynx, lung, all respiratory organs, and all sites combined (except basal-cell carcinoma of the skin) were determined for each work category and by the year of first employment. The expected number of deaths from all causes and the expected number of cases of cancer in the sites mentioned above were determined for each worker in each year of observation between 1953 and 1971 using the appropriate age-, sex-, and time-specific incidence rates from the Norwegian Cancer Registry and from mortality rates for Norway. None of the workers were first employed between 1940 and 1945, since refinery operations were virtually discontinued during World War II. The year of and age at first employment at the refinery, the year of and age at diagnosis, and the interval between first exposure and diagnosis were determined for workers who developed cancers of the nose, larynx, and lungs.

Pedersen et al [43] reported that the incidence of cancer in the county where the nickel refinery was located was about 10% less for nearly all cancer sites than that in the rest of Norway. Because of the lower incidence of cancer in that county and the authors' belief that workers were healthier than the rest of the population, they determined only the O/E ratio of cases of cancer of the respiratory organs in each of the four work category groups. To facilitate comparison with other studies, the O/E ratios of deaths from all causes and the O/E ratios of cases of cancer in the sites mentioned above have been calculated from the available data [43] for workers in all work categories. The data, summarized in Table III-5,

TABLE III-5

DEATH AND CASES OF RESPIRATORY CANCER IN WORKERS AT A NICKEL REFINERY IN KRISTIANSAND, NORWAY*

Exposure Group	Number of Workers	Number of Deaths (all causes)			Cases of Cancer															
					Total			Nasal			Larynx			Lung			All Respiratory			
		O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Roasting and smelting	462	95	75.7	1.25	43	22.9	1.88	5	0.1	50.0	4	0.4	10.0	12	2.5	4.80	21	3.0	7.00
Electrolysis	609	139	108.5	1.28	59	32.7	1.80	6	0.2	30.0	0	0.5	-	26	3.6	7.22	32	4.3	7.44
Other processes	299	37	39.8	0.93	18	12.6	1.43	1	0.1	10.0	1	0.2	5.0	6	1.3	4.62	8	1.6	5.00
Other	546	74	79.7	0.93	22	24.5	0.90	2	0.1	20.0	0	0.3	-	4	2.7	1.48	6	3.1	1.94
Total	1916	345	303.7	1.14	142	92.7	1.53	14	0.5	28.0	5	1.4	3.6	48	10.1	4.75	67	12.0	5.58

*1,916 workers employed for at least 3 years, first employed before 1961 and traced from 1953 to 1971

Adapted from Pedersen et al [43]

show that an increased number of cases of cancer of the nose, of the larynx, of the lungs, of all respiratory organs, and of all sites combined were observed for all Kristiansand nickel refinery workers. The observed number of deaths or cases of cancer at all sites was not consistently greater than expected for all work categories, but the observed number of cancers of the nose, lungs, and all respiratory organs was greater than expected in each of the four work categories. Cases of cancer of the larynx were found only in workers in the roasting and smelting and other processes groups. Of the 67 cases of cancèr of the respiratory organs, 30 occurred in 210 workers who were first employed before April 1940 and who were in either the roasting and smelting or the electrolysis groups. Sixteen cases of cancer of the respiratory organs were identified in the electrolysis group in 57 workers who had been employed at the refinery for at least 15 years; the O/E ratios of cases in these workers were 250:1 for cancer of the nasal cavities (5 observed, 0.02 expected, P<0.05), 23.4:1 for cancer of the lungs (11 observed, 0.47 expected, P<0.05), and 4.2:1 for cancers in all sites combined (19 observed, 4.57 expected, P<0.05); and the O/E ratio of deaths from all causes was 2.1:1 (32 observed, 15.07 expected, P<0.05).

The O/E ratio of cases of cancer of the respiratory organs varied from 14.0:1 in workers first employed at the nickel refinery between 1910 and 1929 (16 observed, 1.14 expected, P<0.05) to 2.7:1 in those first employed between 1955 and 1960 (5 observed, 1.84 expected, P<0.05) [43]. The O/E ratio of cases of lung cancer varied from 10.4:1 in workers first employed before 1910 (10 observed, 0.96 expected, P<0.05) to 2.5:1 in those first employed between 1955 and 1960 (4 observed, 1.57 expected). In addition, 13 of the 14 cases of nasal cancer occurred in workers first employed before 1940, but four of the five cases of cancer of the larynx occurred in those first employed after 1945. Pedersen et al stressed, however, that the decline in the O/E ratio of cases of cancer of the respiratory organs with the year of first employment at the refinery could reflect the long latency period between exposure and development of cancer rather than an actual decrease in exposure to cancer-causing agents at the Kristiansand nickel refinery.

The data summarized in Table III-6 indicate that the interval between first employment at the nickel refinery and the diagnosis of lung cancer was shorter for those older workers first employed after 1945 [43]. In workers first employed before 1945 who developed lung cancer, the average age at first employment was about 30 years and the average interval between first employment and the diagnosis of cancer was about 34 years. In workers first employed after 1945 who developed lung cancer, the average age at first employment was about 43 years and the average interval between first employment and the diagnosis of cancer was about 16 years. Pedersen et al were unable to find any evidence to suggest why the latent period was less for the 27 men first employed after 1945 who developed lung cancer. The occupational histories of 6 of these workers were reviewed, but there were no indications that any of them had been heavily exposed at the refinery, and two of the men had not been process workers. Three had worked on small farms before employment at the refinery; three were nonsmokers, and three were light smokers.

The study by Pedersen et al [43] showed that workers in all of the occupational groups at the Kristiansand nickel refinery, including nonprocess workers, had an increased risk of developing cancers of the respiratory organs, but that the risk was greatest in workers in the roasting and smelting group and in the electrolysis group. In addition, the risk of developing lung cancer was larger in the electrolysis group than it was in the roasting and smelting group, and even larger for electrolysis workers employed at the refinery for at least 15 years than it was in all electrolysis workers. Although exposure of electrolysis workers to nickel-containing dusts and fumes from roasting and smelting processes cannot be ruled out, this study suggests that exposure to agents in the electrorefining process may be associated with the development of cancer of the respiratory organs.

TABLE III-6

AGE AND EMPLOYMENT DATA OF WORKERS WHO DEVELOPED CANCER OF THE RESPIRATORY ORGANS AT A NICKEL REFINERY IN KRISTIANSAND, NORWAY*

Year of Employment	No. of Cases	Age at Employment (years)		Duration of Employment (years)		Age at Diagnosis (years)		Latent Period (years)**	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range
Lung cancer									
1910-1929	10	32	22-42	26.8	13-33	67.6	58-81	35.6	26-47
1930-1940	11	28.1	19-44	13.6	4-32	59.7	43-71	31.6	20-39
1945-1949	11	36.8	22-56	12.9	3-24	55.2	41-72	18.4	10-25
1950-1960	16	46.9	24-62	10.4	3-19	60.6	44-78	13.7	4-20
Nasal cancer									
1910-1929	6	28.2	23-39	30.0	23-42	65.0	52-79	36.8	26-49
1930-1949	8	40.6	28-54	18.3	7-33	68.4	55-79	27.8	18-36
Larynx cancer									
1936-1960	5	47.2	30-63	9	4-16	62.8	52-75	15.6	8-31

*Worker population same as in Table III-5
**Interval between start of employment and diagnosis of cancer

Adapted from Pedersen et al [43]

Information on the processes used to refine nickel, the dusts and aerosols generated, and the concentrations of airborne nickel observed in the last 5-6 years at various areas of the Kristiansand refinery was provided by Wigstol (written communication, April 1977).

Until 1967, all nickel was refined in the following stages: crushing of the converter matte; roasting of the matte to form nickel-copper oxide; leaching with sulfuric acid to remove copper; drying, smelting, and casting of the residue to form nickel anodes; and electrorefining which included the removal of impurities such as iron, arsenic, copper, and cobalt. Since 1967, about 15% of the crushed matte has been refined by hydrochloric acid leaching to dissolve nickel and the resulting nickel chloride is solvent-extracted to remove impurities, crystallized, and oxidized. The nickel oxide formed is then reduced to metallic nickel. A new process, to be completed by 1980, includes the leaching of crushed matte with chlorine to selectively dissolve nickel, with the resulting solution used in electrolysis to produce pure metallic nickel. Part of this process has been operational since 1975; consequently, smelting has been eliminated.

Dusts in the roasting and smelting department have consisted of nickel sulfide or oxide with concentrations of airborne nickel averaging 0.5-0.8 mg/cu m (range 0.3-6.0) except in the casting area, where nickel levels were 0.1-0.2 mg/cu m. Nickel chloride and sulfate were predominant in the electrolytic tankhouse and purification areas. Concentrations of airborne nickel were at or below 0.1 mg/cu m in the tankhouse and 0.2-0.6 mg/cu m in the purification areas. In the production unit opened in 1967, nickel levels have averaged 0.1 mg/cu m (maximum 0.6). In the chlorine leaching plant, nickel concentrations generally have been below 0.01 mg/cu m (maximum 0.1). Information on the methods used to derive these results was not provided.

Recently, Pederson (written communication, November 1976) reported that three cases of kidney cancer in Kristiansand nickel refinery workers had been identified from the Cancer Registry of Norway. The first case, that of a 21-year-old woman who worked as a laboratory assistant at the refinery for five years, was diagnosed in 1961. In 1975, two cases of cancer of the kidney were identified in men who had worked "in various sections of the plant" for 20 and 23 years respectively, but who had terminated their employment 5 years earlier. The expected number of cases of kidney cancer in Kristiansand nickel refinery workers was not determined, but cancer of the kidney is rare in the general population of Norway. Between 1964 and 1966, the incidence rate of kidney cancer in Norway was 8.5/100,000/year for men and 5.3/100,000/year for women [71].

In 1976, Torjussen and Solberg [72] presented a preliminary study of microscopic changes in the nasal mucosa of workers at the Kristiansand nickel refinery. Biopsy samples of tissue from the mucosa of the middle turbinate from 92 nickel workers were compared with those from 37 people without any known exposure to nickel. The nickel workers were randomly chosen for inclusion in the study, but the procedures used to choose the control group were not reported. Information on age, duration of employment, and smoking habits was apparently obtained from these workers, but procedures used to match the group of nickel workers with the control group were not discussed. The samples were examined microscopically by a pathologist who did not know which ones were from the nickel workers or from the control group.

Torjussen and Solberg [72] found inflammatory changes in all samples, but there were more changes, particularly leukocyte infiltration of the mucosa and keratinization and squamous metaplasia of the epithelium, in samples from nickel workers. Although the changes were not described, the authors reported that atypical epithelial changes were found in 17% of the samples from nickel workers, but none were found in samples from the control group. They noted that these changes were not related to age or smoking habits and were found only in workers employed at the refinery for more than 10 years.

This study [72] cannot be assessed adequately because the procedures used to select and match the nickel worker group and the control group and the criteria for the microscopic examination and classification of tissues were not discussed. The study does suggest, however, that microscopic examination of tissues may be useful for detecting malignant and premalignant lesions of the nose in workers exposed to airborne nickel.

Studies on concentrations of nickel in the plasma and urine of workers at the Kristiansand refinery are included in Chapter IV.

(c) Canada

Deaths from cancer in workers at a nickel refinery in Port Colborne, Ontario [44], at a sinter plant in Copper Cliff, Ontario [45], and in four other occupational groups at the nickel smelter complex in Copper Cliff [46] have been studied by Sutherland. In addition, McEwan [56,57] has presented the findings of a sputum cytology screening program for workers formerly employed at the Copper Cliff sinter plant. Sutherland's 1959 epidemiologic study [44] of deaths from cancer in Port Colborne nickel refinery workers was updated by Inco in 1976 [41]. Inco has also provided information on the processes used to roast, smelt and refine nickel in Canada [23,41] that is useful in interpreting the results of these studies.

From 1921 to 1930, the Orford* process was used at the Port Colborne nickel refinery to separate nickel sulfides from copper sulfides [23]. The resulting nickel sulfides were leached with acid to remove the remaining copper, calcined to form nickel oxide, and then reduced by "fire-refining" to form nickel metal [18,23]. By the late 1920's, Dwight-Lloyd sintering machines were used to oxidize impure nickel sulfides and an electrolytic refinery was opened [23]. By 1938, electrorefining had almost completely replaced fire-refining. Sintering operations had ceased at Port Colborne by 1958, but calcining continued at a decreased rate until 1973 [23].

Additional information on the processes used at Port Colborne and a limited amount of environmental data were recently reported by Inco [41]. Between 1926 and 1958, impure nickel sulfides containing nickel subsulfide* were oxidized at Port Colborne in downdraft traveling-grate sintering machines at a temperature of about 1,650 C. The nickel subsulfide feed was mixed with about three times its weight in fine recirculated sinter and with about 2% of its weight in coke to form a feed with less than 6% sulfur. About 80% of the feed was recirculated until the product contained less than 0.5% sulfur. Large amounts of airborne dust were generated at the many locations where the nickel sinter was sized, transported, discharged, or recycled and blended with coke and fine nickel sinter. Recently, Inco reported that convection currents created by hot sintering machines and recirculating sinter were sufficient to suspend particles with diameters of less than 25 μm. Although some particles were captured by impingement, dust reportedly accumulated on horizontal surfaces at a rate of about 1/8-1/4 inch/day until the angle of the dust pile became too steep and it became airborne again. The spread of dust through the sinter plant was not impeded, since the floors were made of open grating.

Between 1921 and 1973, refractory-lined, mechanically agitated calciner furnaces were used at Port Colborne to oxidize impure nickel subsulfide at temperatures of 600-1,200 C [41]. Inco indicated that calciner furnaces were probably less dusty than sinter furnaces since the oxidation temperature was lower and the area for gas-solid contact was smaller in calciner furnaces than in sinter furnaces. However, many workers were probably exposed to high concentrations of calciner furnace dust since manual labor was required to handle feed and product from calciner furnaces [41]. Although smaller amounts of the trace elements would normally be volatilized in the lower-temperature calciner furnaces than in the sinter furnaces, Inco indicated that large amounts of salt were added to the calciner furnace at the Port Colborne refinery and suggested that the so-called "chloridizing" atmosphere might have enhanced the volatilization of trace elements.

The processes used to refine nickel electrolytically at Port Colborne have not changed significantly since the refinery began operation, but only a limited amount of data on nickel exposures is available for electrolysis workers [41]. Recent measurements in two tankhouses at the Port Colborne electrolysis plant showed an average nickel concentration of 0.11 (range 0.022-0.254) mg/cu m for 14 high-volume samples. Concentrations of airborne nickel were determined by personal samples for three cementation* operators (mean 0.19, range 0.11-0.27 mg/cu m), one pressman (0.16 mg/cu m), one anode scrap washer (8.13 mg/cu m), and two tank cleaners

(<0.029 mg/cu m) [41]. In 1953, the Ontario Department of Health collected five high-volume samples in the Port Colborne sinter plant while it was being operated on a part-time basis. Concentrations of total airborne dust averaged 339.6 (range 61-1,075) mg/cu m. Chemical analyses of these dusts were not reported by Inco. One 1958 sample of process dust contained 52.1% nickel, 17.2% sulfur, 2.67% copper, 1.3% iron, 1.2% silicon dioxide, 0.05% lead, 0.32% arsenic, and varying amounts of other trace materials. No other exposure data for these workers are available.

In 1959, Sutherland [44] reported an epidemiologic study designed to assess the risk of death from several causes, including lung cancer and nasal cancer, in Port Colborne nickel refinery workers. This study was updated by Inco in 1976 [41]. In a review of company records, 2,355 men employed at the nickel refinery for at least 5 years between 1930 and 1957 were identified. Occupational histories were used to divide the workers into the eight exposure groups listed below:

(1) Furnace dust: Men who worked for least 5 years at converter, sinter, reducer, or anode furnaces.

(2) Other dust: Men who worked for at least 5 years in dusty operations other than furnace areas, including repairmen, machinists, laborers, and grinders.

(3) Mixed exposure/furnace dust: Men who worked for 3-5 years as furnace workers.

(4) Mixed exposure/other dust: Men who worked for 3-5 years in dusty occupations other than furnace work and for at least 2 years in other occupations at the refinery.

(5) Minimum dust exposure: Men who worked for less than 3 years as furnace workers or in other dusty occupations and for at least 2 years in another occupation at the refinery.

(6) Electrolysis: Men who worked for at least 5 years in the electrolysis department.

(7) Office: Men who worked for at least 5 years as office workers.

(8) Other: Men employed for at least 5 years in jobs such as yardmen or janitors but who did not work throughout the plant.

Information on deaths was compiled by reviewing company insurance records for workers and pensioners and by reviewing the registries of three nearby towns for deaths of former workers ineligible for pensions [44]. Incomplete information was supplemented by searching for death certificates from the Province of Ontario. The number of years at risk was determined for each 5-year period and 10-year age group within each exposure group. The expected number of deaths for each occupational group was determined by multiplying the number of years at risk in each 10-year age group and 5-year period by the corresponding age- and time-specific death rate for men in Ontario.

Sutherland [44] found that the 2,355 men accumulated a total of 42,637 years at risk, 32,342 while employed and 10,295 while on pension. During the study period, the average length of employment at the nickel refinery was 13.7 years, and the average number of years on pension was 4.4 years. The number of observed and expected deaths from lung cancer, nasal cancer, cancer in all sites combined (except Hodgkin's disease and leukemia), respiratory diseases, digestive diseases, and vascular lesions of the central nervous system (CNS) were determined for each exposure group. Since age-specific death rates for nasal cancer were not available in Ontario before 1950, the expected number of deaths for nasal cancer between 1930 and 1957 was based on the age-specific death rate for nasal cancer in Ontario from 1950 to 1957.

The O/E ratios of deaths in Port Colborne nickel refinery workers, summarized in Table III-7, indicate that the ratios were significantly higher than expected for nasal cancer, for lung cancer, and for cancer in all sites combined, but significantly lower than expected for vascular lesions of the CNS, for respiratory diseases, for digestive diseases, and for all causes of death. The number of observed and expected deaths and their ratios in each of the eight exposure groups, summarized in Table III-8, indicate that nearly all of the excess deaths from lung and nasal cancer occurred in the groups with exposure to furnace dust or to other dust in the refinery.

TABLE III-7

DEATHS IN WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO, 1930-1957* AND 1930-1974**

Cause of Death	1930-1957			1930-1974		
	O	E	O/E	O	E	O/E
Malignant disease						
Nasal cancer	7	0.1886	37.12	24	0.47	51.06
Lung cancer	19	8.453	2.24	76	40.95	1.86
Larynx cancer	-	-	-	4	2.14	1.87
Stomach cancer	-	-	-	18	18.46	0.98
Pancreatic cancer	-	-	-	9	8.95	1.01
Gastrointestinal cancer	-	-	-	43	47.1	0.91
Bladder cancer	-	-	-	3	6.35	0.47
Hodgkin's disease and leukemia***	-	-	-	5	7.57	0.66
Nonmalignant disease						
Cerebrovascular disease	14	20.719	0.69	54	70.65	0.76
Cardiovascular disease	-	-	-	349	462.6	0.75
Respiratory disease	13	16.214	0.80	33	51.19	0.65
Digestive disease	9	16.072	0.56	23	37.89	0.61
Accidents and violence	-	-	-	55	69.36	0.79
Nasal and lung cancer	26	8.6416	3.01	100	41.42	2.41
Other cancer***	54	43.188	1.25	107	118.39	0.90
Other causes	165	256.746	0.64	563	694.54	0.90
All causes	245	308.35	0.79	770	854.35	0.90

*2,355 workers employed for at least 5 years and traced between 1930 and 1957; adapted from Sutherland [44]

**2,328 of the same workers, traced between 1930 and 1974; preliminary results adapted from Inco [41]

***Includes Hodgkin's disease and leukemia for 1930-1974 but not for 1930-1957

TABLE III-8

DEATHS FROM CANCERS OF NOSE AND LUNG IN WORKERS AT A NICKEL REFINERY IN PORT COLBORNE, ONTARIO*

Exposure Group	Number of Workers	Nasal Cancer			Lung Cancer		
		O	E	O/E	O	E	O/E
Furnace dust	292	1	0.0348	28.74	6	1.585	3.79
Other dust	296	0	0.0313	-	3	1.356	2.21
Mixed exposure/ furnace dust	257	4	0.0205	195.12	4	1.012	3.95
Mixed exposure/ other dust	476	1	0.0258	38.76	1	1.155	0.87
Minimum dust exposure	608	1	0.0332	30.12	4	1.519	2.63
Elec-trolysis	225	0	0.0210	-	1	0.949	1.05
Office	55	0	0.0067	-	0	0.261	-
Other	146	0	0.0153	-	0	0.617	-
Total	2355	7	0.1886	37.12	19	8.453	2.24

*Employed for at least 5 years and traced between 1930 and 1957

Adapted from Sutherland [44]

In addition, Sutherland [44] reported that the O/E ratios of deaths from all cancers combined were 1.7:1 for the furnace dust group (14 observed, 8.086 expected), 2.4:1 for the mixed exposure/furnace dust group (11 observed, 4.611 expected, P<0.05), and 1.9:1 for the electrolysis group (9 observed, 4.847 expected). The number of deaths from cancer in all nonrespiratory sites was not increased in the furnace dust and mixed exposure/furnace dust groups (10 observed, 10.045 expected). Sutherland identified a total of 25 deaths from cancer in Port Colborne nickel refinery workers classified in the furnace dust or mixed exposure/furnace dust groups; of these, ten were from cancer of the lungs, five from cancer of the nose, three from cancer of the stomach, two from cancer of the bowel, one each from cancer of the tonsil, nasopharynx, and prostate, one from a retroperitoneal sarcoma, and one from a glioma of the brain stem. The death from cancer of the nasopharynx may have been associated with exposure in the nickel refining process. The number of expected deaths from these causes were not reported, but these findings led Sutherland [44] to conclude that workers in the furnace dust and mixed exposure/furnace dust groups had increased risks of death from lung cancer and from nasal cancer, but not from nonrespiratory cancers.

Sutherland [44] also found that the O/E ratio of deaths from nonrespiratory cancers was 2.1:1 for workers in the electrolysis group (8 observed, 3.877 expected, P<0.05), although the risk of death from nasal cancer (none observed, 0.0211 expected) or lung cancer (1 observed, 0.949 expected) was not elevated. Nine deaths from cancer were identified in the electrolysis group: one from cancer of the lungs, one from cancer of the stomach, three from cancer of the bowel, three from cancer of the kidney, and one from a fibrosarcoma of the hip. Sutherland [44] therefore concluded that the increased risk of death from lung and nasal cancer in Port Colborne nickel refinery workers was limited to furnace workers.

The same study [44] indicated that 3 of the 225 workers originally classified in the electrolysis group died from cancer of the kidney. Since this type of cancer is relatively rare in the general population (between 1950 and 1969, the average death rate from cancer of the kidney in white men in the US, adjusted to the 1960 population, was 3.25/100,000 [73]), workers engaged in the electrolytic refining of nickel may also have an increased risk of developing cancer of the kidney.

Sutherland [44] found that the type of job held before 1930 had not been taken into account in classifying the Port Colborne nickel refinery workers into the eight exposure groups. The classification of workers into exposure groups was then revised for workers who died from lung cancer but not for the rest of the workers in the study. Since a revised number of expected deaths in each exposure group cannot be determined from Sutherland's data, the values reported for each exposure group in Table III-8 are inaccurate, but neither the degree of error nor its effects on the findings can be assessed. The manner in which workers were classified into exposure groups tended to favor the inclusion of workers who died from lung or nasal cancer in the mixed exposure/other dust or mixed exposure/furnace dust groups. For instance, a worker employed as a furnace worker for 4 years and as an electrolysis worker for 25 years would have been classified in the mixed exposure/furnace dust group. This was the first epidemiologic study to assess the risk of death from cancer of the respiratory organs in workers in different occupational or exposure groups in a nickel refinery. Because of methodologic problems, however, the study does not provide a complete basis for assessing the risk of death from nasal or lung cancer in various exposure groups.

In 1967, Mastromatteo [74] summarized the study by Sutherland [44] in a review of the effects on health associated with exposure to nickel in the workplace. On the basis of information available at that time, Mastromatteo concluded that "the epidemiological evidence from studies of workers engaged in nickel refining points to an association between the inhalation of freshly heated insoluble dust and/or fume and increased risk of respiratory-tract cancer."

Sutherland's 1959 epidemiologic study [44] was updated by Inco in 1976 [41]. Since 2,328 workers were included in the updated study, it appears that 27 of the 2,355 workers in the Sutherland study [44] were lost to followup (a loss of 1%, however, is probably unimportant). In the Sutherland study [44], deaths that occurred between 1930 and 1956 were identified. In the updated study [41], the period of follow-up was extended by 18 years to include deaths of workers that occurred between 1930 and 1974. The number of years at risk increased from 42,637 in the 1959 study to about 64,000 in the 1976 study.

The numbers of observed and expected deaths between 1930 and 1974 and the O/E ratios of deaths for Port Colborne nickel refinery workers from causes previously identified in the Sutherland study are also shown in Table III-7. The results of the updated study were considered by Inco to be preliminary [41]. The number of deaths from nasal cancer increased from 7 in the 1959 study to 24 in the 1976 study, and the O/E ratio of deaths from nasal cancer increased from 37.1:1 in the 1959 study to 51.1 in the

1976 study. The number of deaths from lung cancer increased from 19 in the 1959 study to 76 in the 1976 study; and the O/E ratio of deaths from lung cancer decreased slightly from 2.2:1 in the 1959 study to 1.9:1 in the 1976 study. The data in Table III-7 suggest that the slight decline in the risk of death from lung cancer is related to the increase in the number of expected deaths from lung cancer as the age of the workers increased.

Although deaths from cancer of the larynx were not reported in the 1959 study [44], four deaths from cancer of the larynx were identified in the updated study [41]; and the O/E ratio of deaths for cancer of the larynx was 1.9:1 in the updated study. The data presented in Table III-7 indicate that the number of observed and expected deaths from stomach cancer and from pancreatic cancer were nearly the same in the 1959 and 1976 studies. The O/E ratios of deaths from bladder cancer and from Hodgkin's disease and leukemia were lower than expected, but the numbers of both observed and expected deaths were small. In both the Sutherland study [44] and the updated study [41], the number of deaths from nonmalignant diseases was smaller than expected. Since those in the study were either actively working or on pensions, it is likely that fewer deaths from nonmalignant chronic diseases would occur in the workers than in the general population. Since the development of cancer has a long latency period, it was concluded in the Inco report [41] that a larger than expected number of cases of cancer of the respiratory organs will continue to occur in Port Colborne nickel refinery workers for some years.

Sutherland [44] reviewed in detail the occupational histories of workers at the Port Colborne nickel refinery who developed nasal cancer or lung cancer before November 1959. Seven of the 12 workers who had developed nasal cancer and 19 of the 22 workers who had developed lung cancer were also included in Sutherland's 1959 epidemiologic study. The occupational histories of an additional 22 workers who had developed nasal cancer and 68 workers who had developed lung cancer were identified in a review of company records up to June 1976 and were recently reported by Inco [41]. The information in Tables XV-3 and XV-4 was derived from the latter report, and the cases originally reviewed by Sutherland [44] are marked with an asterisk. Sutherland's study suggested that the risk of death from lung and nasal cancer was greater in furnace workers than in other workers. In reviewing the occupational histories of the workers who developed nasal or lung cancer up to November 1959, Sutherland noted that 11 of the 12 workers with nasal cancer and 16 of the 22 workers with lung cancer had been employed as cupola furnace workers for at least 6 months or as sinter furnace workers for at least 3 years.

After reviewing these occupational histories, Sutherland [44] concluded that "mortality from respiratory cancer was most closely associated with cupola and sinter furnaces" and that "there was no clear evidence that employees about either the calciner or anode furnace carried an increased risk of sinus or lung cancer." He suggested that the risk of death from either nasal or lung cancer was increased in employees who worked 6 or more months near cupola furnaces, 3 or more years near sinter furnaces, or 5 or more years near calciner furnaces. His conclusion concerning calciner furnaces was based on data from Clydach and not on data from his own study.

Although he did not present the data, Sutherland [44] indicated that a spectrographic analysis of furnace fumes in 1953 showed no essential differences in the composition of fumes from calciner, sinter, and anode furnaces, and that arsenic was not detected in any of the samples. On the basis of his analysis of findings from the epidemiologic study, the occupational histories of workers who developed lung or nasal cancer, and the results of the spectrographic analysis of furnace fumes, Sutherland suggested that "perhaps the most important factor was that of 'dosage' or concentration of furnace dust in the air."

Inco reported that 55 of the 90 Port Colborne nickel refinery workers who developed lung cancer had been employed as calciner or sinter furnace workers for at least 1 year, and that 21 of the 35 remaining workers with lung cancer had been exposed to nickel from electrolysis operations [41]. The report indicated that these 21 cases of lung cancer were "not greater than the number of cases expected, based on Ontario mortality data," although the expected number of deaths or cases of lung cancer was not reported. Of the 36 workers who developed nasal cancer, 9 were exposed to nickel in electrolysis operations and only 4 of these 9 had worked on furnaces for as much as 1 year. Three of the nine workers had apparently not worked in furnace operations or in any other dusty job. It was suggested by Inco that the apparent increase in cases of nasal cancer in workers engaged in electrolysis operations might have been associated with unrecognized dust exposures due to job mobility, physical contamination of the tankhouse by dust from calcining operations, and certain dusty jobs associated with electrolytic purification and the handling of anode slimes* [41].

The data in Table XV-3 indicate that the length of employment at the nickel refinery for the 36 workers who developed nasal cancer averaged 25.5

years (SD=9.1, range 6.9-41.9), and that the number of years between first employment and the diagnosis of, or death from, nasal cancer averaged 32.8 years (SD=8.4, range 6.9-41.9) [41]. The data in Table XV-4 indicate that the length of employment at the nickel refinery for the 90 workers who developed lung cancer averaged 22.5 years (SD=8.3, range 5.4-37.7), and that the length of time between first employment and the diagnosis of, or death from, lung cancer averaged 33.0 years (SD=8.4, range 15-51).

According to Sutherland [44], Port Colborne nickel refinery workers exposed to dusts from cupola furnaces for more than 6 months, to dusts from sinter furnaces for more than 3 years, or to dusts from calciner furnaces for more than 5 years had an increased risk of developing nasal or lung cancer. The occupational histories of workers at the nickel refinery who developed cancer between 1930 and 1974 indicate, however, that increased risks of developing lung and nasal cancer may not be limited to workers exposed to dusts and fumes from cupola, sinter, or calciner furnaces, and that nickel refinery workers in all exposure groups may have an increased risk of developing lung or nasal cancer. Of the workers who developed cancer between 1930 and 1974, 8 (22%) of the 36 who developed nasal cancer, and 36 (40%) of the 90 who developed lung cancer had worked near cupola, sinter, and calciner furnaces combined for less than 6 months. According to the occupational histories presented in Tables XV-3 and XV-4, 6 (17%) of the 36 workers who developed nasal cancer were never employed as cupola, sinter, or calciner furnace workers. Most of the workers who developed nasal or lung cancer were employed in many positions at the nickel refinery, and thus were exposed to dusts and fumes from more than one process. None of the workers who developed lung or nasal cancer were employed only near the cupola, sinter, or calciner furnaces. However, one worker with nasal cancer (case 33) and 5 workers with lung cancer (cases 2, 4, 24, 43, 61) were employed only in nondusty occupations; one worker with nasal cancer (case 22) was employed only in electrolysis operations; another with nasal cancer (case 10) was employed only on the anode furnaces; and three workers with lung cancer (cases 13, 14, and 88) were employed only in other dusty occupations. If the 36 workers who developed nasal cancer are classified according to the occupation in the nickel refinery in which the longest time was spent, then 10 (29%) were sinter furnace workers, 9 (25%) were electrolysis workers, 6 (17%) were calciner furnace workers, 6 (17%) were in occupations that were not dusty, 2 (6%) were anode furnace workers, 2 (6%) were in occupations with exposure to other dusts, and 1 (3%) was a cupola furnace worker. If the 90 workers who developed lung cancer are classified according to the occupation at the nickel refinery in which the longest time was spent, then 21 (23%) were electrolysis workers, 18 (20%) were in occupations that were not dusty, 17 (19%) were in other dusty occupations, 15(17%) were sinter furnace workers, 12 (13%) were calciner furnace workers, 5(6%) were anode furnace workers, 1 (1%) had spent an equal amount of time as a calciner and as a sinter furnace worker, 1 (1%) had spent an equal amount of time as an electrolysis worker and in an occupation that was not dusty, and none were cupola furnace workers. The risks of developing nasal cancer and lung cancer by occupation or exposure group cannot be assessed for these workers since the expected number of cases of nasal and lung cancer in each exposure group was not provided in either report [44,41]. The data indicate, however, that all nickel refinery workers may have an increased risk.

The available data [41] are not adequate to estimate the concentrations of airborne nickel to which workers in various occupations at the Port Colborne nickel refinery may have been exposed. It appears, however, that the concentration of airborne nickel and other compounds and the types of airborne nickel compounds to which workers were exposed varied in different operations at the refinery. Cupola furnace workers handled sulfides of nickel and copper. Sinter and calciner furnace workers were exposed to airborne nickel, including at least nickel subsulfide and nickel oxide at relatively high concentrations, to traces of other substances such as arsenic or coke, and to sulfur dioxide. Anode furnace workers were probably exposed to airborne nickel oxide, to traces of other elements, and possibly to airborne nickel metal. Electrorefining tanks contained nickel sulfate and boric acid until the 1940's, when nickel chloride was also added [23]. Mists of nickel salts and possibly nickel hydrides were formed above the tanks, their composition being dependent on operating conditions such as current density and temperature. At Port Colborne, electrolysis workers would have been exposed to other airborne compounds from auxiliary operations in the electrorefining area. These operations included the formation of secondary anodes from anode slimes, and the purification of electrolytic solutions including both the cementation of copper in which nickel powder was added and cobalt precipitation in which nickel carbonate was added [10]. Recently, a limited amount of electrorefining has been done at Port Colborne by the electrowinning* process [10] during which workers might be exposed to airborne nickel subsulfide.

Exposure to traces of arsenic and coke may have somewhat increased the risk of developing lung cancer for nickel refinery workers. In a review of the epidemiologic literature on the association between occupation and the development of cancer, however, Cole and Goldman [75] indicated that workplace exposure to arsenic has not been associated with the development of nasal cancer in any occupational group. They indicated that an association between workplace exposure to coke and the development of nasal cancer had been suggested, but they did not consider this relationship to have been established. Therefore, the available epidemiologic data indicate that workplace exposure to airborne nickel has increased the risk of developing cancer of the respiratory organs, particularly cancers of the nose, in nickel refinery workers.

The risk of death from lung and nasal cancer in workers at a nickel smelter complex in Copper Cliff, Ontario, has also been studied by Sutherland [45,46]. According to Inco, pentlandite*, an ore containing nickel, has been processed at this complex since it opened in 1888 [41]. Originally, this sulfide ore was smelted at Copper Cliff by processes that included outdoor heap roasting, blast furnace smelting, and converting*. When supplies of high grade ores became depleted, beneficiation by froth flotation was introduced. In 1930, an ore concentrator and an Orford process plant were built and outdoor heap roasting was abandoned. In 1948, slow cooling was introduced as a replacement for the Orford process and acid leaching, and a new sintering plant was installed at Copper Cliff to replace the old unit at Port Colborne. Sintering continued for 15 years at Copper Cliff until 1962, when the conversion to fluid bed roasters, begun in 1960, was completed [23].

In November 1960, a single high-volume sample of total dust (82.1 cu m of air over a period of 40 hours) was collected in the Copper Cliff sinter plant [41]. The concentration of total dust in the air was 46 mg/cu m. From 1950 to 1961, a series of 34 samples of the dust escaping the sinter plant through roof monitors showed that it was composed of 60.9% nickel (SD=15.4) and 4.2% copper (SD=2.9). These findings were corroborated in June 1976, when 10 settled dust samples were taken from the old sinter plant and analyzed. The samples contained 62.3% nickel (SD=10.3), 12.6% sulfur (SD=8.2), 3.2% copper (SD=1.5), 0.54% cobalt (SD=0.18), 0.132% arsenic (SD=0.15), and 21.2% other elements. No other quantitative data are available with which to estimate worker exposure at the Copper Cliff sinter plant. The Inco report [41] speculated that the concentrations of trace elements such as arsenic may have been greater in airborne dust than in settled dust. According to Inco, the temperatures used for the oxidization of nickel may revolatilize trace elements such as arsenic so that smaller airborne particles would tend to contain a greater amount of these trace elements than larger particles.

In 1969, Sutherland [45] reported an epidemiologic study designed to assess the risk of death from lung cancer in sinter furnace workers at the Copper Cliff nickel smelter complex. The sintering process and the furnaces used at Copper Cliff and at Port Colborne were essentially the same [41]. The company provided lists of persons employed at the sinter plant on May 1, 1952, May 1, 1956, and August 1, 1961; in addition, the company provided lists of persons employed as mechanics from 1954 to 1961 or as electricians from 1948 to 1961 who had been employed for the majority of their time at the sinter plant. Sutherland identified 212 men employed at the sinter plant from 6 months to 5 years, 128 men employed from 5 to 10 years, and 143 men employed for more than 10 years from these lists. Not all of the workers employed between 6 months and 5 years, however, were identified by this procedure, and Sutherland did not discuss the comparability of the group of 212 men included in the study to all men employed from 6 months to 5 years. Deaths in the 212 men employed from 6 months to 5 years and the 271 men employed for more than 5 years are therefore considered separately for this review. The dates of birth, dates and places of employment in the company, and dates and places of death, if known, were taken from company employment and insurance records. The number of deaths in all the workers in the study was determined from the company's life insurance records, and the causes of death and ages at death were taken from death certificates. Deaths of sinter plant workers from five causes were determined. These included: lung cancer; other cancer; vascular disease, including heart disease and cerebral hemorrhage; other diseases; and accidents, poisonings, and violence. The number of expected deaths for each category was determined from the corresponding age-, time-, and cause-specific death rates for men in Ontario.

Sutherland [45] found that all but one of the deaths from cancer occurred in workers employed at the sinter plant for at least 5 years. The number of deaths and the O/E ratios of deaths in all five categories for workers employed at the sinter plant for at least 5 years are shown in Table III-9.

TABLE III-9

DEATHS IN WORKERS EMPLOYED AT THE SINTER PLANT
IN COPPER CLIFF, ONTARIO*

Cause of Death	O	E	O/E
Lung cancer	6	0.55	10.91
Other cancer	1	1.64	0.61
Vascular disease	2	5.92	0.34
Other diseases	3	2.05	1.46
All diseases	12	10.16	1.18
Accidents, poisonings, violence	5	2.51	1.99
All causes	17	12.67	1.34

*271 workers employed for at least 5 years and traced between 1948 and June 1968

Adapted from Sutherland [45]

In sinter plant workers employed for at least 5 years, the O/E ratio of deaths from lung cancer was 10.9:1 [45]. The average interval between first exposure and diagnosis of, or death from, lung cancer was 15.5 years, and the shortest interval was 8.3 years for the seven workers in the study and two other workers not included in the study who were later found to have developed lung cancer. The one worker in the study who developed nasal cancer had been employed at the sinter plant for 14.3 years and there was an interval of 17.3 years between first employment and death. This death was listed in Table III-9 as a death from cancer in sites other than the lung. The O/E ratios of death from other diseases; from all diseases; from accidents, poisonings and violence; and from all causes were elevated in sinter plant workers [45], although none of the O/E ratios were statistically significant. Fewer deaths from cancer in other sites and from vascular diseases occurred than were expected, but these ratios were not statistically significant either. Because of the length of time the sinter furnaces were used at Copper Cliff and the length of the followup period in this study, the longest possible interval of employment in the sinter plant was 15 years, and the longest possible interval between first exposure and death was 20 years.

The one death from nasal cancer should have been compared to an expected number of deaths from nasal cancer, rather than to the expected number of deaths from cancer in all sites combined, particularly since nasal cancer occurs rarely in the general population. Furthermore, the number of deaths in the 483 sinter plant workers in the study may have been underestimated, since deaths in former workers ineligible for pensions were not identified.

Sutherland [45] did not indicate the extent to which these workers were exposed to fume or dust from sinter furnaces and did not attempt to identify the cancer-causing agents to which these workers may have been exposed. The group was small, and the average duration of exposure and the interval between first exposure and death were short for an epidemiologic study of cancer, but the study nevertheless makes it clear that workers exposed to dust and fume from sinter furnaces where impure nickel sulfides were oxidized had an increased risk of death from lung cancer.

McEwan [56,57] described a monitoring program designed to identify cases of lung cancer in workers formerly employed at the Copper Cliff sinter plant. Chest X-ray and sputum cytology monitoring programs were described, and the findings of the sputum cytology program in 1973, 1974 [56,57], and 1975 [56] were presented. Four cases of lung cancer in former sinter plant workers who were still with the company were found by chest X-ray examinations conducted in 1969, 1970, and 1972 [56]. The chest X-ray program was then expanded, and after 1972, postero-anterior and lateral X-rays were taken every 6 months. McEwan [56] indicated that X-ray monitoring programs had not improved lung cancer survival rates, so a sputum cytology monitoring program was initiated to identify cases of lung cancer at the in situ or early invasive stage when medical intervention was more likely to be successful. Former sinter plant workers living in the area who were no longer employed by the company and workers who had worked in the sinter plant for short periods, eg, repairmen and electricians, were also included in the program after 1972. Employment histories were obtained from the company and a questionnaire which included inquiries on smoking habits and recent respiratory symptoms or illnesses was completed for each former sinter worker in the program [56]. All slides were reviewed by at least two persons, and slides with abnormal cytology were reviewed by a cytopathologist who considered that malignant cells "may be desquamated from a lesion that is still intraepithelial and may remain so for a period of time, occasionally measured in years." Workers with sputum samples having evidence of at least moderate dysplasia were sent to a physician for a more thorough examination of the respiratory tract, including chest X-rays and bronchoscopy. If no lesion was found, bronchoscopy with multiple brushings and biopsies were repeated at 3-month intervals until a lesion was located.

The initial results of the 1973, 1974, and 1975 sputum cytology screening programs are shown in Table III-10 [56]. The most severe findings from each sample are reported. McEwan reported that many of the workers took part in all three surveys, although some workers were added and others did not participate in subsequent years. Workers with a diagnosis of lung cancer, based on earlier sputum cytology samples, were not included in the results of surveys in subsequent years.

The findings reported by McEwan [56,57] suggest that cigarette smoking is also associated with the development of abnormal sputum cytology in former sinter plant workers. Malignant cells were found in the sputum of smokers and former smokers, but nothing exceeding severe dysplasia was found in the sputum of any nonsmoker. According to McEwan, malignant cells were found in the sputum of 11 of the 412 former sinter plant workers examined between 1973 and 1975. Of these 11 workers, 4 had successful lobectomies, 2 had successful pneumonectomies, and 1 died following surgery; tumors had not yet been found in 4 workers when the study concluded, 1 of whom refused further treatment. All of the lung tumors identified were squamous-cell carcinomas at an early invasive stage, and only one had spread beyond the operated area.

Because the relevant data were not presented, the possible association of abnormal sputum cytology with duration of exposure at the sinter plant, the possible synergistic relationship between cigarette smoking and dust exposure in the sinter plant, and changes in sputum cytology in workers in each successive survey cannot be ascertained from

TABLE III-10

SPUTUM CYTOLOGY IN FORMER WORKERS AT THE SINTER PLANT
IN COPPER CLIFF, ONTARIO

Year and Group	Findings*						
	Malignancy	Severe Dysplasia	Moderate Dysplasia	Mild Dysplasia	Negative	Unsatisfactory	Total
1973							
Smokers	4	2	7	33	32	0	78
Former Smokers**	0	1	4	10	5	1	21
Nonsmokers***	0	0	0	5	4	1	10
Total	4	3	11	48	41	2	109
1974							
Smokers	4	4	11	28	96	6	149
Former smokers**	1	0	2	8	17	5	33
Nonsmokers***	0	0	1	7	30	1	39
Total	5	4	14	43	143	12	221
1975							
Smokers	0	7	32	55	94	12	200
Former Smokers**	0	3	9	13	27	8	60
Nonsmokers***	0	3	5	10	13	10	41
Total	0	13	46	78	134	30	301

* 1973--most severe finding from 12 slides, 4 from each of 3 samples;
  1974, 1975--most severe finding from 5 slides of the blended 3-day sample
**Have not smoked in 10 years
***Includes pipe and cigar smokers

Adapted from McEwan [56,57]

these reports [56,57]. McEwan's study nevertheless suggests the value of a sputum cytology screening program for the detection of lung tumors at an early stage of development in groups with an increased risk of developing lung cancer.

Downdraft traveling-grate sintering machines similar to those used at Copper Cliff were also used at nickel sinter plants in Port Colborne, Coniston, and Falconbridge, Ontario [41]. In the sintering process used at Port Colborne and Copper Cliff, impure nickel sulfides were oxidized at temperatures of about 1,650 C. The sintering process was used at an earlier stage in the refining process at the plants in Coniston and Falconbridge. In these plants, about one-half of the sulfur was removed from the nickel ore or concentrate at temperatures of 1,000-1,100 C. The sintering plant at Coniston, which operated from 1914 to 1972, was dusty, but it was considered by Inco to be less dusty than the sintering plants at Port Colborne and Copper Cliff. The discharge end of the sintering machine was particularly dusty, and the few men working there always wore dust masks [41]. The area where flue dust from the smelter was dumped into receiving lines was also quite dusty. More efficient dust-collecting equipment was installed throughout the Coniston plant between 1968 and 1969. After 1968, the mixed feed of limestone, flue dust, fine ore, and ore concentrates was pelletized, and fine ore was no longer used. From an analysis of high-volume dust samples, Inco concluded that the total dust concentrations at the Coniston sintering plant were 5-125 mg/cu m even after improvements in ventilation and processes were instituted in 1968-1969.

In June 1976, analysis of eight samples of settled dust removed from horizontal surfaces in the Coniston sinter plant showed that it was about 6% nickel, 2% copper, 0.026% arsenic, and 33% sulfur [41]. Since improvements in working conditions were made in 1968-1969, Inco thought it reasonable to assume that concentrations of airborne nickel of at least 3-5 mg/cu m were common at the Coniston sinter plant throughout the first 50 years of its operation. Samples of settled dust from the the Port Colborne and Copper Cliff sinter plants were about 50-60% nickel. The nearly tenfold difference in the percentage of nickel in the settled-dust samples was related to the percentage of nickel in the feed to the sintering machines. The nickel concentrate used as feed in the Coniston sinter plant was about 5-15% nickel, while the impure nickel sulfide used as feed at the Port Colborne and Copper Cliff sinter plants was about 75% nickel. Inco claimed that no cases of nasal cancer have been identified and that the incidence of cancer of the respiratory organs has not been excessive in workers at the Coniston or Falconbridge sinter plants [41]. No data, however, were presented.

In 1971, an epidemiologic study by Sutherland of workers in several departments at the Copper Cliff nickel smelter complex was reported [46]. About 800 workers who had been employed in the complex for at least 5 years at the end of 1950 were selected by the company. About 200 workers were selected from each of the following four areas: converter furnace department, mill and separation departments, the copper refinery division, and an underground nickel mine. These groups were apparently chosen because they were generally exposed to lower concentrations of dust and fume than those who worked at the Copper Cliff sinter plant. Sutherland indicated that exposure to sulfur dioxide and to metal dust and fumes was greatest in the converter furnace department, less in the mill and separation departments, still less in the underground mine, and least in the copper refinery division. Only 831 of the 842 workers selected by the company were included in the study since Sutherland considered the occupational histories of 11 workers to be inadequate. Although the study divided the workers into 12 groups, they are combined in this review into the five groups listed below:

(1) Converter furnace: Men who worked for at least 5 years in the converter furnace department.

(2) Mill and separation: Men who worked for at least 5 years in the mill and separation department.

(3) Copper refinery division: Men who worked for at least 5 years as mechanical, yard, transport, or tank-house workers in the copper refinery division.

(4) Underground mine: Men who worked for at least 5 years in an underground nickel mine.

(5) Mixed: Men who worked for at least 5 years at the nickel smelter complex, but who worked in one of departments listed above for less than 5 years. This group includes Sutherland's other eight exposure groups.

Deaths of workers and pensioners were identified by reviewing the company's life insurance records for 1950-1967, and the age at death and cause of death were taken from death certificates. The expected number of deaths in each group was determined from age-, time-, and cause-specific death rates for men in Ontario by procedures similar to those used in earlier studies by Sutherland [45,44]. By the end of the study period, the 831 men in the cohort had accumulated a total of 13,537 years at risk, 12,141 while employed and 1,396 while on pension. During the period of this study, the average length of employment for the workers was 14.6 years and the average time from the start of the study period until death or the end of the study period was 16.3 years.

The number of years at risk, the numbers of observed and expected deaths, the O/E ratios of deaths from lung cancer, all other cancers, other respiratory diseases, and all causes of death in each of the five exposure groups are listed in Table III-11 [46]. The number of deaths from all causes combined and from all cancers other than lung cancer were slightly less than expected, and the number of deaths from lung cancer and from other respiratory diseases was slightly greater than expected [46]. The O/E ratios of deaths in all exposure groups combined were 1.2:1 for lung cancer but the ratio was not statistically significant and the deaths did not appear to to be concentrated in any of the exposure groups. The O/E ratio of deaths from other respiratory diseases of 2.5:1 in converter furnace workers was the only statistically significant ratio found. The lack of significant findings in this study is probably related primarily to the small number of deaths expected in each of the exposure groups.

Sutherland did not comment on these results or draw any conclusions from this study [46]. Since the procedures used to select the workers were not discussed, it is not evident whether the group of workers included in the study was a random sample. Since deaths of workers in the study were identified from the company's life insurance records, deaths of former workers ineligible for pensions were not included. The study was limited to workers employed in 1950, so the duration of observation for many of the workers may have been quite short, particularly for an epidemiologic study of deaths from cancer. However, the number of deaths from lung cancer and from other respiratory diseases was slightly greater than expected in Copper Cliff workers who were included in this study.

TABLE III-11

DEATHS IN WORKERS AT NICKEL SMELTER IN COPPER CLIFF, ONTARIO*

Exposure Group	Years at Risk	Lung Cancer			Other Cancers			Other Respiratory Diseases			All Causes		
		O	E	O/E	O	E	O/E	O	E	O/E	O	E	O/E
Converter furnace	3,609	3	2.54	1.18	5	6.99	0.72	6	2.36	2.54	50	49.71	1.01
Milling and separation	1,438	1	0.79	1.27	2	2.29	0.87	1	0.78	1.28	12	16.55	0.73
Copper refinery division**	3,134	4	2.24	1.79	5	6.28	0.80	0	2.11	0	35	44.69	0.78
Underground	3,251	3	2.24	1.34	6	6.13	0.98	2	2.05	0.98	40	43.74	0.91
Mixed exposure	2,106	0	1.24	-	3	3.41	0.88	1	1.11	0.86	20	24.74	0.81
Total	13,537	11	9.05	1.22	21	25.10	0.84	10	8.41	1.19	157	179.43	0.88

*831 workers employed at least 5 years and traced between 1950 and 1967
**Tank house, mechanical, and yard workers

Adapted from reference 46

Environmental data for past exposures were not available for these workers. Recent data are available for some areas, but since new equipment had been installed in these areas, environmental concentrations of dust and fume were probably greater in earlier years [41]. Dust measurements in the Sudbury district where the Copper Cliff smelter complex is located indicate that underground miners were recently exposed to nickel at concentrations of 0.006-0.04 mg/cu m using a personal sampler with a cyclone. High-volume samples were taken recently, and they showed concentrations of airborne nickel to be 0.17-15.3 mg/cu m in the matte separation area, undetectable to 2.8 mg/cu m in the mill area, and 0.03-0.2 mg/cu m in the converter furnace area [41]. No other environmental data were reported. It appears, however, that all four groups were exposed to lower concentrations of airborne nickel dust and fume than sinter furnace workers.

(d) United States

In 1976, Enterline [47] reported to NIOSH on an epidemiologic study of a group of retired workers from a plant in Huntington, West Virginia, where nickel alloys are produced. Deaths that occurred before the end of 1971 were identified in company records for a group of 815 men who retired from the plant between 1941 and 1970. Before 1955, workers could retire either at 65 with a service pension or at any age with a disability pension. Starting in 1955, an optional early-service pension plan allowed workers to retire at the age of 60. Of the 815 retired workers over 60 years of age, 515 had retired with a service pension, and 300 had retired with a disability pension and had lived to at least age 60. Enterline indicated that the 190 salaried employees included clerical workers, inspectors, foremen, engineers, laboratory workers, and management personnel, all of whom probably had received less exposure to nickel than the 629 workers paid by the hour. The average length of employment was about 30 years for salaried workers and 27 years for hourly workers.

From company records, Enterline [47] determined that 328 of the 815 pensioners (40%) had died before the end of 1971. Death certificates were obtained for all but two of these workers, and deaths were classified by cause according to the seventh revision of the WHO classification [70].

The expected numbers of deaths from several causes were estimated using age- and time-specific death rates for white men in the United States. The numbers of observed and expected deaths and the O/E ratios of deaths from several causes in both salaried employees and hourly workers are shown in Table III-12.

The O/E ratios of deaths from nasal cancer and lung cancer were increased for retired hourly workers but not for retired salaried workers [47]. For retired hourly workers, the O/E ratio of deaths from nasal cancer was 15.4:1. Of two deaths from cancer of the ethmoid sinuses, both occurred in the 1960's. One worker who died from nasal cancer was a 62-year-old man who had been a bricklayer and had retired after 20 years of employment in 1948 on a disability pension because he had heart disease. The other worker who died from nasal cancer was a 62-year-old man who had, for 27 years, until shortly before his death, been a laborer in a wide variety of jobs, none of which, according to Enterline, appeared to involve unusual exposure to nickel. The O/E ratio of deaths from lung cancer was higher in retired hourly workers than in retired salaried workers, but neither ratio was statistically significant.

In addition, Enterline [47] found that the O/E ratios of deaths from several causes were greater in retired workers who died between the ages of 60 and 64 than in those who died at the age of 65 or over. In retired workers who died between the ages of 60 and 64, the O/E ratios were 3.1:1 for lung cancer (8 observed, 2.6 expected, $P<0.05$), 2.0:1 for all causes of cancer (18 observed, 8.8 expected, $P<0.05$), and 1.3:1 for heart disease

TABLE III-12

DEATHS IN WORKERS RETIRED FROM A NICKEL ALLOY PLANT
IN HUNTINGTON, WEST VIRGINIA*

Cause of Death	ICD Number**	Hourly Workers			Salaried Workers			All Retired Workers		
		O	E	O/E	O	E	O/E	O	E	O/E
Cancer of the nose	160	2	0.13	15.38	-	-	-	-	-	-
Cancer of the lung, bronchus, trachea, and pleura	162-163	14	10.1	1.39	3	2.8	1.07	17	12.9	1.32
Cancer of the digestive system	150-159	14	16.0	0.88	5	4.5	1.11	19	20.5	0.93
Other cancer	-	15	17.6	0.85	7	5.2	1.35	24	22.8	1.05
Other diseases of the respiratory system	470-527	8	15.1	0.53	2	4.3	0.47	10	19.4	0.52
Cerebral vascular lesions	330-334	35	28.2	1.24	10	8.1	1.23	45	36.3	1.24
Coronary heart disease	420	92	96.4	0.95	37	27.6	1.34	129	124.0	1.04
Other heart disease	-	19	22.9	0.83	7	6.4	1.09	26	29.3	0.89
Other causes	-	47	48.1	0.98	9	13.9	0.65	56	62.0	0.90
All cancer	140-205	47	43.9	1.07	15	12.5	1.20	62	56.4	1.09
All heart disease	400-443	111	119.3	0.93	44	34.0	1.29	155	153.3	1.01
All causes	-	248	254.6	0.97	80	72.8	1.10	328	327.4	1.00

*815 workers, including 190 salaried employees and 625 employees paid by the hour who retired between 1941 and 1970 and who died before the end of 1971
**Classification number from the seventh revision of the WHO classification of causes of death [70]

Adapted from Enterline [47]

(26 observed, 20.4 expected). In retired workers who died at the age of 65 or over, the O/E ratios of deaths were 0.87:1 for lung cancer (9 observed, 10.3 expected), 0.92:1 for all causes of cancer (44 observed, 47.6 expected), and 0.97:1 for heart disease (129 observed, 132.9 expected). The reason for this dramatic difference in the O/E ratios of deaths for the two age groups is not clear. The group of retirees between the ages of 60 and 64 may have contained more disabled workers than did the group of those aged 65 or over, or the pension records might have been inconsistent or incomplete.

Although it is difficult to interpret the results of this preliminary study [47], the two deaths from nasal cancer and the increased, though not statistically significant, O/E ratio of deaths from lung cancer in retired hourly workers suggest that these workers at the Huntington nickel alloy plant may have had an increased risk of death from cancer of the respiratory organs. Enterline suggested that differences in the O/E ratios of deaths from heart disease in salaried and hourly workers may be related to differences in the degree of physical activity required in their jobs. A more comprehensive epidemiologic study of all workers at the nickel alloy plant is needed to determine conclusively if these workers had an increased risk of developing cancer of the respiratory organs.

A preliminary study of deaths in workers and pensioners at the Huntington nickel alloy plant was reported by Inco in 1976 [41]. The study included men who were on the company payroll on January 1, 1948, and who had been employed at the plant for at least one year. There were 1,852 workers in the cohort, and in 1948, 1,634 were actively employed (88%), 16 were receiving service pensions (1%), 126 were receiving disability pensions (7%) and 76 had been laid off and later recalled to active employment (4%). About 10% of the workers had terminated employment for reasons other than death or retirement before the end of 1974. The number of years at risk for the these workers was included until employment was ended, but accounted for only 3% of the total of nearly 40,000 years at risk for all workers between 1948 and 1975. Of the 1,852 workers, 1,132 were first employed between 1922 and 1939 (61%), and 720 were first employed between 1940 and 1947 (39%). In 1948, the average age of the cohort was 43 years.

Workers were classified into exposure groups according to their complete work histories since the plant opened in 1922 [41]. Workers were included in a pure exposure group unless they had been employed for more than one year in another exposure area. In this review, the four mixed exposure groups from the original report have been combined into one group. The exposure groups are listed below:

(1) Furnace: Men who worked in areas where nickel was melted and cast, or near the calciner furnaces (between 1922 and 1948, nickel-copper sulfide was converted to nickel-copper oxide in calciner furnaces).

(2) Pickling: Men who worked in areas where nickel metal bars were dipped in acid baths to remove nickel oxide formed on the surface during heating and cooling and to give the bar a clean finish.

(3) Grinding dust: Men who worked in areas where nickel oxide was removed from the surface of a bar of nickel metal by grinding, chipping, or polishing.

(4) Office: Men who worked in offices, laboratories, or in the yard.

(5) Mixed: Men who worked in more than one exposure group for more than one year.

Workers and pensioners in the study who died between January 1, 1948, and December 31, 1974, were identified by reviewing company records [41]. Death certificates were obtained, and the causes of death were classified according to the WHO classification [70]. The number of years at risk was determined for workers in each exposure group, each 5-year duration of exposure group, each 10-year age group, and each 5-year period. To determine the expected number of deaths in each group, the number of years at risk was multiplied by the appropriate age- and time-specific death rate for white men in the US between 1949 and 1970. Of the 1,852 workers, 608 had died before the end of 1974 (33%), the average age at death was 67 years, and the average interval between their first employment and death was 34 years [41]. The average age of the 1,244 workers in the study who were alive at the end of the study period was 64 years, and the average interval between first employment at the nickel plant and the end of the study period was 38 years.

The number of observed and expected deaths and the O/E ratio of deaths from cancer of the respiratory organs, all sites of cancer, and all causes for each of the five exposure groups are shown in Table III-13 [41]. For all of the nickel alloy plant workers in the study, the O/E ratio of deaths was 0.75:1 for all causes combined, 0.73:1 for all causes other than cancer (483 observed, 644.54 expected $P<0.05$), 0.05), 0.88:1 for cancer in all sites combined, and 0.97:1 for cancer of the respiratory organs [41].

TABLE III-13

DEATHS IN WORKERS AT A NICKEL ALLOY PLANT
IN HUNTINGTON, WEST VIRGINIA*

Exposure Group	Number of Workers	Cancer of Respiratory Organs			All Cancer			All Causes		
		O	E	O/E	O	E	O/E	O	E	O/E
Furnace dust	118	3	2.47	1.21	12	8.37	1.43	52	46.55	1.12
1-19 yr	-	0	0.49	-	2	2.05	0.98	11	12.94	0.85
20 yr or more	-	3	1.98	1.51	10	6.32	1.58	41	33.61	1.22
Pickling	225	5	5.62	0.89	11	20.31	0.54	92	116.77	0.79
1-19 yr	-	0	0.95	-	3	4.21	0.71	26	27.09	0.96
20 yr or more	-	5	4.67	1.07	8	16.10	0.50	66	89.68	0.74
Grinding dust	139	3	4.00	0.75	16	14.99	1.07	73	87.32	0.84
1-19 yr	-	0	0.66	-	2	2.85	0.70	17	18.06	0.94
20 yr or more	-	3	3.34	0.90	14	12.14	1.15	56	69.26	0.81
Office	110	0	2.10	-	2	7.27	0.28	30	41.32	0.73
1-19 yr	-	0	0.21	-	0	0.82	-	4	5.40	0.74
20 yr or more	-	0	1.89	-	2	6.45	0.31	26	35.92	0.72
Mixed	1,260	29	26.89	1.08	84	91.02	0.92	361	514.54	0.70
1-19 yr	-	2	4.24	0.47	17	18.16	0.94	87	120.48	0.72
20 yr or more	-	27	22.65	1.19	67	72.86	0.92	274	396.06	0.69
Total	1,852	40	41.08	0.97	125	141.96	0.88	608	806.50	0.75
1-19 yr	-	2	6.55	0.81	24	28.09	0.85	145	183.97	0.79
20 yr or more	-	38	34.53	1.10	101	113.87	0.89	463	622.53	0.74

*1,852 workers employed in 1948 and traced between 1948 and 1974

Adapted from Inco [41]

According to Inco, the decrease in the risk of death from all causes other than cancer in nickel alloy plant workers may have been related to selective factors for diseases such as heart disease that favor the working population over the total population. In workers in the furnace dust exposure group, the O/E ratios of deaths from all causes, from all causes of cancer, and from cancer of the respiratory organs were slightly increased but not statistically significant; the O/E ratios were 1.1:1 for all causes, 1.4:1 for all sites of cancer, and 1.2:1 for cancer of the respiratory organs. Deaths from cancer of the respiratory organs do not account for all of the slight excess of deaths from cancer in the furnace dust group, since the O/E ratio of deaths from nonrespiratory cancers was 1.5:1. In workers in the mixed exposure group who were employed for more than 20 years, the O/E ratio of deaths from cancer of the respiratory organs was 1.2:1, slightly elevated. In none of the exposure groups, however, did the O/E ratio of deaths from cancer of the respiratory organs differ significantly from 1.0.

Inco noted that two of the deaths from cancer of the respiratory organs were caused by nasal cancer [41] (apparently these deaths were also identified in an epidemiologic study of deaths by Enterline [47]). One of the workers was in the furnace dust exposure group, the other in the mixed exposure group. Inco suggested that both deaths from nasal cancer were related to exposure resulting from calcining operations, which were terminated at Huntington in 1948 [41]. A third worker died from nasal cancer in 1976. Inco reported that this worker apparently was not exposed to dusts and fumes from calciner furnaces and contended that this case of nasal cancer was unrelated to workplace exposure.

This preliminary epidemiologic study [41] does not conclusively determine whether nickel alloy plant workers have an increased risk of death from cancer of the respiratory organs or from cancer in other organs. Within each exposure group, the numbers of both observed and expected deaths from cancer of the respiratory organs were too small to permit a reliable estimate of the O/E ratio of deaths. Two of the three deaths from nasal cancer were probably related to work in areas near the calciner furnaces. Furthermore, since deaths from nasal cancer are quite rare in the general population (between 1950 and 1969, the death rate from nasal cancer in white men in the United States, adjusted to the age distribution of the 1960 population, was 0.43/100,000 [76]), the third death from nasal cancer in the cohort of 1,852 nickel alloy plant workers also may have been related to workplace exposure, and thus may not represent the normal incidence of death from nasal cancer in the general population.

The death rate from lung cancer is not uniform throughout the United States. Between 1950 and 1969, the death rate from lung cancer in white men adjusted to the age distribution of the US population in 1960 was 37.98/100,000 for the United States, 35.18/100,000 for West Virginia, and 32.11/100,000 for Cabell County, West Virginia, where the nickel alloy plant is located [76]. To determine if the risk of death from cancer of the respiratory organs is elevated in workers in the nickel alloy plant in West Virginia, the number of observed deaths in these workers should also be compared with the expected number of deaths estimated from death rates for the population of West Virginia or the population of the region. Including workers on the payroll before 1948 in the study cohort would increase the number of both observed and expected deaths and thus increase the reliability of the O/E ratios. Inco noted that this epidemiologic study is preliminary and that this cohort of nickel alloy plant workers will be studied in more detail [41].

The information on past operations at the Huntington nickel alloy plant provided by Inco [23,41] was limited. Between 1922 and 1948, impure copper-nickel sulfides, containing nickel subsulfide, were crushed and ground, and then oxidized at temperatures of 600-1,200 C in refractory-lined mechanically agitated calciner furnaces similar to those used at Clydach, Wales, and at Port Colborne, Ontario [41]. A few measurements of the concentration of airborne dust in the nickel alloy plant were made between 1939 and 1945. Airborne dust was sampled by a midget-impinger technique in the calciner building and the adjacent melt shop, and the results were expressed as mppcf. The concentration of airborne dust in mg/cu m was estimated from the measurements in mppcf, using a conversion factor of 7 for the calciner building and 5 for the melt shop. The derivation of these conversion factors was not discussed in the report. From two measurements, taken in 1939 and 1945, the concentrations of airborne dust near the ball mill where impure copper-nickel sulfide was ground and crushed were estimated to be 58 and 72 mppcf or 400-500 mg/cu m. From four measurements, the concentrations of airborne dust between the calciner furnaces were estimated to range from about 0.4-3.3 mppcf or 3-25 mg/cu m between 1939 and 1945. The fine dust from the calciner furnaces, where impure copper-nickel sulfides from Canada were oxidized, contained 45% nickel. The fine dust from calciner furnaces, where impure copper-nickel sulfide from New Caledonia was oxidized between 1941 and 1948, contained about 70% nickel. In the melt shop, one reading in 1939 indicated that the concentration of airborne dust between two electric arc furnaces was 32.6 mppcf or about 163 mg/cu m, and four measurements indicated that the concentration of airborne dust in other areas of the melt shop ranged from 0.25-7.8 mppcf or about 1.3-39 mg/cu m in 1939-1942.

From these data on particle counts and the nickel content of dusts, it was estimated that workers near the calciner furnaces were exposed to about 5-15 mg/cu m of airborne nickel and to about 10-20 mg/cu m of total airborne dust; workers near the grinding and crushing machines were exposed to about 20-350 mg/cu m of airborne nickel, and to about 50-500 mg/cu m of airborne dust; and workers in the melt shop were exposed to about 5-150 mg/cu m of airborne dust [41]. Although Inco did not estimate it, the percentage of nickel in airborne dust near the furnaces in the melt shop would presumably reflect the high percentage of nickel in most of the alloys produced at this plant. Even though the data on the concentrations of airborne dust and the estimates of the concentrations of airborne nickel are limited, they seem to suggest that the concentration of airborne nickel near the calciner furnaces in the Huntington nickel alloy plant were in the same range as those near the calciner furnaces installed at the Clydach nickel refinery in the 1930's.

(e) USSR

In 1970, Saknyn and Shabynina [58] reported the results of an epidemiologic study of deaths from cancer in a USSR plant where nickel oxide ore was processed. The authors indicated that there were three major operations at the nickel plant: preparation and drying of the ore, roasting and smelting operations, and recovery of cobalt and arsenic. Sulfur was added to process nickel oxide ores in the USSR [10] and Saknyn and

Shabynina [58] indicated that workers engaged in roasting and smelting operations were exposed to dusts containing nickel sulfides as well as nickel oxides. The authors apparently used company records to identify workers who died from cancer between 1955 and 1967. They determined the age- and sex-adjusted death rates from cancer in nickel plant workers and in the population of the city adjoining the plant, but they reported only the ratio of the cancer death rates in these two populations. Saknyn and Shabynina noted that the age- and sex-adjusted death rate from cancer in workers at the nickel plant was 1.5 times greater than that in the adjoining city. The death rate from cancer of the lungs in workers at the nickel plant was 1.8 times greater than that in the adjoining city, and the average duration of employment of nickel workers who died from lung cancer was 13 years. They also noted that the death rate from sarcomas, mostly osteosarcomas and pulmonary sarcomas, was 6.2 times greater in nickel workers than it was in the adjoining city and that the death rate from stomach cancer was elevated, but these findings were not reported in detail. The authors did not present information on the number of workers at the nickel plant, their occupational histories, the procedures used to identify deaths in workers or in the general population, or the numbers of observed and expected deaths in nickel workers. Because this information is lacking, the study suggests but does not adequately demonstrate that workers engaged in roasting and smelting nickel oxide ore may have an increased risk of death from cancer.

In 1973, Saknyn and Shabynina [59] analyzed the death rates from cancers of the lung and stomach and from sarcomas in workers at the plant studied in 1970 and in three additional nickel refineries. The same methods were used and similar results were found.

In 1960, Tatarskaya [49] investigated changes in olfactory function and in the nasal mucosa of 486 workers in USSR plants that refined nickel electrolytically. On the basis of their occupational histories, Tatarskaya divided the workers into four groups: electrolysis workers; workers in the cleaning section; persons who occasionally worked in the cleaning and electrolysis sections, eg, technicians and installers; and administrative personnel. The majority of the workers had been employed at the refinery for at least 5 years, and nearly two-thirds of them were under 40 years of age. Reexamination of 223 of the workers were conducted 1.5 years after the initial examination, and the 50 workers with the most severe damage to the nasal mucosa were examined three times in the same 1.5 year period. Tatarskaya reviewed symptoms and morphologic changes in the nose, pharynx, and larynx, as well as changes in olfactory function. Olfactory function was assessed qualitatively by determining whether workers could detect the odor of ammonium hydroxide, vinegar, tincture of valerian, 70% alcohol, or a 10% solution of cocaine. Anosmia was diagnosed if the worker failed to detect the odor of any substance, including ammonia; and hyposmia was diagnosed if the worker was unable to detect one or more of the test substances.

Tatarskaya noted that symptoms changed in number and kind with the duration of employment and were not related to age [49]. In the first few days and weeks of work in the electrolysis and cleaning shops, workers complained of sneezing, a sense of constriction in the nose, and runny nose. Later, nasal hemorrhages occurred in some workers, then either stopped or became rare or slight. As the duration of employment increased, the number of workers with complaints of dryness of the nose, formation of crusts, and olfactory disorders increased. Pain in the upper respiratory tract and difficulty in nasal breathing were also noted. The author observed that the number and severity of changes in respiratory tract mucosa also increased as the duration of exposure increased and were not related to age. Morphologic changes were most common in the nose, followed by the pharnyx and larynx. So-called subatrophic, atrophic, and dry rhinitis were noted in 10-16% of the workers, and chronic catarrhal rhinitis was noted in about 5% of the workers. Erosions, perforations, and ulcers were limited to the nose; 13% of the workers had erosions, 6% had perforations, and about 1.4% had ulcers. About 10% of the workers had subatrophic pharyngitis and about 3% had atrophic pharyngitis. About 3% of the workers had chronic tonsillitis, and about 3% had chronic laryngitis. Tatarskaya claimed that 160 workers (32.9%) had anosmia and 149 workers (30.6%) had hyposmia, but he reported that there was no definite relationship between the morphologic condition of the nasal mucosa and the degree of olfactory impairment.

On the basis of changes in morphology of the upper respiratory tract seen in workers examined more than once, Tatarskaya [49] concluded that, in most workers, erosion of the nasal septum showed no clear tendency to progress as the duration of employment increased. Only one case of erosion of the septum progressed to perforation in the 1.5 years between observations. Erosions and superficial ulcers tended to heal while workers were on vacation, but the damage reappeared in some cases. The author reported that the size and shape of nasal perforations did not change significantly in the 1.5-year observation period. Tatarskaya concluded that exposure to an aerosol produced by the nickel compounds (primarily nickel sulfate) used in electrorefining caused damage to the nasal mucosa similar to that caused by exposure to aerosols containing chromium, fluoride, and arsenic. In addition, exposure to aerosols from solutions of nickel compounds seemed to affect olfactory function independently of effects on the morphology of the nasal mucosa.

Although Tatarskaya [49] divided the nickel workers into four occupational groups, the data were presented for all groups combined. If information had been presented on the concentrations of airborne nickel, duration of employment, and diagnostic procedures, and if there had been a control group, the significance of Tatarskaya's findings could be more adequately assessed. The extent of damage to the nasal mucosa and to olfactory function, however, seemed to have been fairly extensive, considering that all workers, including those with apparently minimal or intermittent exposure, were included in the analysis. Moreover, Tatarskaya's findings indicate that exposure to aerosols of nickel compounds produced or used in electrorefining can cause mild to severe changes in the morphology of the nasal mucosa, as well as changes in olfactory function.

In 1970, Kucharin [50] conducted on an examination of the nasal cavities and sinuses of 458 workers in a nickel electrorefining plant in the USSR. The author stated that 347 of the workers had been exposed to nickel in electrorefining operations for at least 10 years, while 111 workers were employed in auxiliary work; but he reported findings for only 302 of the 458 workers. Kucharin noted that the concentrations of airborne nickel ranged from 0.02 to 4.5 mg/cu m in the electrolysis and cleaning departments, where workers were also exposed to chlorine and sulfuric acid fumes and to high temperatures. The workers were given an undescribed clinical examination, and the nasal cavities and sinuses were examined using both rhinoscopic and radiographic procedures. The radiographic findings were compared with the rhinoscopic findings to estimate the extent of damage in the nasal cavities and sinuses. Disorders of the nose were grouped, apparently on the basis of radiologic findings, into three categories: acute sinusitis; chronic sinusitis; and cysts or cystlike lesions. Rhinoscopic findings were grouped into five categories; subatrophic changes of the nasal mucosa, atrophic changes of the nasal mucosa, erosions, perforations, and nasal polyps. Of the 302 workers on whom Kucharin reported, 199 (66%) had aberrations of the nasal cavities and sinuses detected by X-ray, 145 of whom (73%) also had associated findings in the rhinoscopic examination. Some complained of bleeding, dryness, formation of scales, or pain in the nose. Those with nasal erosions or perforations complained of periodic nosebleeds, stuffiness of the nose, frequent colds, and mucous discharge. However, not all of the workers with microscopic nasal lesions such as erosions and perforations reported symptoms. Of the 251 workers with chronic sinusitis, 104 (41%) had nasal erosions, 66 (24%) had subatrophic changes of the nasal mucosa, 17 (7%) had atrophic changes, 16 (6%) had nasal perforations, and 8 (3%) had nasal polyps. The pattern of microscopic changes was similar in the 31 workers with cysts or cystlike formations and the 17 workers with acute sinusitis. Olfactory function was reduced in 98 of the 215 workers with chronic sinustis (45%), while somewhat fewer of the workers with acute sinusitis or cysts were affected.

Kucharin [50] did not explain how workers had been selected for the study, nor was the extent or duration of exposure considered. Diagnostic procedures were not adequately described, and no basis was given for classification either by radiographic or rhinoscopic procedures. The results were not reported for all workers, and it is unclear if workers with more than one symptom or type of lesion were counted in several groups. Since electrolysis and cleaning department workers were exposed to other potentially harmful compounds, such as chlorine and sulfuric acid fumes, the information in this report is insufficient to establish that the symptoms and the microscopic lesions of the nose in electrolytic nickel refinery workers resulted specifically from exposure to nickel. Although the etiologic agents cannot be determined from this study, its findings do indicate that exposure to airborne compounds in the electrolysis and cleaning departments of a nickel refinery may cause damage to the nasal cavities even when the concentration of airborne nickel was reported to be at or below 4.5 mg/cu m.

(f) Other Countries

In 1965, Tsuchiya [60] reported an epidemiologic study comparing death rates from cancer, particularly lung cancer, in the population with death rates in workers in various occupations in Japan. A questionnaire was sent to the health supervisors of 200 randomly selected industries from all Japanese industries with more than 1,000 employees. There was good agreement between the general population of Japan and the different occupational groups studied for the relative frequencies of different types of cancer with the exception of lung cancer. Therefore, Tsuchiya concluded that reports from the industrial health supervisors were reasonably reliable and that the sample was fairly representative of the working population. The industries were divided into 12 groups according to exposure to substances considered by Tsuchiya to be potential carcinogens, eg, benzene, aniline, X-rays, nickel, and chromium, but the procedures used were not reported. The number of deaths from stomach, liver, and lung cancer in each of the 12 exposure groups was compared with the expected number of deaths derived from age-adjusted death rates for the entire sample. Tsuchiya identified 19 deaths from lung cancer in industries using nickel (chemical forms unspecified), and reported that the number of deaths was significantly greater than expected ($P<0.01$).

In the second part of the study, the number of deaths in all Japanese industries handling nickel or chromium was compared with the number of deaths in all Japanese industries that did not handle nickel or chromium [60]. The number of observed and expected deaths was not adjusted by age, but only deaths in workers between the ages of 20 and 59 were considered. Tsuchiya found 22 deaths from lung cancer in workers in industries handling nickel or chromium; the O/E ratio was 2.2:1 ($P<0.05$). Since data from industries that handle either nickel or chromium were combined, the proportion of deaths from lung cancer that may be associated with exposure to nickel cannot be determined from these data. The results of the first part of the study suggest, however, that workers in industries that handle nickel have an increased risk of death from cancer of the lungs.

In 1959, Rockstroh [61] described 45 confirmed cases of lung cancer that occurred between 1928 and 1956 in workers at a nickel smelting plant in Germany where nickel-arsenide ore was processed. In addition, 39 cases of defects in the nasal septa were found in an examination of 90 workers at the plant, and 2 cases of skin cancer were reported in an 11-year period. Rockstroh noted that workers were exposed to nickel, arsenic, cobalt, copper, bismuth, and benzopyrene at the nickel smelting plant, although data were not presented. Because only 2 cases of skin cancer, the type of cancer usually associated with exposure to arsenic, were found, whereas 45 cases of lung cancer were diagnosed, Rockstroh concluded that arsenic was not the only cancer-causing agent to which workers at the nickel smelter were exposed.

Animal Toxicity

(a) Carcinogenicity

(1) Inhalation or Intratracheal Exposures

Kasprzak et al [77], in a study reported in 1973, administered 5 mg of nickel subsulfide suspended in 0.1 ml of 5% sodium carboxymethyl cellulose in a single intratracheal injection to each of 13 male Wistar rats weighing about 200 g. The mean particle size was 10 μm (range 1-30) and penetration into the small bronchioles and alveolar spaces was verified by microscopic examination of lungs of other rats similarly exposed. All the rats survived through the observation period of 15 months and were subsequently killed for examination. One liver tumor, without metastases, was seen. The lungs of nine of the rats, including the rat with the liver tumor, were unaltered, but the lungs of the other four showed peribronchial adenomatoid proliferation, and two of these had inflammatory reactions in the bronchial walls.

In another study with nickel subsulfide, Ottolenghi et al [78] reported the effects on Fischer rats of both sexes following its