Mesothelioma and Lung Tumors Attributable to Asbestos Among Petroleum Workers

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Background *Asbestos exposure has been definitively found to be associated with both mesothelioma and lung cancer. Nevertheless, in the overall population of oil refinery workers potentially exposed to asbestos, many studies clearly show a definitely increased risk of mesothelioma, but no proven excess of lung cancer after comparison to the general population. Through the presentation of new data and the re-appraisal of two recent and independent epidemiological studies conducted in Liguria, Italy, and Ontario, Canada, we attempt to shed light on this apparently paradoxical finding.*

Methods *Lung cancer mortality was studied among maintenance workers exposed to asbestos, and among two other subgroups of refinery employees: blue collar and white collar workers.*

The comparison with blue collar workers was performed in order to take into account the role of healthy worker effect, smoking habit, and the socioeconomic level. The comparison with white collar workers was performed to control for other occupational lung carcinogens.

Results and Conclusions *Results reveal a consistency between the two studies and show that 96–100% of the mesotheliomas and 42–49% of the lung tumors arising among maintenance workers were attributable to asbestos exposure.*

Our new analysis, estimating two cases of asbestos-related lung cancer for each case of mesothelioma, confirms published findings on the magnitude of asbestos-related tumors in oil refineries. Am. J. Ind. Med. 37:275–282, 2000. *© 2000 Wiley-Liss, Inc.*

KEY WORDS: maintenance workers; occupational epidemiology; refinery workers; oil refinery; lung cancer; mesothelioma; pleural tumor; mortality; smoking; asbestos

INTRODUCTION

Oil refineries throughout the world total more than 700 [American Petroleum Institute, 1987]. In 1994 approximately 1,219,000 workers were employed [International Labour Office, 1998] in the production of nearly 2,500 different substances, including liquified petroleum gases, gasoline, kerosene, aviation fuels, diesel fuels, lubricants, bitumen, and other feedstocks for the petrochemical industry. The refining of petroleum shows constant development with about 3.5 billion tons produced in the world in 1997 [International Energy Agency, 1997] and is subject to innovation in both processes and facilities, including the introduction of occupational safety measures, such as the removal of asbestos and asbestos-containing materials, long used for purposes of thermal insulation in refineries and long recognized as posing the potential risk of the onset of lung cancer and mesothelioma. However, while such policy is

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implemented in industrialized nations, similar primary prevention measures are still insufficient in developing countries [Pearce et al., 1994].

The scientific literature has long reported hygienic data that documents asbestos exposure in oil refineries [Smyth et al., 1971; Darby et al., 1978; Lilis et al., 1980; Nicholson et al., 1982; Liveright et al., 1986; International Agency for Research on Cancer, 1989; Mehlman, 1991a,b; Gennaro et al., 1995]; moreover, the mortality for mesotheliomas suggests that inhalation of fibers occurs [von Bittersohl, 1971; von Bittersohl and Ose, 1971; Kaplan, 1986; Christie et al., 1991; Schnatter et al., 1992; Gennaro et al., 1994, 1995; Honda et al., 1995; Finkelstein, 1996; Tsai et al., 1996a,b; Dement et al., 1998]. Nearly all epidemiological studies analyzing mortality for mesotheliomas in oil refineries have highlighted statistically significant excesses of risk, ranging from 2 to 24 times above baseline (Table I).

By contrast, evidence on lung cancer mortality in oil refineries is still contradictory: a meta-analysis conducted by Wong and Raabe [1989] reported a significant reduction in mortality from this cause (Standardized Mortality Ratio (SMR) = 0.77), without, however, providing any analysis by job title. On the other hand, other studies [Gottlieb, 1980; Gennaro et al., 1995; Finkelstein, 1996, 1999; Raabe et al., 1998], as well as projections [Nicholson et al., 1982], showed an increase in lung cancer mortality among refinery maintenance workers.

The first objective of the present work was to evaluate the association between asbestos and lung cancer emerging from the studies performed by Gennaro et al. [1994, 1995] and by Finkelstein [1996]. Each of these studies, in Italy and in Canada, considered the elevated risks for mesotheliomas as sentinel events for asbestos exposure, thus permitting identification of specific occupational tasks, i.e., maintenance work, in which asbestos exposure occurred at different levels.

The second objective was to calculate the ratio between the number of asbestos-related lung cancer cases and the number of mesothelioma cases in both the Italian and the Canadian studies. The resulting ratios were then compared with previous estimates [Nicholson, Perkel, Selikoff, 1982; Health and Safety Executive (HSE), 1991, 1993; De Vos Irvine et al., 1993]. These ratios could prove useful to better understand the real magnitude of asbestos-related diseases, lung cancers included, among maintenance workers, which represent the main subgroup (36%) of refinery workers, as reported by Nelson et al. [1983].

TABLE I. Standardized Mortality Ratios (SMR) for Mesothelioma Reported in Epidemiological Studies Conducted in Oil Refineries

Study	SMR	Number of cases
Kaplan [1986]	2.4	9
Gennaro et al. [1991a]	4.8	5
Christie et al. [1991]	3.9[a]	3
Schnatter et al. [1992]	5.7	7
Hornstra [1993, unpublished]	4.0	16
Gennaro et al. [1994]	2.7–16.6[b]	10
Honda et al. [1995]	2.0[a]–3.2[c]	9
Finkelstein [1996]	24.4[d]	6
Tsai et al. [1996a]	2.2[a]	7
Tsai et al. [1996b]	4.3	5

[a]Not statistically significant at $P < 0.05$.
[b]Local and National reference, respectively.
[c]Time periods considered: 1942–1989 and 1980–1989, respectively.
[d]Odds Ratio.

MATERIALS AND METHODS

The present work re-appraises a cohort study conducted in Liguria (Italy) [Gennaro et al., 1994], and a lung cancer and mesothelioma death certificate-based case–control study performed in Ontario (Canada) [Finkelstein, 1996]. In addition, the Italian study was updated with new data. While descriptions on study populations and methods are found in the corresponding sections of the original studies, the present work focuses on asbestos-related lung cancer and thus provides more specific details and related results.

Description of the Studies

A first cohort study conducted in 1991 in Liguria, among refinery workers [Gennaro et al., 1991], was integrated with an analogous study performed in another refinery of the same region [Gennaro et al., 1994]. Overall, the cohort, covering the period 1950–1991, included 2,300 subjects working at least one day for a total of 58,000 person–years. This integrated study showed a statistically significant increased mortality for pleural tumor, based on ten cases, after comparison with both local (SMR = 2.66; 95% Confidence Interval [CI] 1.28–4.89) and national (SMR = 16.63; 95% CI 7.97–30.58) populations. This extremely large difference in the SMRs is likely due to the large difference in the proportion of subjects occupationally and environmentally exposed to asbestos due to the high concentration of industrial plants in the local area. Given that only one plant (in which all three types of fibers, namely, amosite, crysotile, and crocidolite were detected) provided a description of main occupational tasks, only this cohort was re-analyzed in the present study. In this refinery, among personnel classified as maintenance workers (357 subjects, 9,548 person–years), five pleural mesotheliomas were observed, yielding a highly increased mortality risk after comparison with both local (SMR = 5.47; 95% CI 1.78–12.76) and national (SMR = 29.27; 95% CI 9.51–68.31) reference populations. A statistically significant excess of lung tumor deaths ($N = 16$) was also detected after internal comparison with white collar workers (SMR = 1.97; 95% CI 1.13–3.20) [Gennaro et al., 1995]. To increase the stability of expected frequencies, and consequently to reduce statistical variability, we decided to increase the size of the internal referent population by combining the two similar groups of white collar workers in the two Italian refineries. Overall, 16,500 person–years and 12 lung cancer cases were analyzed in this group.

The Canadian study, a death certificate-based case–control analysis, was conducted by using information from the Ontario Mortality Registry for the years 1980–1992. Each of the 17 men who died of mesothelioma was randomly matched with three others of the same age and year of death who had died of any cause other than lung cancer, mesothelioma, or leukemia. Lung cancer deaths were identified in persons between 45 and 74 years of age. Each of the 487 lung cancer victims was matched with a single comparison subject. The final total of subjects with useable data was 17 men with mesothelioma and 46 controls, and 424 men with lung cancer and 431 controls. Ten of the 17 men with mesothelioma had worked in petrochemical industries. Six had been employed as maintenance workers, among whom a statistically significant increased mortality from mesothelioma (Odds Ratio [OR] = 24.5; 90% CI 3.1–102.0) and, after internal comparison, also an increased mortality from lung tumor (OR = 1.73; 90% CI 0.83–3.60) were found. No control subjects had pulmonary fibrosis or asbestosis. Since this was a population-based study, and since these are rare conditions, this is not surprising.

These two studies seemed reasonably comparable since they:

1. Identify asbestos as a specific risk factor to be studied in refineries;
2. Identify a main and specific subgroup of blue collar workers i.e., maintenance workers, probably exposed to asbestos, given their high mortality from mesothelioma;
3. Analyze two specific asbestos-related tumors, i.e., mesotheliomas and lung tumors;
4. Use white collar (Italy) and other workers (Canada) as a reference population.

The present work does not take into account the recent paper by Dement et al. [1998], whose study design does not address asbestos exposure, or the report by Tsai and colleagues [1996a,b], since it underwent previous evaluation [Finkelstein, 1996].

Statistical Analysis

Given that not all pleuro-pulmonary tumors observed among maintenance workers are *a priori* attributable to asbestos exposure, the proportion of asbestos-related tumors among exposed workers was estimated by using the formula of the attributable risk percent (AR):

$$AR = \frac{(RR - 1)}{RR} \times 100$$

where RR represents an estimate of relative risk (i.e., SMR or OR resulting from cohort and case–control studies, respectively) [Rothman, 1986]. Finally, 95% CI for AR was calculated as reported by Greenland [1987].

RESULTS

The Italian cohort comprised 932 subjects: 22% were white collar, 38% maintenance workers, and 40% other blue collar workers. Table II shows the main characteristics of deaths from lung tumors among the three groups of workers. In maintenance workers, the minimum duration of employment was greater than nine years and the minimum time elapsed since hire was greater than 11 years. The mean age of death was 63 years, which is five years before than that observed among other blue collar and white collar workers.

Table III shows selected cause-specific SMRs by job title based on Italian mortality rates. With the exception of pleural tumor mortality, which was significantly increased among maintenance workers, the cause-specific SMRs were reduced or not significantly elevated among all three job categories of workers.

In particular, the total number of observed deaths among maintenance workers was reduced, but not significantly, for all causes combined (SMR = 0.90; 95% CI = 0.76–1.05), and significantly reduced (SMR = 0.64; 95% CI = 0.47–0.85) for cardiovascular diseases. The number of observed deaths was not significantly elevated for all cancers (SMR = 1.21; 95% CI = 0.90–1.59), lung cancer (SMR = 1.42; 95% CI = 0.81–2.30), and gastro-intestinal cancers (data not shown). All observed cause-specific mortality among white collars did not differ significantly from what was observed among other workers, including cardiovascular diseases (SMR = 0.82; 95% CI = 0.58–1.12). These results support the hypothesis that white collar workers represent a better referent population for maintenance workers, in view of their similar SMRs for well-known smoking-related cardiovascular diseases, and because, unlike other blue collar workers, they are normally not exposed to occupational carcinogenic agents (for example, hydrocarbons) having lung as a target organ.

When internal comparisons were performed for mesothelioma (Table IV), statistically significant increased risks in terms of SMR and OR were observed. Asbestos fibers seem to account for practically all mesotheliomas observed in the two groups of maintenance workers (AR = 96–100%). In the Italian cohort, no mesothelioma

TABLE II. Main Characteristics of Lung Tumor Deaths in One Italian Oil Refinery Cohort by Job Category

	White collar workers Mean (S.E.)[a] Range	Blue collar workers Mean (S.E.)[a] Range	Maintenance workers Mean (S.E.)[a] Range
Number of deaths	8	16	16
Age at hire	27 (2.1)	34 (2.1)	33 (1.5)
	17–35	22–50	23–46
Age at death	68 (4.0)	68 (2.1)	63 (2.6)
	51–81	54–83	42–81
Duration of employment	31 (1.8)	24 (2.0)	21 (1.6)
	25.5–39.4	9.3–38.6	9.5–28.3
Time since hire	41 (3.5)	34 (3.2)	29 (2.3)
	26.0–57.3	12.1–55.6	11.0–43.1
Year of hire	1926–1950	1929–1952	1938–1960

[a]S.E. = Standard error.

TABLE III. Selected Causes of Death in One Italian Oil Refinery Cohort. Number of Cases (Obs), Standardized Mortality Ratio (SMR) and 95% Confidence Interval (95% CI). (Reference: Italian general population)

	White collar workers			Blue collar workers			Maintenance workers		
Cause of death (ICD VIII)	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All Causes (000–999)	85	0.76	0.61–0.94	135	0.82	0.69–0.97	151	0.90	0.76–1.05
Malignant neoplasms (140–209)	20	0.69	0.42–1.07	40	0.92	0.66–1.26	51	1.21	0.90–1.59
Larynx (161)	0	0.00	0.00–2.86	0	0.00	0.00–1.90	1	0.65	0.02–3.65
Lung (162)	8	0.99	0.43–1.96	16	1.32	0.76–2.15	16	1.42	0.81–2.30
Pleura (163)	0	0.00	0.00–21.58	0	0.00	0.00–14.34	5	29.27	9.51–68.31
Bladder (188)	0	0.00	0.00–2.22	3	1.49	0.31–4.37	2	1.04	0.13–3.75
Circulatory system (390–459)	39	0.82	0.58–1.12	54	0.78	0.58–1.01	47	0.64	0.47–0.85
Respiratory system (460–519)	5	0.53	0.17–1.23	13	0.94	0.50–1.60	19	1.29	0.78–2.01

TABLE IV. Mesothelioma Mortality Among Italian and Canadian Oil Refinery Maintenance Workers: Relative Risks Estimate (RR), Their 95% Confidence Interval (95% CI) and Asbestos Attributable Risk Percent Among Exposed (AR)

Area	Study design	RR (95% CI)	AR (95% CI)	Reference population
Liguria (I)	Cohort	29.3 (9.5–68.3)[a]	96.6 (92.0–98.6)	Italian
		—	100	White collar workers[b]
Ontario (CA)	Case–control	24.5 (3.1–102.0)[c]	95.9 (70.0–99.6)	Ontario

[a]Standardized Mortality Ratio.
[b]Because of the absence of mesothelioma cases among white collar workers, it was not possible to perform an internal comparison.
[c]Odds Ratio (90% CI).

deaths (vs. 0.3 expected) among unexposed workers were observed.

Table V shows RR estimates as often observed in oil refinery studies when the *overall* group of blue collar workers is compared with different reference populations. Among blue collar workers, heterogeneous RRs for lung cancer are observed (range 0.92–1.47). Conversely, after distinguishing between *maintenance* and other blue collar workers (Table VI), maintenance personnel, both in Italy (16 deaths; SMR = 1.97; 95% CI 1.13–3.20) and Canada (28 deaths, OR = 1.73; 90% CI 0.83–3.60), appear to be at higher risk for lung tumor in an internal comparison with other workers. These results were confirmed by a Poisson regression analysis (analysis in progress). With respect to

TABLE V. Relative Risks (RR) Estimate and 95% Confidence Interval (CI) for Lung Cancer Mortality Among Italian and Canadian Oil Refinery Blue Collars (*Including* Maintenance Workers)

Area	Number of deaths	RR (95% CI)	Reference population
Liguria (I)[a]	48	1.17 (0.86–1.55)[b]	Italian population
”	”	1.47 (1.08–1.94)[b]	White collar workers
Ontario (CA)	49	0.92 (0.59–1.50)[c]	Other workers

[a]Two cohorts.
[b]Standardized Mortality Ratio.
[c]Odds ratio (90% CI).

TABLE VI. Lung Cancer Mortality (Relative Risk [RR] Estimate and 95% Confidence Interval [CI]) Attributable to Asbestos Exposure Among Italian and Canadian Oil Refinery Maintenance Workers

Area	Number of deaths	RR (95% CI)	Attributable risk %	Reference population
Liguria (I)	16	1.97 (1.13–3.20)[a]	49.2 (26.4–72.4)	White collar workers[b]
Ontario (CA)	28	1.73 (0.83–3.60)[c]	42.2 (10.8–82.6)	Other workers

[a]Standardized Mortality Ratio.
[b]Two cohorts.
[c]Odds Ratio (90% CI).

TABLE VII. Mesothelioma and Lung Cancer Mortality Among Oil Refinery Maintenance Workers: Ratio Between Number of Lung Cancer and Mesothelioma Deaths Attributable to Asbestos Directly Observed in Italian and Canadian Cohorts and Comparison with Published Provisions

	Deaths attributable to asbestos		
Area	Lung cancer/Mesothelioma	Ratio[a]	Reference populations
Liguria (I)	7.8/5	1.6	White collar workers[b]
Ontario (CA)	11.8/5.7	2.1	Ontario

[a]Following Health and Safety Executive [1991, 1993] and Nicholson, Perkel, Selikoff [1982], the ratios Lung/Mesothelioma were 2 and 2.6 respectively.
[b]No mesothelioma deaths were observed among white collar workers.

Table V, Table VI highlights a *dilution effect* that, as recently reported by Dement et al. [1998], prevents detecting high risks for lung cancer. This effect usually arises when two subpopulations of workers, one subject to high level and the other to low level of asbestos exposure, i.e., maintenance workers and other blue collar workers, respectively, are combined.

Analyses for ARs (Table VI) revealed that 42.2% (95% CI 10.8–82.6) of lung cancer cases in the Canadian plant and 49.2% (95% CI 26.4–72.4) of those observed in the Italian plant were attributable to asbestos exposure. The observed lung cancer mortality among maintenance workers was compared with that observed among other workers likely unexposed to asbestos and with comparable smoking related-diseases, as shown by Italian data (Table III).

Table VII shows the ratios between the number of lung tumor and mesothelioma deaths attributable to asbestos found in Liguria (1.6) and in Ontario (2.1). These values appear surprisingly similar to estimates calculated by HSE (two lung cancer deaths for each mesothelioma death) and by Nicholson et al. [1982] (2.3 lung cancer deaths, range 2.0–2.7, for each mesothelioma death). This last estimate was calculated considering only a time-window of year of death corresponding to that analyzed in both the Italian (1955–1992) and the Canadian (1980–1992) studies.

DISCUSSION

The risk for mesothelioma and lung tumor related to asbestos exposure in oil refineries has emerged as a public health issue [Gennaro et al., 1991, 1994, 1995; Wong, 1995; Finkelstein, 1996; Tsai et al., 1996a,b; Dement et al., 1998]. In fact, asbestos has been widely used in refineries as a thermal insulator for boilers and pipes that can often extend for many kilometers. In our experience, the demolition of only some parts of one Italian refinery, in which five pleural mesotheliomas were discovered, revealed an amount of asbestos, prevalently amosite, estimated at nearly 700 tons.

Although asbestos is currently banned in nine countries, it is still present in many others in which potential exposure risk exists for maintenance, repair, renovation and removal workers of various types of production facilities, refineries included. Moreover, it is entirely feasible that asbestos-containing materials are increasingly used in the majority of refineries located in developing countries where regulation on asbestos use is not yet well defined and, at the same time, the long term harmful effects on workers' health of the fibers are not often considered a priority issue.

Underestimation of Asbestos Exposure in Oil Refineries

Previously, a possible underestimation of asbestos exposure effects in oil refineries could be due to at least three concomitant elements. First, asbestos exposure in oil refineries probably does not reach the usual high average values observed in other workplaces [Nicholson et al., 1982]. Second, epidemiological studies, focusing on other specific pollutants, such as aromatic hydrocarbons and their possible effects on hemolymphopoietic tissues, respiratory and central nervous systems, have investigated asbestos exposure in only few refineries. Third, while asbestos is present in many plants, it is often handled only by workers from external firms.

Mesothelioma as Sentinel Event

Mesothelioma, the only specific asbestos-related tumor, is a very rare disease, and most likely the evidence derived from the low number of cases has not prompted its consideration as a high priority problem. Often, when mesotheliomas emerged in refinery studies, they were not regarded as sentinel events of asbestos exposure and were classified as "other or respiratory tumors."

In our opinion, the high risks of mesothelioma among specific subgroups of workers allow the detection of uncontrolled asbestos exposure in oil refineries and, consequently, the identification of subjects at higher risk for respiratory tumors.

In addition, a causal relationship refinery–asbestos–mesothelioma is upheld in our study by some observations of the Italian cohort: first, job analysis shows that all five mesotheliomas were observed among maintenance workers; second, length of employment was always longer than 10 years (range 11–33); third, the induction–latency analysis revealed a time, since first exposure, greater than or equal to 20 years for four cases out of five. These elements taken together support our decision to use mesothelioma as a sentinel event of asbestos exposure.

Possible Underestimation of the True Risk of Lung Cancer in Refineries

As already mentioned, mortality from lung tumor has often been estimated in the overall group of workers, where exposed and unexposed (to asbestos) populations—which consequently are at different levels of risk of lung tumor—are combined or not completely separated: in this way, it is very difficult to detect, when present, an increased risk of lung tumors (dilution effect). The misclassification of asbestos exposure engenders an underestimation of the true risk for asbestos-related tumors. This bias, which is not strong enough to eliminate the very high risks for mesotheliomas, is sufficient to mask the usually less elevated risks for lung tumor.

In other studies, high but not statistically increased RRs for lung cancer were interpreted as being due to chance, while slightly elevated RRs were attributed to exposure to hydrocarbons. Simultaneously, the long induction–latency period for both lung tumors and mesotheliomas hampers attempts to determine the association of the disease with the etiologic factor.

Proportion of Tobacco Smokers in the Referent Population

The high rates of lung cancer observed among maintenance workers do not seem to be dependent on cigarette smoking. In fact, oil refinery workers in general, and blue collar workers in particular, are subject to rigid smoking restrictions dictated by safety reasons, such as high risk of fires and explosions. Epidemiological studies, health surveys and questionnaires to workers and next-of-kin have confirmed that cigarette smoking is not a particularly diffuse habit among oil refinery workers [Van Peenen et al., 1984; Levin et al., 1990] compared to the general population that, as a consequence, does not appear to constitute the best reference.

Our study shows SMRs from smoking related disorders, i.e., cardiovascular and respiratory diseases and bladder cancer, among maintenance workers that are lower than or similar to those expected in the general population (Table III); in particular, the mortality from cardiovascular diseases is lower compared to white and blue collar workers. This statistically significant reduction seemingly confirms both that healthy worker effect exists and that the prohibition of smoking imposed for safety reasons is essentially respected.

Finally, the presence of a low percentage of smokers has most likely prevented the full view of the known synergistic (multiplicative) effects between smoking and inhalation of asbestos on lung tumor mortality [Hammond et al., 1979].

Choosing the Internal Referent Population

In a *nested case–control* study conducted in oil refineries, blue collar workers provide a good comparison group for maintenance workers and they are used in the hope of controlling for other risk factors and unidentified confounding factors for lung cancer (i.e., tobacco smoking). Nevertheless, it is likely that blue collar workers were exposed to hydrocarbons and other synergistic occupational carcinogens, including asbestos, having lung as *common* target organ.

Conversely, in *a cohort study*, to detect the attributable risk due to relevant levels of occupational carcinogens, including asbestos exposure, we prefer to compare the group of maintenance workers with white collar workers, clearly an unexposed group. Consequently, we might provide an estimate of the real attributable risk taking into account the overall contribution of asbestos, other occupational carcinogens, smoking habit, and the role of the healthy worker effect given that only white collar workers usually are hired not primarily on the basis of their initial good health condition.

CONCLUSIONS

As often observed in cohort studies, our study is somewhat limited, particularly by the lack of direct information on hygienic data and smoking habits among oil workers. Despite these limitations, our results highlight that:

1. In the two refineries studied, the frequency of mesotheliomas attributable to asbestos exposure among maintenance workers was very high;
2. After internal comparison, the percentage of lung tumors attributable to asbestos (AR) among maintenance workers ranged between 42% and 49%, (Ontario and Liguria figures), respectively;
3. The ratio between the number of asbestos-related lung tumor cases and the number of mesothelioma cases observed ranged from 1.6 to 2.1 (Liguria and Ontario, respectively). This observation is in strong agreement with provisions calculated by the Health and Safety Executive [HSE, 1993], and by Nicholson et al. [1982], which reported 2 and 2.6 cases, respectively. In terms of public health, this ratio could be useful to estimate the real magnitude of asbestos-related diseases, including respiratory and gastrointestinal tumors, when only mesothelioma cases are known (for example, in areas covered by mesothelioma registries);
4. In both studies considered, the causal relationship [Bradford Hill, 1965] between lung tumor and asbestos exposure in refineries is supported by strength of the association, coherence, biological plausibility, temporal criteria, dose–response relationship, and consistency of association.

Finally, this investigation underlines the need to identify both exposed to asbestos and internal referent populations exposed to comparable—other than asbestos—level of carcinogens (tobacco and hydrocarbons, for instance) having the same target tissue (i.e., lung). Our results also suggest the importance of eliminating exposure to asbestos where the use of these carcinogenic fibers is still permitted.

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