ONLINE APPENDIX

Carcinoma of the pharynx and tonsils in an occupational cohort of asphalt workers

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Supplemental Material, part 1

1. Company description

Information on the two factories was gleaned from records of the Local Health Authority (public Occupational Health Unit) interventions. An academic Occupational and Environmental Health specialization thesis (1989–90) dedicated to the plant provides detailed information concerning the production cycle, manufacturing processes and materials used, duties/movements of each group of workers and the layout of the newer factory.

The company under investigation started in 1964, based in a factory situated in the Province of Bologna (Italy) producing industrial waterproof varnishes and bituminous emulsions. Production of asphalt roofing rolls for the building sector began in 1968 and rapidly became the company's main activity, remaining so until its closure in November 1997. After the original factory burned down in June 1979, a new plant was built about 1 km away, outside the built-up area.

Until 1979, asbestos was used in the production of both the asbestos rolls and the bituminous emulsions. Asbestos was officially changed to calcium carbonate in 1979, following pressure from the Local Health Authority (public Occupational Health Unit, *Servizio di Medicina Preventiva e Igiene del Lavoro*) and an injunction issued by the local mayor.

The subcontracted warehouse workers unwrapped the asbestos and loaded it onto a conveyor belt located inside the production line sectors, where they also helped out with various tasks as required.

In both factories, manufacture of asphalt roofing rolls involved continuous open-space preparation and frequent pouring of a mixture of boiling (170–180°C) bitumen (apparently the only binder used), polypropylene, and asbestos (until 1979) or calcium carbonate (from 1980) so as to produce a paste. The mixture was then pumped into soaking chambers containing fiberglass sheets and/or polyester felts. After cooling, the resulting product was rolled out into the desired thickness. Apart from the change of asbestos to calcium carbonate, the production process itself remained largely the same in the old and new factories. No handling precaution was taken for the asbestos, which was

reportedly even sprinkled on the floor of the production line department as an alternative to sawdust. Workers frequently smoked on factory premises. Each of the production-line workers ('boilermen', 'pasters', and 'rollers') performed a single task. The original factory had no extractor fan until 1977–78; health inspectors reported dense fumes.

Both plants also had a sector dedicated to production of emulsions, mastics and varnishes, as well as a conventional workshop sector.

2. Available exposure data

Environmental monitoring was carried out by the Local Health Authority (public Occupational Health Unit, *Servizio di Medicina Preventiva e Igiene del Lavoro*) between 1977 and 1985.

Old factory

In 1977, measurements were performed to evaluate the environmental concentrations of volatile organic compounds (VOCs). Passive samplers were placed for 6 hours in three key-positions along the production line at a height of 150 cm. Samplers were positioned close to the workstations to evaluate the exposure levels of production operators. The values obtained were as follows: 60 mg/m^3 hexane; 60 mg/m^3 heptane; 130 mg/m^3 toluene.

Between 1977 and 1979 samples were taken outside the factory, presumably in the proximity of the chimneys.

- 1977: hexane, 834 mg/m^3; heptane, 572 mg/m^3.
- 1979: three consecutive sets of measurements recorded values, ranging as follows (lowest–highest measured value): hexane, 7800–11,660 mg/m^3; benzene, 11,140–16,700 mg/m^3; toluene, 11,270–16,850 mg/m^3; xylene, 13,960–20,900 mg/m^3.

In 1977, samples of particulate matter taken in workstations during loading of the binding agent revealed asbestos concentrations as high as 2.6 $fibre/cm^3$ when the bitumen containers were open and, and 0.3 $fibre/cm^3$ when they were closed. In the same year, asbestos concentrations were also

measured at the exit of the stock warehouse (0.4 fiber/cm^3), at the beginning of the drive belt loading system (1.6 fiber/cm^3), and in the proximity of the control panel 25 minutes after loading (0.2 fiber/cm^3). X- ray diffraction of a sample labeled “company asbestos” (provenance not specified) revealed the following mineralogical components: chrysotile (predominant), calcite, hematite, magnetite. However, it is not possible to exclude presence of other types of asbestos at lower concentrations: even though the asbestos used by the company was composed mainly of chrysotile, deposits of chrysotile can be contaminated by amphibolic fibers, especially of the tremolite series,[1] contributing to the hazardous potential of occupational exposure.

New factory

In 1983, phase-contrast and polarized-light microscopy examination of a sample of industrial talcum powder extracted from the soaking chambers revealed a “rather high number” of asbestiform fibrils of about 1 μm thick of very variable length (a finding not necessarily attributable to in-factory contamination).[2] Similar examinations conducted in 1988 and 1990 did not reveal evidence of asbestos.

In 1985, concentrations of environmental pollutants (VOCs/PAH) were measured on samples collected from the fume extraction system situated above the bitumen containers. The environmental monitoring of an air sample through active carbon filters showed presence of benzo-alpha-anthracene (1.9 μg/m^3) and the following values for solvents: hexane, 228.3 mg/m^3; heptane, 17.8 mg/m^3.

3. Health surveillance data

In 1977, the Local Health Authority (public Occupational Health Unit, *Servizio di Medicina Preventiva e Igiene del Lavoro*) first conducted health monitoring of workers assigned to the production sectors (those most exposed to the bitumen and asbestos fumes), including otorhinolaryngologic (ORL) and oncologic examinations. The oncologic tests carried out on the

most exposed workers led to identification of three cases of carcinoma of the pharynx. Subsequently, all 60 workers assigned to the production that year and other 34 long-term workers employed by the company were submitted to extensive medical check-ups. Based on a preliminary evaluation of risk, the following assessments were done to identify signs of respiratory system disease: cytological examination of the sputum for asbestos fibers; respiratory function; chest X-rays; blood and urine tests; ORL examination. In 1978, the final report documented the following chronic inflammatory pathologies of the airways: pharyngitis in 55/94 (59%) workers; tonsillitis in 28 (30%); laryngitis in 13 (14%); rhinitis in 11 (12%). The workers assigned to the fusion vats were reportedly the most affected. Fifty workers considered to be “exposed” were each submitted to two series of X-ray examinations in two separate clinics, which reported lesions compatible with asbestosis in 6/50 (12%) and 11/50 (22%) workers, respectively.

In 1981, further checks were carried out on 91 workers: ORL examination revealed inflammatory alterations of the pharyngeal and laryngeal mucosa in 47 (52%) workers. Cytological examination of the hypopharynx of 74 workers showed signs of metaplasia of the pharyngeal mucosa in 4 (5%).

References

1. McDonald JC and McDonald AD. 1997. Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg 41:699-705.

2. Paoletti L, Caiazza S, Donelli G, Pocchiari F. 1984. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. Regul Toxicol Pharmacol 4:222-235.

Supplemental Material, Part 2

1. Description of the workers affected by pharyngeal carcinoma

eTable 1 provides descriptive information on the five subjects of the cluster of carcinoma of the pharynx/tonsils: they were all male blue-collar workers of the “old” factory production line.

2. Cause-specific SMR for the entire cohort

eTable 2 reports cause-specific SMR for the entire cohort. Mortality from carcinoma of the lip, oral cavity and pharynx (ICD-9 140–149) was 10-fold higher than expected. We also recorded ~3-fold excess mortality rate for gastric cancer, but no evidence of increased mortality from lung cancer or cardiovascular diseases, at least during the follow-up period.

3. Mantel-Haenszel estimates of rate ratios (RR), adjusted for latency

We calculated the Mantel-Haenszel estimates of the RR for all causes and all cancers (adjusted for latency), comparing categories of workers with different occupational exposures within the entire cohort, taking the least exposed as the reference category.

It was possible to highlight a different excess of risk between categories of workers in relation to different levels of exposure (see eTable 3). As expected, production line blue-collar workers had higher death rates from all causes and all cancers in comparison with white-collar workers. It should also be noted that, risk for death from all causes and all cancers in production line blue-collar workers were higher in comparison with non-production line blue-collar workers (see eTable 3). The excess risks experienced by production line workers cannot readily be attributed to socioeconomic status alone. It seems plausible that the health status of production line blue-collar workers may have been affected by workplace conditions such as the particular mixture of toxic substances that was present until 1979. Of note, number considerations precluded separate calculation of Mantel-Haenszel estimates for each subcohort.

eTable 4 reports SMR for selected diseases of interest stratified by latency (in terms of years between first exposure and death). Broadly similar trends in mortality were apparent for both carcinoma of the lip, oral cavity and pharynx, and for gastric cancer, characterized by large excesses both at 5–10 years and beyond 30 years of exposure.

eTable 1. Characteristics of the workers (all men) affected by pharyngeal carcinoma.

	Pharyngeal cancer patients				
	No. 1	No. 2	No. 3	No. 4	No. 5
Job task	Subcontracted warehouse worker	Paster	Smelter	Paster	Smelter
Period of continuous employment	1967–1987	1972–1981	1972–1978	1978–1980	1972–1982
Working years	20.3	8.7	6.1	1.7	9.5
before June 1979	12.0	7.0	6.1	0.6	6.6
after June 1979	8.3	1.7	–	1.1	2.9
Year (age) of diagnosis	1977 (50 y)	1978 (48 y)	1978 (52 y)	n.a.	n.a.
Year (age) of death	2000 (73 y)	1996 (66 y)	1986 (60 y)	1985 (48 y)	1982 (53 y)
Localization of tumor	palatine tonsil	palatine tonsil	rhino-pharyngeal	pharynx	pharynx
Smoking status	n.a.	smoker	n.a.	n.a.	n.a.

Abbreviation: n.a., not available.

eTable 2. Mortality by cause of death in the entire cohort (Reference population, Regione Emilia-Romagna).

Cause of death	ICD-9 code	Obs	Exp	SMR	95% CI
All causes	001–999	40	46.3	0.9	0.6–1.2
All cancers	140–208	25	17.6	1.4	1.0–2.1
Lip, oral cavity and pharynx	140–149	5	0.5	10.0	4.2–24.1
Digestive organs and peritoneum	150–159	9	6.0	1.5	0.8–2.9
Stomach	151	5	1.8	2.8	1.1–6.6
Colon	153	1	1.1	0.9	0.1–6.3
Rectum, rectosigmoid junction, and anus	154	1	0.5	2.0	0.3–14.0
Liver and intrahepatic bile ducts	155	2	0.9	2.3	0.6–9.2
Respiratory and intrathoracic organs	160–165	5	6.2	0.8	0.3–1.9
Trachea, bronchus, and lung	162	5	5.6	0.9	0.4–2.1
Other skin	173	1	0.05	20.8	2.9–147.9
Genitourinary organs	179–189	2	1.7	1.2	0.3–4.7
Prostate	185	1	0.6	1.8	0.3–12.9
Kidney and other urinary organs	189	1	0.5	2.1	0.3–15.2
Eye, brain, and other parts of nervous system	190–192	1	0.5	1.8	0.3–13.0
Brain	191	1	0.5	2.0	0.3-14.0
Lymphatic and hematopoietic tissue	200–208	2	1.4	1.4	0.4–5.7
Leukemia	204–208	2	0.6	3.6	0.9–14.3
Myeloid leukemia	205	1	0.3	3.6	0.5–25.4
Benign neoplasm of brain and other parts of nervous system	225	1	0.025	40.0	5.6-283.7
Cerebral meninges	225.2	1	0.018	54.8	7.7-389.2
Disorders involving the immune mechanism	279	1	0.7	1.5	0.2-10.8
Circulatory system diseases	390–459	7	14.3	0.5	0.2–1.0
Ischemic heart disease	410–414	5	7.0	0.7	0.3–1.7
Acute myocardial infarction	410	5	4.8	1.0	0.4–2.5
Cerebrovascular diseases	430–438	2	3.0	0.7	0.2–2.7

eTable 2. (cont.). Mortality by cause of death in the entire cohort (Reference population, Regione Emilia-Romagna).

Cause of death	ICD-9 code	Obs	Exp	SMR	95%CI
Respiratory system diseases	460–519	1	1.7	0.6	0.1–4.1
Digestive system diseases	520–579	1	2.6	0.4	0.1–2.7
Chronic liver disease and cirrhosis	571	1	1.7	0.6	0.1–4.1
Unknown causes	799	1	0.2	4.5	0.6–32.3
External causes of injury and poisoning	E800–E999	3	5.6	0.5	0.2–1.7

Abbreviations. ICD-9: International Classification of Diseases, 9th revision; Obs: observed; Exp: expected; SMR: standardized mortality ratio; 95% CI: 95% confidence interval.

eTable 3. Mantel-Haenszel estimates of rate ratios (RR), adjusted for latency, for all cause mortality and all cancer mortality among categories of workers with different occupational exposure characteristics, taking the least exposed as the reference category (Reference population, Regione Emilia-Romagna).

	RR (95% CI)
All causes	
Non-production line blue-collar workers vs white-collar workers	1.3 (0.4–4.6)
Blue-collar workers exposed to the production line vs non-production line blue-collar workers	2.0 (0.9–4.6)
Blue-collar workers exposed to the production line vs white-collar workers	2.8 (1.0–7.9)
All cancers	
Non-production line blue-collar workers vs white-collar workers	0.8 (0.1–12.0)
Blue-collar workers exposed to the production line vs non-production line blue-collar workers	11.7 (1.6–87.6)
Blue-collar workers exposed to the production line vs white-collar workers	8.8 (1.2–65.6)

Abbreviation: 95% CI, 95% confidence interval.

eTable 4. Cause-specific SMR (with 95%CI) according to latency in terms of years between first exposure and death (Reference population, Regione Emilia-Romagna).

Latency (years)	All causes SMR (95% CI) [Obs; Exp]	All cancers SMR (95% CI) [Obs; Exp]	Lip, oral cavity and pharynx cancer SMR (95% CI) [Obs; Exp]	Stomach cancer SMR (95% CI) [Obs; Exp]	Trachea, bronchus, and lung cancer SMR (95% CI) [Obs; Exp]	Circulatory system diseases SMR (95% CI) [Obs; Exp]
0-5	- [0; 4.2]	- [0; 1.1]	- [0; 0.03]	- [0; 0.15]	- [0; 0.3]	- [0; 1.0]
5-10	1.6 (0.8–3.0) [9; 5.7]	2.8 (1.1–6.6) [5; 1.8]	35.7 (8.9–142.7) [2; 0.056]	4.4 (0.6–31.5) [1; 0.23]	- [0; 0.5]	0.6 (0.1–4.4) [1; 1.6]
10-20	0.6 (0.3–1.1) [10; 17.0]	1.3 (0.6–2.5) [8; 6.4]	5.2 (0.7–37.1) [1; 0.19]	2.9 (0.7–11.6) [2; 0.69]	1.0 (0.2–3.9) [2; 2.0]	- [0; 5.4]
20-30	1.1 (0.7–1.7) [18; 16.8]	1.3 (0.7–2.4) [9; 7.1]	5.2 (0.7–36.6) [1; 0.19]	1.5 (0.2–10.9) [1; 0.65]	0.8 (0.2–3.4) [2; 2.4]	1.1 (0.5–2.4) [6; 5.5]
>30	1.2 (0.4–3.7) [3; 2.5]	2.6 (0.8–7.9) [3; 1.2]	38.1 (5.4–270.6) [1; 0.026]	9.8 (1.4–69.7) [1; 0.10]	2.5 (0.4–17.7) [1; 0.4]	- [0; 0.8]

Abbreviations. SMR: standardized mortality ratio; 95% CI: 95% confidence interval; Obs: observed; Exp: expected.