Ann Ist Super Sanità 2022 | Vol. 58, No. 3: 197-203
DOI: 10.4415/ANN_22_03_09

Proportionate mortality among workers exposed to hardwood dust in Italy

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Abstract
Aims. The main aim of this study is to estimate the impact on workers' health caused by hardwood dust exposure in selected industrial sectors in Italy.
Methods. Proportionate mortality ratios (PMR) by cancer site were calculated by linking the information on occupational exposure to carcinogens from the Italian national registry (SIREP, 1996-2018) to the national mortality archives (ISTAT, 2005-2018), assuming a Poisson distribution of the data.
Results. An elevated proportion of deaths from sino-nasal cancer was found in male exposed workers (PMR=4.25, CI 95%=1.37-13.23). Increased proportions of deaths were also found from stomach cancer in both genders (PMR=3.14, CI 95%=1.41-7.00 women; PMR=1.64, CI 95%=1.22-2.19 men).
Conclusions. Although hardwood dust is a known human carcinogen, there are still many high-risk occupational exposure settings. Epidemiological surveillance and continuous monitoring of workers is highly recommended in order to ensure compliance with regulatory obligations and limit the burden of associated mortality causes.

Key words
- occupational exposure
- carcinogenic risk
- proportionate mortality ratios
- surveillance systems
- nasal cancer

INTRODUCTION

Wood dust is generally classified into two categories: dust from "softwood" which is a wood cheap to produce and easy to work, such as pine; and dust from "hardwood" which is hard heavy wood mostly from deciduous trees as oak, beech, birch, mahogany and others. The International Agency for Research on Cancer (IARC) provides an evaluation of carcinogenicity for wood dust as a whole (both soft and hard), while the European Union (EU) has classified only hardwood dust as a carcinogen (directive no. 1999/38/EC) [1]. The association between sino-nasal cancer and exposure to wood dust is well-known, particularly for adenocarcinoma and exposure to hardwood dust [1]. Sino-nasal cancer is a relatively rare tumour worldwide, with a ratio of mortality rate to incidence rate varying from 0.21 to 0.48 in men and 0.12 to 0.69 in women [2]. Based on literature data, however, other occupational cancers may contribute to the disease burden in workers exposed to wood dust [3]. In particular, many studies have investigated the association of wood dust (both soft and hard) exposure and lung cancer risk, suggesting a possible role for the exposure to hardwood dust [4-6]. Another study observed an effect on laryngeal cancer risk for exposure to wood dust, particularly strong for hardwood (OR=2.6, 95% 1.3-5.2) [7]. Workers exposed in Italy to wood dust (both soft and hard) were first estimated by the WoodEx project at about 351,000 in the period 2000-2003 [8]. Subsequently, on the basis of the Italian Information System on Occupational Exposure to Carcinogens (SIREP) at 31 December 2011, and only for some specific sectors, workers potentially exposed to hardwood dust in Italy were estimated at around 117,000 [9].

The present study intends to estimate the possible impact of hardwood dust exposure on the health of workers by studying the proportionate mortality in a national registry-based occupational cohort. The analysis was only possible for hardwood dust as the notification of exposed workers is mandatory merely for this type of woods. Indeed, the Italian law specifically classifies hardwood dust as a carcinogen according to EU directive no. 1999/38/EC.

METHODS

Data on exposed workers were collected from the occupational exposure databank (SIREP), a relational database gathering information on exposures to carcinogens in the workplaces. The SIREP system has been fully described elsewhere [10]. In brief, according to the Italian regulation on health surveillance at workplace (Italian Law Decree n. 81/2008), data on exposures to occupational carcinogens have to be collected by employers and regularly sent (every three years) to the SIREP system. Employers are required to report the carcinogens used

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or produced during industrial process, data on exposed employees and the exposure levels. The workers reported to the SIREP system in the period from 1996 to 2018 as exposed to hardwood dust were selected. The underlying cause of death of exposed workers was retrieved from the mortality archives of the Italian National Institute for Statistics (ISTAT) for the period 2005-2018 [11]. The number of deaths retrieved was 8,345,104, of which 52% for women. The record linkage was performed using an anonymous worker identification code. Approval from an Ethics Committee was not required as the record linkage was requested by a public institution using an anonymized code. Gender specific proportionate mortality ratios (PMRs), standardized by 5-year age ("20-24", "25-29", …, "85 and over") and 3-year calendar period (except for the last period of only 2-years), were evaluated in order to estimate the relative risk of death from a specific cause among workers exposed to hardwood dust. The 10th International Classification of Diseases (ICD) codes were used to classify the cause of death, and proportional mortality of the whole Italian population was taken as the standard. A Poisson distribution of the data was assumed for calculating the PMRs and 95% confidence intervals (CIs). Sub-analyses by industry, job profession, and cumulative exposure were performed, and the results for the most significant cancer sites found in the main analysis *(see Table 1)* were reported in *Figures 1, 2* and *Table 2* respectively. Occupational groups were coded using the international standard classification of occupations (ISCO-88) at the

Table 1
Proportionate mortality ratios (PMRs) for hardwood dust exposed workers by gender and cause of death (2005-2018)

Gender	Cause of death (ICD X code)	Observed*	Expected**	PMR	95%	CI
Women	All causes of death	78	78.0	1.00	-	-
	Malignant neoplasm (C00-C97)	56	45.5	1.23	0.95	1.60
	Malignant neoplasm of stomach (C16)	6	1.9	3.14†	1.41	7.00
	Malignant neoplasm of colon (C18)	4	3.0	1.33	0.50	3.55
	Malignant neoplasm of bronchus and lung (C34)	16	6.6	2.42†	1.48	3.95
	Malignant neoplasm of breast (C50)	4	11.6	0.35	0.13	0.92
	Malignant neoplasm of ovary (C56)	3	2.96	1.01	0.32	3.14
	Diseases of the respiratory diseases (J00-J99)	3	2.1	1.44	0.46	4.46
Men	All causes of death	1,157	1,157.0	1.00	-	-
	Infectious and parasitic diseases (A00-B99)	23	36.5	0.63	0.42	0.95
	Malignant neoplasm (C00-C97)	545	462.8	1.18†	1.08	1.28
	Malignant neoplasm of nasopharynx (C11)	3	1.73	1.73	0.56	5.39
	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx (C14)	6	1.9	3.24†	1.45	7.22
	Malignant neoplasm of oesophagus (C15)	14	9.6	1.46	0.86	2.47
	Malignant neoplasm of stomach (C16)	45	27.5	1.64†	1.22	2.19
	Malignant neoplasm of colon (C18)	35	33.9	1.03	0.74	1.44
	Malignant neoplasm of rectum (C20)	7	9.3	0.75	0.36	1.58
	Malignant neoplasm of liver and intrahepatic bile ducts (C22)	43	35.3	1.22	0.90	1.64
	Malignant neoplasm of other and unspecified parts of biliary tract (C24)	10	4.7	2.13†	1.14	3.96
	Malignant neoplasm of pancreas (C25)	35	32.5	1.08	0.77	1.50
	Malignant neoplasm of other and ill-defined digestive organs (C26)	12	4.7	2.55†	1.45	4.50
	Malignant neoplasm of nasal cavity and of accessory sinuses (C30-C31)	3	0.7	4.25†	1.37	13.23
	Malignant neoplasm of larynx (C32)	4	8.5	0.47	0.18	1.26
	Malignant neoplasm of bronchus and lung (C34)	129	121.6	1.06	0.89	1.26
	Malignant melanoma of skin (C43)	13	9.7	1.34	0.78	2.31
	Mesothelioma (C45)	10	5.4	1.86†	1.00	3.47
	Malignant neoplasm of other connective and soft tissue (C49)	10	3.8	2.64†	1.42	4.92
	Malignant neoplasm of prostate (C61)	25	12.4	2.01†	1.36	2.98
	Malignant neoplasm of kidney, except renal pelvis (C64)	15	12.6	1.19	0.72	1.97
	Malignant neoplasm of bladder (C67)	13	12.6	1.03	0.60	1.77

Continues

Table 1
Continued

Malignant neoplasm of other and unspecified urinary organs (C68)	3	2.1	1.43	0.46	4.43
Malignant neoplasm of brain (C71)	26	22.0	1.18	0.81	1.74
Malignant neoplasm, without specification of site (C80)	17	11.8	1.44	0.89	2.32
Other and unspecified types of non-Hodgkin lymphoma (C85)	13	11.4	1.14	0.66	1.96
Multiple myeloma and malignant plasma cell neoplasms (C90)	7	7.0	0.99	0.47	2.09
Lymphoid leukaemia (C91)	4	4.4	0.90	0.34	2.41
Myeloid leukaemia (C92)	7	9.1	0.77	0.37	1.62
Malignant neoplasms of independent (primary) multiple sites (C97)	4	3.7	1.07	0.40	2.86
Neoplasms of uncertain or unknown behaviour (D37-D48)	18	12.6	1.43	0.90	2.27
Diabetes mellitus (E10-E14)	24	29.2	0.82	0.55	1.23
Obesity and other hyperalimentation (E65-E68)	6	5.3	1.12	0.50	2.50
Mental and behavioural disorders due to psychoactive substance use (F10-F19)	6	5.6	1.07	0.48	2.39
Diseases of the nervous system (G00-G99)	26	33.5	0.78	0.53	1.14
Hypertensive diseases (I10-I15)	13	21.2	0.61	0.36	1.06
Ischaemic heart diseases (I20-I25)	107	116.9	0.92	0.76	1.11
Acute myocardial infarction (I21)	84	70.1	1.20	0.97	1.48
Chronic ischaemic heart disease (I25)	20	40.4	0.49	0.32	0.77
Other forms of hearth diseases (I30-I51)	50	61.5	0.81	0.62	1.07
Cerebrovascular diseases (I60-I69)	31	44.4	0.70	0.49	0.99
Diseases of arteries, veins and lymph nodes (I70-I89)	12	13.9	0.86	0.49	1.52
Diseases of the respiratory system (J00-J99)	26	40.6	0.64	0.44	0.94
Chronic liver diseases (K70-K74)	34	40.3	0.84	0.60	1.18
Alcoholic liver disease (K70)	5	10.9	0.46	0.19	1.10
Toxic liver disease (K71)	9	4.2	2.13†	1.11	4.10
Fibrosis and cirrhosis of liver (K74)	19	23.3	0.82	0.52	1.28
Ill-defined and unknown causes of mortality (R95-R99)	17	19.6	0.87	0.54	1.40
All external causes of death (S-T)	164	136.6	1.20†	1.03	1.40

Only causes with more than two cases are shown; *Observed deaths in the cohort of SIREP exposed workers; **Expected deaths in the cohort of SIREP exposed workers based on Italian general population deaths; †=p<0.05.

lowest group level (four-digit code), and economic activity sectors were classified using the international statistical classification of economic activities (NACE rev. 1) at the division level (two-digit code). Person-years at risk were assessed from the year of first exposure to the date of death. The year of first recorded exposure was to 1947, the last was 2016. Cumulative exposure, in milligrams per cubic meter-year (mg/m^3-years), was calculated for each cohort member having measurement data. Categorical cumulative exposure was modelled on the basis of the quartile distribution (≤4.5, 4.5 to ≤25.6, >25.6 mg/m^3-years). Co-exposures of selected workers were ascertained, and mean latency for the major cancer sites was calculated. The data were collected routinely as an institutional activity and were analysed anonymously using R software v.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The cohort of workers exposed to hardwood dust was selected from the SIREP database. The subjects linked to the ISTAT mortality archives were 77,311, of which 68,578 men and 8,733 women. A total of 1,235 deaths among exposed workers (1,157 men and 78 women) were identified in the period 2005-2018. Even if the ISTAT mortality archive covers the whole Italian population, uncertainty persists on the vital status of the unmatched subjects due to possible errors in the anonymized code linking the two databases. The mean age at death of the study population was 56.3 years with a standard deviation of 12.0, 54.1 (9.4) in women and 56.4 (12.1) in men. Cohort members having measurement data were 1,100, 94% of whom men. There was an elevated proportion of bronchus and lung cancer deaths in the group of female exposed workers (PMR=2.42, CI 95%=1.48-3.95) compared to the general population. The highest increase in PMR was found for malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx in men (PMR=3.24, CI 95%=1.45-7.22). As expected, a significant excess mortality from malignant neoplasm of the nasal cavity and accessory sinuses was found (four-fold greater than in the gen-

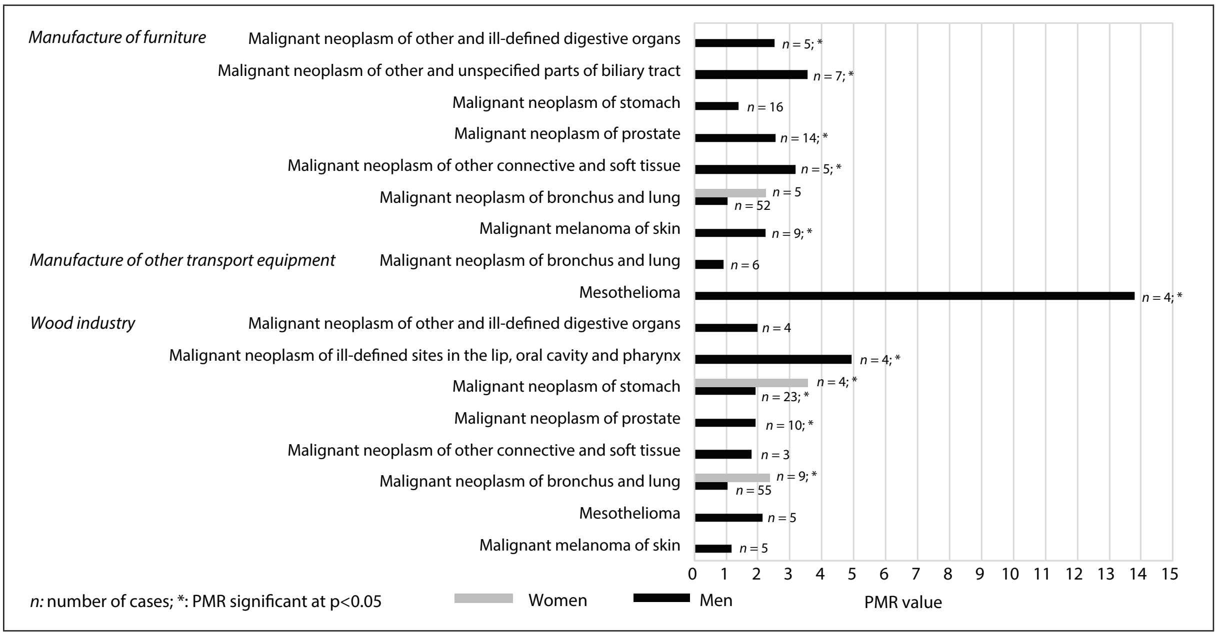

Figure 1
Proportionate mortality ratios (PMRs) for hardwood dust exposed workers by activity sector and gender at selected cancer sites (2005-2018).

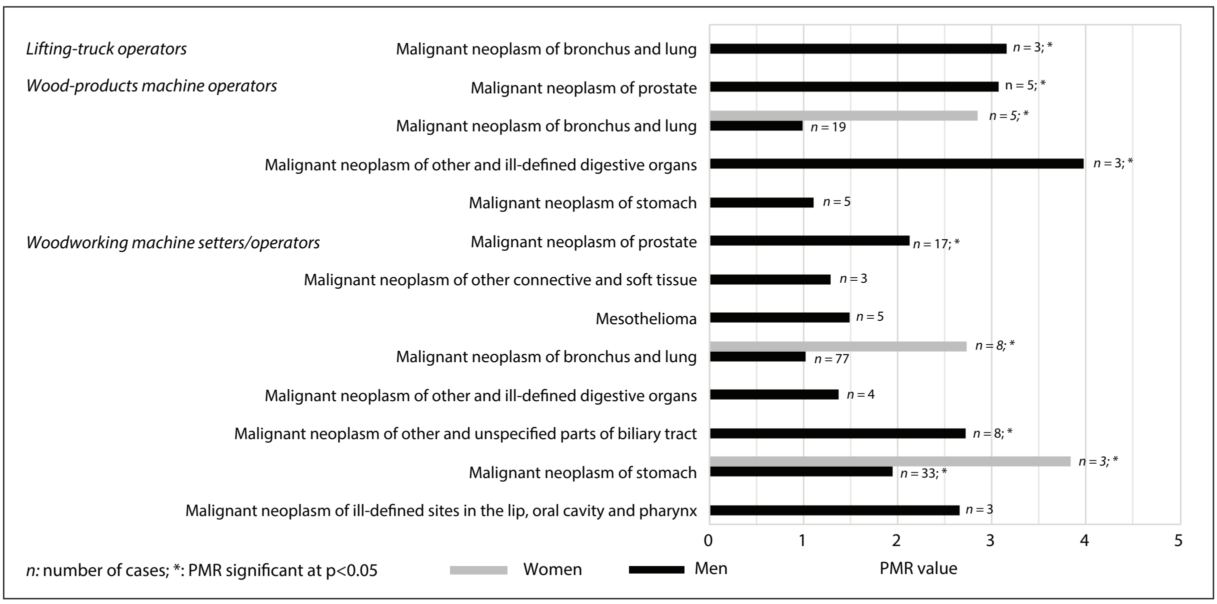

Figure 2
Proportionate mortality ratios (PMRs) for hardwood dust exposed workers by occupational group and gender at selected cancer sites (2005-2018).

eral male population). Among malignant neoplasms, increased proportions of deaths were also found from stomach cancer (in both genders), malignant neoplasm of other and unspecified parts of biliary tract, malignant neoplasm of other and ill-defined digestive organs, and malignant neoplasm of other connective and soft tissue. *Table 1* shows the PMRs for causes of death with more than 2 cases. The significant excess of lung cancer mortality in women was also confirmed in the sub-analysis by economic activity for the wood industry sector (n=9, PMR=2.35, CI 95%=1.22-4.52), as well as the increased risk for gastric cancer in both genders (n=4, PMR=3.55, CI 95%=1.33-9.47 in women; n=23, PMR=1.93, CI 95%=1.28-2.91 in men). An increased mortality risk was detected in the manufacture of furniture for malignant neoplasms of other and unspecified parts of biliary tract (n=7, PMR=3.55, CI 95%=1.69-7.46 in men) and of connective tissue and other soft tissues (n=5, PMR=3.19, CI 95%=1.33-7.67 in men), whereas an excess for mesothelioma was found in the manufacture of other transport equipment in men (n=4, PMR=13.80, CI 95%=5.17-36.77). *Figure 1* displays the

Table 2
Proportionate mortality ratios (PMRs) for hardwood dust exposed workers by gender, cause of death and cumulative exposure at selected cancer sites (2005-2018)

Gender	Cause of death (ICD X code)	Cumulative exposure (mg/m³-years)	PMR	95%	CI
Women	Malignant neoplasm of bronchus and lung (C34)	≤4.5	0.59	0.08	4.17
		4.5-25.6	3.86†	2.08	7.18
		>25.6	1.31	0.33	5.23
Men	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx (C14)	≤4.5	4.93†	1.23	19.7
		4.5-25.6	2.39	0.60	9.55
		>25.6	2.40	0.34	17.1
	Malignant neoplasm of stomach (C16)	≤4.5	1.71	0.92	3.17
		4.5-25.6	1.55	0.99	2.42
		>25.6	1.72	0.95	3.11
	Malignant neoplasm of other and unspecified parts of biliary tract (C24)	≤4.5	2.09	0.52	8.36
		4.5-25.6	1.94	0.73	5.17
		>25.6	2.57	0.83	7.96
	Malignant neoplasm of other and ill-defined digestive organs (C26)	≤4.5	1.02	0.14	7.22
		4.5-25.6	2.39	0.99	5.74
		>25.6	1.82	0.45	7.27
	Malignant neoplasm of bronchus and lung (C34)	≤4.5	1.09	0.75	1.59
		4.5-25.6	0.86	0.64	1.15
		>25.6	1.32	0.96	1.80
	Malignant melanoma of skin (C43)	≤4.5	0.89	0.22	3.54
		4.5-25.6	1.57	0.75	3.29
		>25.6	1.49	0.48	4.63
	Mesothelioma (C45)	≤4.5	0.93	0.13	6.61
		4.5-25.6	2.14	0.89	5.14
		>25.6	2.21	0.71	6.84
	Malignant neoplasm of other connective and soft tissue (C49)	≤4.5	2.24	0.56	8.95
		4.5-25.6	2.30	0.86	6.14
		>25.6	5.30†	1.99	14.1
	Malignant neoplasm of prostate (C61)	≤4.5	1.72	0.65	4.59
		4.5-25.6	2.10†	1.17	3.80
		>25.6	2.65†	1.38	5.10

Only causes with complete data by cumulative exposure categories are shown; †=p<0.05.

results for sub-analysis by economic activity and gender at selected cancer sites, for causes of death with more than 2 cases. As regards the sub-analysis by occupational group, male woodworking machine setters/operators resulted to be at excess risk of mortality from sino-nasal cancer (n=2, PMR=5.93, CI 95%=1.48-23.82). An excess risk for gastric cancer was also found in this occupational group in both genders (n=33, PMR=1.94, CI 95%=1.38-7.73 in men; n=3, PMR=3.83, CI 95%=1.24-11.88). *Figure 2* illustrates the results of the sub-analysis by occupational group and gender at selected cancer sites, for causes of death with more than 2 cases. Lastly, cumulative exposure seems not to be associated with any excess of mortality risk across categories and tumours sites, with a few exceptions *(see Table 2)*. Co-exposed workers resulted to be 29 (3 women), of which 12 co-exposed to formaldehyde mainly in the sector of wood industry (80%). The average latency from the date of first exposure was 14 years for lung cancer in females, 12 and 18 years for stomach cancer in females and males respectively, 14 years for sino-nasal cancer in males.

DISCUSSION

In the present study, we performed a proportional mortality analysis of a cohort of workers exposed to hardwood dust in Italy in the period 1996-2018. The methodological approach used, applied on data of an exposure surveillance system compulsory by law, has allowed to detect significant excesses of mortality risk for sino-nasal and other site cancers (e.g., stomach cancer, malignant neoplasm of other connective and soft tissue, etc.). To estimate the relative mortality risk among workers exposed to hardwood dust, PMR analysis was used according to the characteristics of the cohort, as already applied in other similar studies [12-14]. This decision was made as data on the entire population at risk were not known. The healthy worker effect could have influenced the study results and must be taken into account in their interpretation [15]. This effect particularly influences the PMR estimate since, if one or more causes of death are lower (e.g., some cardiovascular diseases as in our study), systematically the other causes, such as tumours, will be higher. These higher values, however, do not always correspond to a real risk. The particular characteristics of our occupational sample, based on a wide number of firms with a heterogeneous workforce, have probably limited the size of this effect on the estimates. A limit of the PMR method is that, in small population studies, the results might be overestimated by up to 20%, depending on the sample size ratio [16]. Although PMR analysis does not provide a true estimate of risk, it has the advantage of being a quick and efficient method of detecting unusual or elevated causes of death. Moreover, the misclassification of the death cause due to inaccurate reports may have been a source of bias in our study. A possible extra-Poisson variation (overdispersion) might have occurred due to the presence of an excessive number of zeros in the data, although the Pearson's chi-square ratio with its degrees of freedom (χ^2/df) in the applied models was mostly low (typically less than 2), suggesting that no statistical intervention was required [17].

Despite the low number of sino-nasal cancer deaths found in the study population, possibly explained by the relatively low fatality of this tumour site (representing less than 1% of all cancer in Italy), the findings confirm an increased risk in workers exposed to hardwood dust [2-3, 18-19]. Meta-analyses of published studies have demonstrated a clear causal association between sino-nasal cancer incidence or mortality and exposure to wood or leather dust, supporting the need of a systematic surveillance system for these diseases in exposed workers cohorts and in the general population [20-21]. Nasopharyngeal cancer, another cancer site specifically addressed by IARC in its Monograph on wood dust, presents a more than expected number of deaths but without reaching statistical significance. Currently, the IARC classification of wood dust carcinogenicity for this type of cancer is characterized by limited evidence [1]. Moreover, in our analysis, an excess of mortality from lung cancer was found, even if limited to female exposed workers. A number of previous studies support a causal relationship between occupational exposure to wood dust and occurrence of lung cancer even after controlling for smoking, suggesting also a differential effect for hardwood and softwood dusts [4]. The worker exposure has been defined on the basis of data from a national exposure surveillance system which are collected and reported under the responsibility of employers, thus minimizing the misclassification of exposure and covering most of the industrial sectors involved. The increased risk of lung cancer in our study was found mainly in the same sectors (wood industry) and occupations (woodworking machine setters/operators) as for sino-nasal and gastric cancers. Evidences of an association between wood dust exposure and gastric cancer are still scarce, but our findings uphold the opportunity of further studies on this issue [22-24]. A clear confounding effect of asbestos exposure is recognizable for mesothelioma mortality in the sector of manufacture of transport equipment [25], whilst the excess mortality for cancers of biliary tract and of connective tissue in workers exposed to hardwood dust, emerged from our analysis in the manufacture of furniture, needs further investigations in order to exclude possible unrecorded co-exposures. In the last decades a decreasing trend in occurrence of sino-nasal cancer was documented, mainly attributed to increased implementation of prevention and protection measures at workplace [2, 26]. Our study shows a still measurable excess risk of cancer among Italian workers exposed to hardwood dust. The lack of a risk trend in the cumulative exposure analysis may be due, on the one hand, to the lack of measurement data (not all cohort members have measurements) and, on the other hand, to the greater number of measurements in more recent years, at which is hypothesized a greater attention by companies to the implementation of more restrictive control measures, to adapt to increasingly stringent regulations. The low mean age at death of the cohort of exposed workers could be due to the young age of the epidemiological surveillance system (fully operational only since 2008 after the enactment of the law that provided for the procedure rules of exposure data transmission), and the relatively short follow-up study period. It is plausible that at the next follow up, the number of subjects linked between SIREP exposure data and ISTAT mortality archives will increase. Despite knowing about the risk of sino-nasal cancer from furniture manufacturing studies, there is still evidence that hardwood dust is not still sufficiently controlled at workplace. Beyond the long latency of this and other cancers possibly related to hardwood dust, it is noteworthy that, based on the still relevant number of preventable tumours estimated, the European Commission has recently lowered from 5 to 2 mg/m^3 (provisionally 3 mg/m^3, until January 17, 2023) the limit value for occupational exposure to this carcinogen. The implementation of the European Directive n. 2017/2398 should further support technical interventions and good working practices, and increase the use of personal protective equipment in the sectors involved, with the real goal of reducing the level of workers' exposure and preventing the onset of cancer.

In conclusion, prevention actions against occupational carcinogens are a priority for safeguarding the health of workers, and the analysis of exposure risks is useful for the implementation of OSH policies, including the development of occupational exposure limit values. In this study, the record linkage between data from an exposure surveillance system and health statistics provided valuable insight into the occupational cancer risk associated with hardwood dust exposure, suggesting greater efforts to ensure compliance with regulatory obligations, even by increasing the effectiveness of labour inspections, and claiming the need for future researches.

Conflict of interest statement

The Authors declare they have no competing financial interests. The Authors declare they have read and approved the paper.

Received on 22 April 2022.
Accepted on 23 June 2022.

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