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Bladder cancer and occupational exposure: estimating the workers potentially at risk in Italy

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Summary. Bladder cancer is one of the most common occupational tumours. The objective of this study is to evaluate the number of workers potentially at risk in Italy. Economic activities entailing bladder cancer risk were selected on the basis of the excesses resulting from studies reporting risk estimates. Firms and the number of workers potentially at risk were retrieved from the National Institute for Occupational Safety and Prevention (ISPESL) database of enterprises. Excluding low level exposures, the number of workers (blue-collars) likely exposed to bladder cancer risk in the industry and services is 366 175 ± 11 096 (248 573 ± 7 533 men, and 117 603 ± 3564 women). The North-Western area of Italy shows the majority of workers potentially at risk (86 625 ± 2625 men, and 27 225 ± 725 women). Quantify the number of exposed workers is the first step for performing analyses on occupational cancer risks. National database of enterprises may be useful in identifying potential risk situations for worker's health.

Key words: bladder cancer, occupational exposure, risk, database.

Riassunto *(Tumore della vescica ed esposizione professionale: una stima dei lavoratori potenzialmente a rischio in Italia)*. Il cancro della vescica è uno tra i più comuni tumori di origine occupazionale. L'obiettivo di questo studio è valutare il numero di lavoratori potenzialmente a rischio in Italia. Le attività economiche associate al rischio di cancro alla vescica sono state selezionate sulla base degli eccessi derivanti da studi che riportano stime di rischio. Le aziende e il numero dei lavoratori potenzialmente a rischio sono stati estratti dalla banca dati delle imprese istituita presso l'Istituto Superiore per la Prevenzione e Sicurezza del Lavoro (ISPESL). Escludendo le esposizioni di basso livello, il numero di lavoratori (operai) potenzialmente a rischio di cancro alla vescica nel settore dell'industria e servizi è di 366 175 ± 11 096 (248 573 ± 7533 uomini e 117 603 ± 3564 donne). Nel nord-ovest d'Italia si concentra il maggior numero di lavoratori potenzialmente a rischio (86 625 ± 2625 uomini e 27 225 ± 725 donne). La quantificazione del numero di lavoratori esposti è il primo passo per l'attuazione di indagini sui rischi di tumore professionale. L'esistenza di una banca dati delle imprese a livello nazionale può essere utile per l'individuazione di situazioni a potenziale rischio per la salute dei lavoratori.

Parole chiave: cancro della vescica, esposizione professionale, rischio, database.

INTRODUCTION

Bladder cancer is one of the most frequent tumours which can be caused by either long or short occupational exposure to carcinogenic agents [1, 2]. An amount of 8.3% of bladder cancer cases with histories of occupational exposure to aromatic amines in dyestuff, rubber and cable manufacture, in the textile, leather, shoemaker, pharmaceutical and print industries, has been estimated in 2004 in Great Britain [3]. In a recent study, the mean European age-standardised 5-year relative survival was estimated to be 72% for this cancer site [4]. This percentage was inversely proportional to the increase of age and was higher in men than in women. In Italy latest estimates show, on yearly average, that there were 70.7 new bladder cancers per 100 000 men and 16.3 per 100 000 women [5]. Epidemiological research on bladder cancer started at the end of the 19th century in Germany, with the discovery of the relation between aniline production and cancer of the bladder in workers of a chemical industry [6]. Other studies report that during the middle of the nineties a relevant percentage of British and American workers developed bladder cancer due to exposure to arylamines, 4-aminobiphenyl, 2-naphthylamine and benzidine [7-9].

Currently, arylamines and other well known carcinogenic aromatic amines are no longer in use in dyes and in the rubber industry [10-12], thus to be considered, in Western countries, not a strong risk factor as in the past [8, 11]. Farmers are one of the

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occupational categories which underwent a decrease in bladder cancer risk exposure [13]. Longshoremen resulted highly exposed to bladder cancer until the reduction of the amount of carbon black and the improvement of packaging of the hazardous substance [14]. The occupations more at risk for bladder cancer have been recently identified in industrial activities related to salt mining, manufacture of carpets, paints, plastics and industrial chemicals, as well as coal gasification, iron and steel founding, aluminium production, the rubber industry, magenta and auramine production, shoe and leather manufacture [15, 16]. The workers categories more at risk are painters, metal, textile and electrical workers, miners, transport operators, and excavating-machine operators, due to their exposure to PAHs, chlorinated solvents, benzene, tar or pitch, and diesel engine exhaust [11, 15, 16]. However, in published studies there is uncertainty about jobs and carcinogens involved in occupational bladder cancer risk.

OBJECTIVE

This study is part of a research project aimed to estimate the number of workers potentially exposed to carcinogenic agents associated with bladder cancer risk in Italy by industrial sector and geographical location. Some preliminary results were published in a short communication [17]. In this paper, data on economic and geographic distribution of workers potentially exposed are described in details. The estimate refers to the lists of industrial activities identified by earlier analyses of pooled data of case-control studies on bladder cancer, and is based on the database of enterprises operating in Italy in 2004, held by the National Institute for Occupational Safety and Prevention (Istituto Superiore per la Prevenzione e Sicurezza del Lavoro, ISPESL).

METHODS

The selection procedure of activity sector codes is fully described elsewhere [17]. Briefly, economic activity codes (according to the NACE Revision 1.1 European classification) have been selected from two distinct studies of pooled data on occupational risks of bladder cancer, one for men and the other for women [15, 16]. The industrial sectors with a statistically significant excess risk derived from the aforementioned studies have been selected. The selected NACE codes were as follows (at the 3-digit level): 14.4, 17.5, 19.3, 20.5, 24.1, 24.2, 24.3, 24.6, 24.7, 25.1, 25.2, 31.4, 34.3, 36.1, 36.6, 37.2 in men; 16.0, 19.3, 20.1, 20.2, 20.3, 20.4, 20.5, 26.1, 26.2, 26.3, 26.4, 26.5, 26.6, 26.7, 26.8, 27.4, 31.6, 36.6, 52.4 in women. The National Institute of Statistics (ISTAT) census data on work force was used to perform estimates gender-based [18].

Following the codes selection, a list of firms and their number of workers was extracted from ISPESL database of enterprises, updated on December 31, 2004. ISPESL database design is fully described elsewhere [19]. In summary, it is a database obtained by matching, through the value added tax (VAT) number, enterprises in the archives of the National Chamber of Commerce (Unioncamere) and in the National Social Security Institute (INPS). For each enterprise, information about the local units (*e.g.* a workshop, factory, warehouse, office, mine or depot geographically identified), and the number of employees (blue and white-collar) were selected. To estimate the number of workers at risk, white-collars and blue-collars were analysed separately, considering only the latter as potentially exposed to bladder cancer risk. Moreover, in order to avoid the bias due to the lack of data about workers' occupations (which likely to overestimates the potential exposures), the percentage of workers exposed to a low level (close to the non-occupational background) was excluded from the estimate. This percentage (15-20%) was retrieved from a previous study on the estimate of occupational exposures to carcinogens in Europe [20]. The agriculture sector and the Public administration and defence were not considered due to a lack of information on job type (distinction between blue and white-collars was not available for these sectors). None analysis was done by workers' occupation (job-title) since this information was not available in the ISPESL database. In order to evaluate the geographical distribution of data, the number of potentially exposed workers (blue-collars) for each Italian province was mapped using MapInfo software. The total number of exposed workers, separately for men and women, was categorized in quartiles.

Moreover, for evaluating the correlation between exposed workers and bladder cancer deaths, the rate between exposed workers and per 100 000 resident population (E), and the rate between deaths and per 100 000 resident population (D) for each i_{th} province and gender have been estimated. The resident population was taken from the last population census (ISTAT, 2001) and the number of bladder cancer deaths from 2001 ISTAT mortality data statistics. After having verified the statistical significance of such correlation, it has been performed a linear regression analysis. The linear model was: $D_{i,j} = \alpha+\beta*E_{i,j}+\varepsilon_{i,j}$, for i = 1 to 103 (Italian provinces) and j = 1 to 2 (1 = male, 2 = female). The statistical significance of estimated regression coefficients (α, β) and the goodness of fit (r-squared) between empirical and predicted values were also evaluated. All statistics were performed using SAS Software.

RESULTS

The number of blue-collars selected from the ISPESL database of enterprises is 443 849 (301 300 men and 142 549 women). Excluding low level exposures (those close to the non-occupational background, evaluated in about 15-20% of the total exposed workers), our estimated figures turn into 366 175 ± 11 096 (248 573 ± 7533 men and 117 603 ± 3564 women) blue-collars potentially exposed to bladder cancer risk in the industrial sector in Italy. Since the percentage of low level exposures is not a fixed number but a range (15-20%), the estimated figures include half the range of variability (5%).

Table 1 shows the distribution of exposed workers according to gender and economic activity (3-digit level codes) in industry and services sector. The distribution of workers (blue-collar) at risk of blad-

Table 1 | *Number of workers (blue-collars) by economic activity sector*

Activity sector (3-digit level NACE code)		Blue-collars	Blue-collars at risk*
Men		**301 300**	**248 573 ± 7533**
36.1	Manufacture of furniture	77 042	63 560 ± 1926
25.2	Manufacture of plastic products	61 178	50 472 ± 1529
19.3	Manufacture of footwear	40 828	33,683 ± 1021
34.3	Manufacture of parts and accessories for motor vehicles and their engines	39 354	32,467 ± 984
24.1	Manufacture of basic chemicals	19 119	15 773 ± 478
36.6	Miscellaneous manufacturing n.e.c.	13 083	10 793 ± 327
25.1	Manufacture of rubber products	12 888	10 633 ± 322
20.5	Manufacture of other products of wood; manufacture of articles of cork, straw and plaiting materials	10 128	8356 ± 253
24.6	Manufacture of other chemical products	9707	8008 ± 243
24.3	Manufacture of paints, varnishes and similar coatings, printing ink and mastics	7571	6246 ± 189
24.7	Manufacture of man-made fibres	3612	2980 ± 90
37.2	Recycling of non-metal waste and scrap	3428	2828 ± 86
31.4	Manufacture of accumulators, primary cells and primary batteries	1943	1603 ± 49
17.5	Manufacture of other textiles	670	553 ± 17
24.2	Manufacture of pesticides and other agro-chemical products	489	403 ± 12
14.4	Production of salt	260	215 ± 7
Women		**142 549**	**117 603 ± 3564**
19.3	Manufacture of footwear	49 900	41 168 ± 1248
31.6	Manufacture of electrical equipment n.e.c.	20 911	17 252 ± 523
52.4	Other retail sale of new goods in specialized stores	14 821	12 227 ± 371
36.6	Miscellaneous manufacturing n.e.c.	12 251	10 107 ± 306
26.3	Manufacture of ceramic tiles and flags	8685	7165 ± 217
26.1	Manufacture of glass and glass products	6811	5619 ± 170
20.3	Manufacture of builders' carpentry and joinery	6033	4977 ± 151
26.7	Cutting, shaping and finishing of stone	4209	3472 ± 105
20.5	Manufacture of other products of wood; manufacture of articles of cork, straw and plaiting materials	4144	3419 ± 104
26.6	Manufacture of articles of concrete, plaster and cement	3223	2659 ± 81
20.1	Sawmilling and planing of wood; impregnation of wood	2864	2363 ± 72
27.4	Manufacture of basic precious and non-ferrous metals	2387	1969 ± 60
20.2	Manufacture of veneer sheets; manufacture of plywood, laminboard, particle board, fibre board and other panels and boards	2179	1798 ± 54
20.4	Manufacture of wooden containers	1228	1013 ± 31
26.8	Manufacture of other non-metallic mineral products	1057	872 ± 26
26.4	Manufacture of bricks, tiles and construction products, in baked clay	802	662 ± 20
26.5	Manufacture of cement, lime and plaster	595	491 ± 15
16.0	Manufacture of tobacco products	267	220 ± 7
26.2	Manufacture of non-refractory ceramic goods other than for construction purposes; manufacture of refractory ceramic products	182	150 ± 5
All subjects		**443 849**	**366 175 ± 11 096**

**Evaluated excluding the low level exposure (15-20%); n.e.c. = not elsewere classified.*

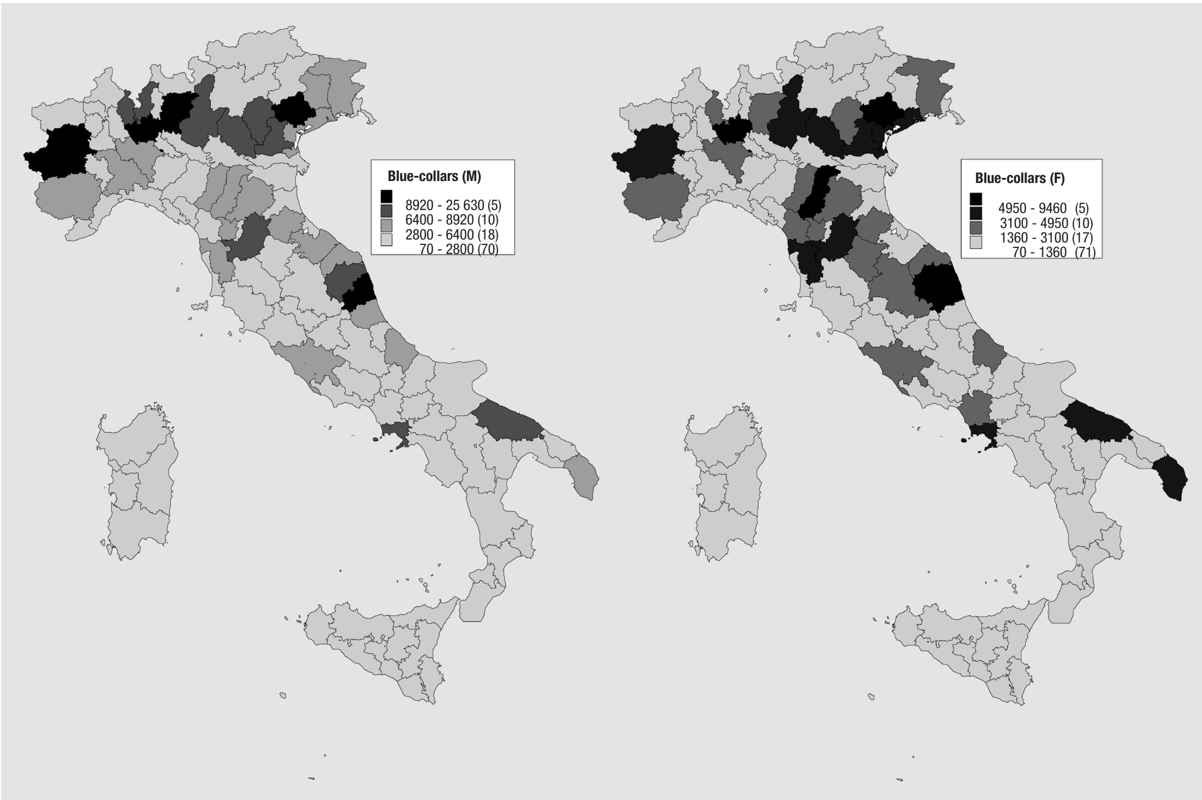

Fig. 1 | *Distribution of workers (blue-collars) at risk of bladder cancer by gender and Italian provinces.*

der cancer by Italian provinces is shown in *Figure 1*, separately for men and women.

The industrial sectors highly involved in bladder cancer risk in men result to be "Manufacture of furniture" (NACE 36.1) followed by "Manufacture of plastic products" (NACE 25.2) and "Manufacture of footwear" (NACE 19.3), while for women sectors at risk are "Manufacture of footwear" (NACE 19.3), "Manufacture of electrical equipment n.e.c." (NACE 31.6) and "Other retail sale of new goods in specialized stores" (NACE 52.4). These sectors account for about 60% of the total exposed workers, respectively in men and women.

In Italy, the North-Western area shows the majority of exposed workers (about 86 625 ± 2625 men and 27 225 ± 825 women), while the Southern and Islands present the minority (about 39 600 ± 1200 men and 23 925 ± 725 women). North-East and Central Italy have, respectively, 105 600 ± 3200 (71 775 ± 2175 male and 33 825±1025 female) and 81 675 ± 2475 (48 675 ± 1475 male and 33 000 ± 1000 female) exposed workers. In the North-West the highest number of workers at risk results in "25.2-Manufacture of plastic products" (22 345 ± 677 blue-collars), whereas in the North-East area the highest values result in "36.1-Manufacture of furniture" (28 848 ± 874). In the Central, Southern and Islands Italy, the sector with the major number of potentially exposed workers is "19.3-Manufacture of footwear" (36 504 ± 1106 and 16 204 ± 491 respectively).

Concerning the distribution by region and activity sector, in absolute terms, Marche is at first place with 6% of exposed workers (22 311 ± 676 blue-collars in the "19.3-Manufacture of footwear"), followed by Veneto (16 522 ± 501 blue-collars in the "36.1-Manufacture of furniture") and Lombardy (15 982 ± 484 blue-collars in the "25.2-Manufacture of plastic products"). These figures account for about 15% of the total exposed workers. For male workers, Veneto is the first region with 16 522 ± 501 blue-collars at risk in the "36.1-Manufacture of furniture", while for women Marche has the highest number of blue-collars (12 271 ± 372) in the "19.3-Manufacture of footwear".

As regards the Italian provinces, Milan presents the greatest number of exposed male workers (21 138 ± 641 blue-collars) followed by Turin (16 317 ± 494) and Treviso (13 283 ± 403), while for women the highest values are reported for Ascoli Piceno (7801 ± 236), Milan (6211 ± 188) and Modena (4943 ± 150). Ascoli Piceno is also the province with the highest percentage of exposed workers (more then 20%) in relation to the total workforce in the province, while Rome has the lowest percentage (less then 1%).

The correlation between D and E results statistically significant ($p = 0.0002$), with a Pearson's correlation coefficient $r = 0.25$. The regression analysis

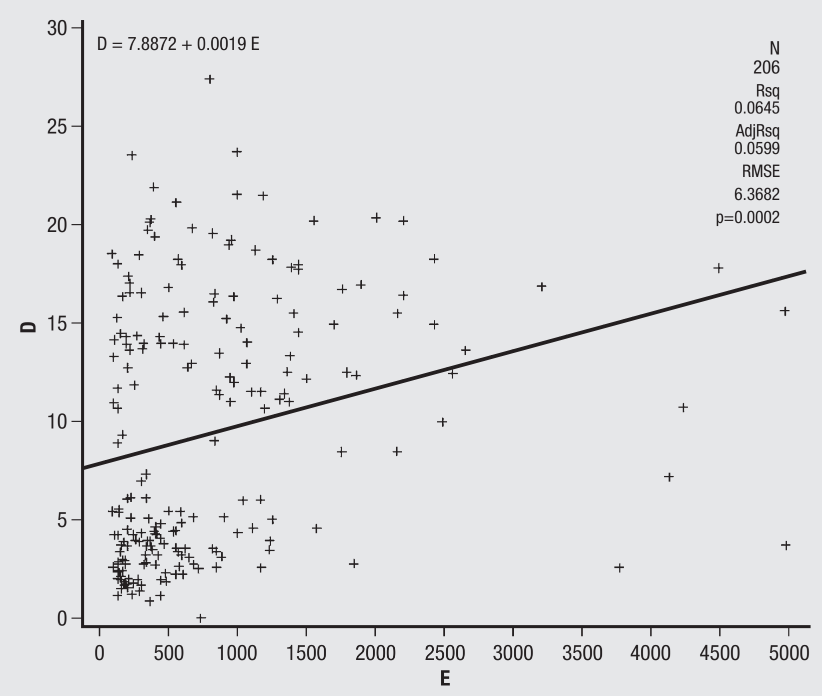

Fig. 2 | *Regression analysis plot between bladder cancer deaths rate (D) and exposed workers rate (E).*

finds a positive relationship between D and E with a β coefficient of 0.0019 (p = 0.0002) and r-squared of 0.0645 *(Figure 2)*.

DISCUSSION

The estimate of workers exposed to carcinogens is important in epidemiological studies, particularly to assess the burden of occupational cancers. Exposure data are not always available at national level and, in most cases, job exposure matrices or indirect measures are used as a surrogate of exposure assessment. Driscoll and colleagues in estimating the global burden of disease due to occupational carcinogens excluded bladder cancer for insufficient global data on the exposure associated to this risk [21]. Detailed data on proportion of exposed workers by industry sector presented here, combined with relative risk measures, may be useful for estimate the attributable fraction caused by workplace exposure for this cancer site. Attributable fractions assess the proportion of cases in a population attributable to certain risk factors [22], and in Italy a recent study was conducted to estimate the proportion of cancer attributable to occupation in different geographical areas [23].

The strengths and limitations of ISPESL database have been described elsewhere [19, 24]. Briefly, it is necessary to remind the origin of the archives, which is represented by administrative-social security sources [25]. The evaluation of exposed workers is based on administrative data source instead of direct measurement of exposure levels. This kind of derivation implies an inherent overestimation of the number of exposed workers. To avoid this problem, occupations made by blue-collars were considered separately from those made by white-collars. Indeed, white-collars include workers not directly exposed, like those employed in account and administration sections. Furthermore, the percentage of low level exposed workers (close to the non-occupational background) was excluded from the estimate. This percentage may be considered as an evaluation of the intensity of the inherent overestimation of the analysis. The impossibility of being detailed in the industrial activity of enterprises (the estimate is based on 3-digit level codes), together with the possible inaccuracy of NACE codes in the initial archives (INPS and Unioncamere), may produce further misclassification. The lack of data on workers' occupation may represent a potential bias of the study, given that job task is highly related to the exposure [17].

A point of strength of the current study is that the estimate is gender-based and, as previously highlighted [26], there are potential gender-related differences in exposures. However, the use of a percentage calculated from the last workforce census data for gender-based analysis instead of the actual rates because of lack of data (information on gender is not stored in ISPESL database) may have been a source of uncertainty. The low cost of construction and maintenance are other advantages of this database. Data stored in the ISPESL enterprises database were already used to evaluate the exposed workers potentially at risk of lung cancer, and the findings were in-line with previous epidemiological estimates (*i.e.*, CAREX project) [20]. Moreover, our estimate, compared to that of CAREX, is based on excess risks for bladder cancer by industrial sector rather than on exposures to some specific bladder carcinogens (*e.g.*, benzidine, methylene-bis-orthochloroaniline, etc.), and thus may be considered more representative [27]. The use of a standard classification (NACE) for coding industrial sectors in this study may be helpful for international use and comparisons among studies. Classifications of industries are frequently used tools in population-based studies, although their use is far from being standardized. The structure of classification systems is often more suitable for other purposes (*e.g.*, economic analyses) than for epidemiological studies. The lack of standardization derives also from the little importance given to the methodological aspects of using these classifications in performing preventive measures for health surveillance in workplaces [28].

Considering that the average latency time for bladder cancer is 20 years, it is important to remember that past exposures still have consequences on today's bladder cancer incidence [7]. Nevertheless, industrial sectors mainly at risk of bladder cancer seem to change over time. Latest studies [13, 15] did not observe excess bladder cancer risk for many of the occupations and industries identified as being a priori at high risk, suggesting that this is probably due to improved working conditions, technological progress, reduction in workers exposure levels, increased workers' health controls and stricter regulations [29]. As a result, the current percentage of occupational bladder cancers in European men decreased from 20% to 5-10% [15].

Currently, the occupational risk of bladder cancer is due also to new bladder carcinogens or new mixtures of well known bladder carcinogens. Since the middle of the twentieth century, the production of carcinogenic aromatic amines has been banned in many countries. However, during the last decades, the introduction of new chemical substances such as 4,4'-diamino diphenylmethane, o-tolidine, and o-dianisidine in clinical and biochemical laboratories resulted to be new hazards in working environment [12]. In addition, epidemiological studies reported that also PAHs, chlorinated hydrocarbons (trichloroethylene and tetrachloroethylene) and benzene, are likely to be new occupational bladder carcinogens [10, 11, 30]. A research conducted in a European country highlighted that furniture makers, engravers and painters are exposed to carcinogenic paint components; smiths, coal miners, metal foundry workers and maintenance workers in coking industry result highly exposed to PAHs; marine engineers, car mechanics and lorry drivers are exposed to diesel exhausts; whereas vulcanisers in the rubber industry and cable industry workers appear to be highly exposed to aromatic amines [31]. In Italy, an elevated risk for bladder cancer was found to be associated to dyestuff production, chemical industry, leather and shoe manufacture, and rubber industry [32-35]. All these risk-sectors are well represented in our estimate.

CONCLUSIONS

The existence of a database which permits the identification and territorial localization of enterprises with activities linked to bladder cancer risk, allows to plan territorial programs for a real and detailed characterization of situations at risk for the health of workers. Identifying and estimating exposed workers in emerging high-risk occupations and industries is of primary importance in order to periodically reconsider risk assessments.

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Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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