Occupational exposure to solvents and bladder cancer: A population-based case control study in Nordic countries

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Novelty and Impact statements

This study provides evidence of an association between occupational exposure to trichloroethylene, perchloroethylene, aliphatic and aromatic hydrocarbon solvents, benzene and toluene and bladder cancer risk. Among these solvents, only benzene and trichloroethylene are currently classified as group 1 carcinogens to humans.

Abstract

The objective of the study was to assess the relationship between exposure to selected solvents and the risk of bladder cancer. This study is based on the Nordic Occupational Cancer (NOCCA) database and comprises 113,343 cases of bladder cancer diagnosed in Finland, Iceland, Norway and Sweden between 1961 and 2005 and 566,715 population controls matched according to country, sex and birth year. Census-based occupational titles of the cases and controls were linked with the job exposure matrix created by the NOCCA project to estimate quantitative cumulative occupational exposures. A conditional logistic regression model was used to estimate hazard ratios (HR) and their 95% confidence intervals (95% CI). Increased risks were observed for trichloroethylene (HR 1.23, 95% 95% CI 1.12-1.40), toluene (HR 1.20, 95% CI 1.00-1.38), benzene (HR 1.16, 95% CI 1.04-1.31), aromatic hydrocarbon solvents (HR 1.10, 95% CI 0.94-1.30) and aliphatic & alicyclic hydrocarbon solvents (HR 1.08, 95% CI 1.00-1.23) at high exposure level versus no exposure. The highest excess for perchloroethylene was observed at medium exposure level (HR 1.12, 95% CI 1.02-1.23). The study provides evidence of an association of occupational exposure to trichloroethylene, perchloroethylene, aromatic hydrocarbon solvents, benzene and toluene and the risk of bladder cancer.

Key words:

Aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, job exposure matrix, risk, toluene, trichloroethylene, urothelial carcinoma.

Abbreviations:

NOCCA: Nordic Occupational Cancer study, HR: Hazard Ratio, IARC: International Agency for Research on Cancer, FINJEM: Finnish Job –exposure Matrix, NOCCA-JEM: Nordic occupational cancer study- Job exposure matrix, RR: Relative risk

Introduction

The International Agency for Research on Cancer (IARC) has identified about 100 workplace carcinogens, and a similar number of additional workplace exposures have been classified as possible carcinogens [1]. Some epidemiological studies have demonstrated excess risks of certain cancers in relation to occupational exposure to some solvents. It is further estimated that as many as 20% of all bladder cancer incidence in industrialized countries may be attributable to occupational carcinogens [2, 3]. There was sufficient evidence of carcinogenicity in humans for 4-amino biphenyl, aristolochic acid, benzidine, 2-napthylamine, o-toluidine, arsenic, x-radiation, gamma radiation, tobacco smoking, chlornaphazine and cyclophosphamide [1]. Excess risk of bladder cancer has been reported among several occupational groups such as painters, rubber industry workers, hairdressers and barbers, dry cleaners, transportation workers and printers [1]. These groups may be exposed to aromatic amines, polycyclic aromatic hydrocarbons, diesel exhaust and chlorinated hydrocarbons, and these chemicals have been implicated as the causative bladder carcinogens even if their exact role is debatable [1, 2, 4-6]. A study of painters suggests that the occupation-related risk of bladder cancer may be predominantly seen in the younger age categories [7]. While some study findings have been consistent, others have been inconsistent or limited [1, 6]. In this large population-based study, we assess the relationship between occupational exposure to solvents (aliphatic and aromatic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, chlorinated hydrocarbon solvents, other organic solvents, perchloroethylene, trichloroethylene, 1,1,1 trichloroethane) and the risk of bladder cancer using a Nordic job exposure matrix (NOCCA-JEM).

Materials and methods

The present study is based on the Nordic Occupational Cancer (NOCCA) project. The NOCCA cohort of 14.9 million individuals from Denmark, Finland, Iceland, Norway and Sweden consists of individuals from all five Nordic countries who participated in one or more population censuses in 1960, 1970, 1980/1981 and 1990. As we did not have access to individual data records from Denmark, we had to restrict the study to the remaining four Nordic countries. Occupational information was obtained from computerized census records from censuses 1960, 1970, 1980 and 1990 in Sweden, censuses 1960, 1970 and 1980 in Norway, censuses 1970, 1980 and 1990 in Finland, and census 1981 in Iceland. Personal identity codes were used to link the census records with data from cancer registries and national population registries for information on cancer, death and emigration. Each person was followed until the date of emigration, death or end of the study, which was December 31st of the following years: 2003 in Norway, 2004 in Iceland, 2005 in Finland

and Sweden. Details of the NOCCA study have been described previously [8]. Information on smoking, socioeconomic status and other non-occupational risk factors was not available. This study was approved by the ethical committee and the data inspection boards in each of the Nordic countries.

All incident cases of bladder cancer were extracted from the NOCCA cohort. For each case, five controls were selected, matched by birth year and sex, and were randomly selected from among individuals who were alive and free from bladder cancer at the date of diagnosis of the case (index date). Cases and controls could have a history of any cancer type other than bladder cancer. Persons with a minimum age of 20 years at index date and having occupational information from at least one census record before the index date were included in this study.

Exposure to solvents and other agents was quantitatively estimated based on linkage between occupational codes and NOCCA-JEM. NOCCA JEM was developed from the Finnish job exposure matrix (FINJEM). It covers more than 300 specific occupations as they are coded in the national census data, 29 exposure agents and 4 calendar periods: 1945-59, 1960-74, 1975-84 and 1985-94. Exposure agents are characterized by the proportion of exposed (P) and the mean level of exposure among the exposed persons (L) in a specific occupation and time period. Many prevalence and level estimates of FINJEM were modified to be in better accordance with measurement data available from the Nordic countries [9]. Eight new agents that were not included in FINJEM (six solvents and two other agents) were added to the NOCCA-JEM. FINJEM has been used to compare with many other JEMS [9]. We assumed that the solvent exposures before 1945 could be taken as zero. An occupational code was assigned for each case and control based on the occupational codes recorded in the censuses. For each occupational code and year of exposure, the exposure estimate was calculated as the product of proportion and level of exposure (P*L) from NOCCA JEM. These year-specific values were then added up for the entire employment period (T).

Exposure was assumed to start at the age of 20 years and end at the index date or at 65 years, whichever occurred first. If there were different occupational codes in the census records for a given person, the individual was assumed to have changed occupations at the mid-point of two known census years. In that case, the exposure history of the person consisted of more than one P*L*T value. The cumulative exposures of these individuals was estimated by summing up all their P*L*T values over their entire working career. This procedure was repeated for all the exposure agents. Variables were selected using ‘purposeful selection of covariates’. The univariate analysis of each variable with a significant univariate test was selected for further multivariate analysis based on the Wald test from logistic regression and p-value ≤ 0.25.

In this study, we quantified exposure to the following individual solvents: aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, toluene, chlorinated hydrocarbon solvents, perchloroethylene, 1,1,1 trichloroethane, trichloroethylene and other organic solvents. We also quantified exposures to ionizing radiation, asbestos, benzo[a]pyrene, diesel engine exhaust and sulphur dioxide, which, along with age and sex, were considered as potential confounders in our analysis. Benzene and toluene were highly correlated with aliphatic and alicyclic hydrocarbon solvents as well as with each other. We used, therefore, two main effect models (model 1 and 2). In model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents, and in model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.

Hazard ratios (HR) and 95% confidence intervals (95% CI) for each solvent were estimated using conditional logistic regression. For the purpose of categorization, exposure values were defined as follows: below the 50^{th} percentiles among the exposed cases and controls as low exposure level, between the 50^{th} and 90^{th} percentile inclusive as moderate and >90^{th} percentile as high exposure level. Individuals with no exposure were used as reference. Pearson’s chi square test for linear trend was performed to assess the dose response relationship between exposure variables and bladder cancer risk. The unexposed group was excluded from the trend test. Analyses were repeated with different lag times of 0, 10 and 20 years. We present results with a 10 year lag, meaning that we did not count the exposures during the 10 last years before the index date. HRs are mutually adjusted for exposure to other solvents and chemicals.

Results

This study included 113,343 cases and 566,715 controls. Three fourths of the study subjects were male, and more than half were from Sweden. 56.8% of the cases and controls were born before 1920, and thus, likely to have some employment and possible exposure before 1945, during periods for which NOCCA-JEM provides no exposure estimate (Table 1). The proportion of exposed among the cases and controls was 17.5% and 82.5% respectively. Table 2 shows the occupations with the highest solvent exposure with specific solvents based on NOCCA- JEM.

Statistically significant increased risks with HR>1.10 were observed for trichloroethylene, toluene and benzene at high exposure level and perchloroethylene at medium exposure level. Although some of the HRs were statistically significant, the risk estimates were generally close to 1.0. The results from both models were similar. Hence, we chose to present the results for aliphatic and alicyclic hydrocarbon solvents from model 2 and for all other exposures from model 1 (Table 3).

The HRs tended to be higher for cancers diagnosed at ages <50 years for aliphatic and alicyclic hydrocarbon solvents, benzene and toluene, while for trichloroethylene, the HR was highest in the older age component at high exposure level (Table 4). We did not observe any significant interactions indicating that the dose response trend patterns would be different in males and females (Table 5).

Discussion

The findings of this study show a statistically significant increased risk of bladder cancer among individuals employed in occupations where exposures to solvents likely occur. Associations were estimated at different exposure levels for aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, perchloroethylene, benzene, toluene and trichloroethylene.

IARC first classified trichloroethylene as probably carcinogenic to humans (group 2A), but later it was re-evaluated as a group 1 carcinogen [10]. In our study, the estimated exposure to trichloroethylene was significantly associated with an increased risk of bladder cancer, and the excess risk was observed at high exposure level. Dry cleaners and aircraft and aerospace workers were reported as highly exposed to trichloroethylene [10]. Similarly, perchloroethylene, which is commonly known as tetrachloroethylene, is mainly used in dry cleaning and to a lesser extent in the printing and textile industries [10].

A German study observed an increased risk of bladder cancer among those exposed at a substantial exposure level of trichloroethylene [odds ratio (OR) 1.8, 95% CI 1.2-2.7] and tetrachloroethylene (OR 1.8, 95 % CI 1.1-3.1) in males, using the job task exposure matrix [11]. Smoking was adjusted for in the analysis, and the substantial exposure level was similar to that of high exposure level in our study. Likewise, an American study observed an increased risk of bladder cancer among those exposed to trichloroethylene at the highest exposure level (risk ratio, 1.98, 95% CI 0.93-4.22). The study observed a dose response relationship with exposure to trichloroethylene, and it also reports that confounding due to smoking was very small [12].

In a Nordic study, excess risk of bladder cancer was observed among dry cleaning assistants exposed to tetrachloroethylene [rate ratio 1.44, 95% CI 1.07-1.93] regardless of the duration of employment [13]. In the Nordic countries, trichloroethylene was used mainly for degreasing metals and little in dry cleaning, whereas perchloroethylene was used extensively in dry cleaning [14]. Hence, the results for perchloroethylene in the Nordic dry cleaner study and the present study are not independent because of a marked overlap of the data in these two studies. A meta-analysis study of the exposure of tetrachloroethylene among dry cleaning workers observed the overall metarelative risk (mRR) of 1.47 (95% CI 1.16-1.85) [15]. In our study, exposure to perchloroethylene was associated with a significantly increased risk of bladder cancer at medium exposure level compared with no exposure. Trichloroethylene and perchloroethylene are the subcategories of chlorinated solvents. Hence, it is difficult to disentangle their individual effects. According to IARC, exposure to trichloroethylene was categorized as a group 1 carcinogenic, whereas perchloroethylene (tetrachloroethylene) was categorized as probably carcinogenic to humans (group 2A).

The broad category of aromatic hydrocarbon solvents includes benzene (as well as toluene, xylene and others) so that it becomes difficult, if not impossible to disentangle their effects. According to IARC, occupational exposure to benzene occurs through inhalation or dermal absorption of solvents in manufacturing industries such as for rubber and paint, crude oil refining, transport of crude oil and gasoline service stations [16]. In our study, we observed a dose response risk of bladder cancer exposed to benzene, aliphatic and alicyclic hydrocarbon solvents and aromatic hydrocarbon solvents. Previous epidemiological studies have observed an elevated risk of bladder cancer among painters (RR 1.28, 95% CI 1.15-1.43), transportation workers (OR 1.6, 95% CI 1.1-2.6), gas and electrical services workers (OR 3.9, 95% CI 1.1-2.6), gasoline workers (OR 1.21, 95% CI 1.03-1.42) and rubber workers (OR 2.5, 95% CI 0.9-7.3) [2, 17-19]. These occupations are exposed to solvents such as benzene, toluene, aliphatic and alicyclic hydrocarbon solvents and aromatic hydrocarbon solvents, and hence the resultant outcome may be due to the combined effect of these solvents at the workplace [1, 20].

A Finnish study observed increased risk estimates of all exposure categories studied in bladder cancer exposed to solvents such as aliphatic and alicyclic hydrocarbon solvents and aromatic hydrocarbon solvents [21]. This effect could be due to benzene exposure and their chemical nature of combination. Smoking was adjusted for, and the observed association was true only among women in the study. In our study, we did not observe any significant differences in the risk estimates between males and females for exposure to any of the solvents such as aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents and benzene.

Exposure to toluene usually occurs among those occupationally exposed to painting, varnishing, cleaning chemicals, laboratories, transportation, chemical dyes, pharmaceuticals, detergents and explosives [22]. In our study, we observed a significantly increased risk of bladder cancer for those exposed to toluene at a high exposure level, but no effect was observed at low and medium exposure levels. Epidemiological studies have observed that exposure to toluene in painters is associated with a positive risk of bladder cancer [7, 17], but according to the IARC, the total evidence of the carcinogenicity in humans is inadequate [23]. The concurrent exposures of toluene to other solvents make it difficult to disentangle their specific effect. We observed that the HR for benzene and toluene at a high exposure level was especially elevated for bladder cancer in the younger age category. Our finding is in line with a study from New Zealand that observed a 2.3-fold statistically significant risk of bladder cancer among painters aged 20-59 years as compared to a 1.3-fold excess in the older age groups [7].

Earlier studies have suggested an association between exposures to other agents such as asbestos, diesel engine exhaust, sulphur dioxide and ionizing radiation and an increased risk of bladder cancer [24-26]. In our study, exposures to asbestos (low and high exposure level), diesel engine exhaust (low and medium exposure levels), sulphur dioxide (low and medium exposure levels) and ionizing radiation (high exposure level) were observed as significant increased risks of bladder cancer.

Only small proportions of the populations of Norway, Finland, Sweden and Iceland had considerable exposure to solvents. This limited our choice of cumulative exposure categorization in our study. Therefore, the threshold of the highest exposure level had to be set to a modest exposure level. Variation in exposure levels within occupational categories means the use of average exposure estimates for everyone in the occupational category, and that may under- or overestimate the true exposure for some individuals. Such misclassification dilutes the contrast between the categories in this study. Individual work histories were based on census records at one to four census dates. Hence, if persons changed occupation before, between or after the known census years, it may have caused further misclassification of the exposure estimate and biased the observed effect towards null [27-28]. We assumed no solvent exposure before 1945. In our study, 68.8% of both cases and controls were born before 1925 and hence had part of their estimated work career before 1945. According to a recent study on bladder cancer in Finland [29], the proportion of localized-stage bladder cancers is higher in certain occupations that appear to be related to higher diagnostic activity. Such occupations in our study are typically in the non-exposed group, and therefore the possible surveillance bias would increase the bladder cancer incidence in the reference category, consequently decreasing the HR estimates in the exposed groups.

The confirmed association between smoking and bladder cancer makes it important to estimate the role of smoking as a potential confounder. We did not have direct information about smoking of the individuals of the NOCCA cohort, but the aggregate level information can be estimated, e.g. on the basis of lung cancer risk in each of the occupations [8]. If the risk of lung cancer in a given occupation is elevated and there are no other work-related exposures than smoking, then the risk of bladder cancer should also be elevated due to smoking, but not as much as for lung cancer (because the relative risk (RR) due to smoking is lower for bladder cancer than for lung cancer). The RRs for bladder cancer clearly differ from this pattern [30]. Those occupational groups at the highest risk of bladder cancer were also commonly identified as having an elevated risk of lung cancer, which lends support to the hypothesis that at least some occupational variation in bladder cancer risk can be explained by occupational differences in smoking. In earlier studies in populations with smoking patterns similar to the Nordic countries, the risk estimates for bladder cancer did not significantly change when adjusted with smoking [11-12, 20-21, 31]. Though smoking is a well-established risk factor for bladder cancer, occupational differences in bladder cancer risk do not appear to be solely due to smoking [31].

This study is to our knowledge the largest study to explore the relationship between occupational solvents exposure and the risk of bladder cancer so far. The study covered the populations of four Nordic countries followed up for a long period of time. Due to the large number of cases and controls from different Nordic countries, this study presents a higher external validity. NOCCA-JEM has been used in the study, due to which we could generate quantitative exposure estimates for different solvents such as aliphatic and alicyclic hydrocarbon solvents, aromatic hydrocarbon solvents, benzene, toluene, perchloroethylene, trichloroethylene and a number of potentially confounding exposures. In this study, we were able to control for exposure to multiple other agents and variation of exposure levels over time. In recent years, there have been changes in exposure levels with time in some of the occupations such as dry cleaning and the transportation industry. For example, the occupational safety limit for the use of tetrachloroethylene used in the dry cleaning industry was decreased in all Nordic countries after 1970 [13]. Similarly, in the transportation industry, the qualities of fuel used in vehicles have been improved, showing a reduced risk of urinary bladder cancer among motor vehicle drivers [32].

The study provides evidence of an association between occupational exposure to trichloroethylene, perchloroethylene, aliphatic and aromatic hydrocarbon solvents, benzene and toluene and bladder cancer risk. Among these solvents, only benzene and trichloroethylene are currently classified as group 1 carcinogens. Future studies are required with high quality quantitative exposure measurement to explore in more detail the association of agent-specific exposure and the risk of bladder cancer.

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Table 1. Demographic characteristics of bladder cancer cases and controls.

Characteristics	Cases		Controls	
	N	%	N	%
Sex				
Male	84629	74.7	423145	74.7
Female	28714	25.3	143570	25.3
Country				
Finland	18521	16.3	92605	16.3
Iceland	804	0.7	4020	0.7
Norway	28938	25.5	144690	25.6
Sweden	65080	57.4	325400	57.5
Year of birth				
≤1910	30751	27.1	153755	27.1
1911 – 1920	33674	29.7	168370	29.7
1921 – 1930	28474	25.1	142370	25.1
1931 – 1940	12980	11.5	64900	11.5
1941 – 1950	6285	5.5	31425	5.5
1951 - 1960	1179	1.0	5895	1.0
*Age at index date**				
20 – 29	6878	6.1	34390	6.1
30 – 39	19211	16.9	96055	16.9
40 – 49	31359	27.7	156795	27.7
50 – 59	38005	33.5	190025	33.5
60 +	17890	15.8	89450	15.8
Total	113343	100	566715	100

*Index date is defined as the date of diagnosis for the case in each case-control set.

Table 2: Occupations with highest solvent exposures in NOCCA- JEM.

Occupations	**Exposures**
Printers	Toluene
Painters	Toluene
Graphics	Toluene, other organic solvents
Plastic product workers	Aromatic hydrocarbons solvents
Rubber workers	Aliphatic and alicyclic hydrocarbons solvents, Aromatic hydrocarbons solvents, toluene
Upholsterers	Aromatic hydrocarbons solvents, toluene
Laster and sole fitters	Aliphatic and alicyclic hydrocarbons solvents, benzene, other organic solvents, trichloroethylene
Chemical process workers	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, toluene
Refinery workers and others in chemical industry	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, toluene
Painters, lacquerers and floor layers	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, other organic solvents
Metal plating and coating work	Chlorinated hydrocarbons solvents, perchloroethylene, trichloroethylene, 1,1,1 trichloroethane,
Wood workers	Trichloroethylene
Distillers	Toluene
Laundry workers	Aliphatic and alicyclic hydrocarbons solvents, aromatic hydrocarbons solvents, chlorinated hydrocarbon solvents, perchloroethylene, trichloroethylene,
Crusher, grinders and calender operators	Other organic solvents
Paper and cardboard mill workers	Other organic solvents
Chemists	Aromatic hydrocarbons solvents, chlorinated hydrocarbon solvents
Footwear workers	Aliphatic and alicyclic hydrocarbons solvents, benzene, other organic solvents
Bookbinders	Other organic solvents
Machine and engine mechanics	Trichloroethylene
Maintenance crews and supervisors	Aromatic hydrocarbons solvents, toluene
Lithographers	Other organic solvents
Service station attendants	Benzene, toluene
Assemblers and other machine & metal ware occupations	Trichloroethylene
Electrical and electronic equipment assemblers	Trichloroethylene

Table 3. Hazard ratios (HR) and 95% confidence interval (95% CI) of bladder cancer associated with exposure to solvents and other co factors. HR estimates for aliphatic and alicyclic hydrocarbon solvents are from model 2 and other HR are from model 1*.

Agent** (unit)*** Category (unit-years)	**Cases**	**Controls**	**HR**	**95% CI**	**P for trend**
Solvents					
Trichloroethylene (ppm)					
Unexposed	106437	534996	1.00	Reference	0.07
<32.80	3433	15884	1.07	1.02-1.12	
32.80– 129.50	2714	12738	1.07	1.00-1.13	
>129.50	759	3097	1.23	1.12-1.40	
Perchloroethylene (ppm)					
Unexposed	111777	559670	1.00	Reference	0.10
<13.60	747	3560	1.00	0.92-1.09	
13.60 – 87.55	660	2783	1.12	1.02-1.23	
>87.55	159	702	0.94	0.73-1.22	
Aliphatic and alicyclic hydrocarbon solvents (ppm)					
Unexposed	106132	534110	1.00	Reference	0.51
<18.73	3648	16276	1.00	0.94-1.05	
18.73 – 337.40	2836	13075	1.05	1.00-1.13	
>337.40	727	3254	1.08	1.00-1.23	
Aromatic hydrocarbon solvents (ppm)					
Unexposed	107281	537691	1.00	Reference	0.02
<11.15	2954	14590	1.00	0.94-1.03	
11.15 – 298.93	2469	11565	1.06	1.00-1.14	
>298.93	639	2869	1.10	0.94-1.30	
Benzene (ppm)					
Unexposed	105363	530478	1.00	Reference	0.07
<5.68	3953	18167	1.00	0.92-1.08	
5.68 – 15.04	3172	14510	1.05	1.00-1.15	
>15.04	855	3560	1.16	1.04-1.31	
Toluene (ppm)					
Unexposed	105139	529444	1.00	Reference	0.68
<57.25	4140	18607	1.00	0.92-1.08	
57.25 – 707.50	3230	14952	1.00	0.91-1.07	
>707.50	834	3712	1.20	1.00-1.38	
1, 1, 1- trichloroethane (ppm)					
Unexposed	105469	530443	1.00	Reference	0.67
<5.60	6011	27807	0.98	0.93-1.02	
5.60 – 10.15	1160	5231	1.00	0.92-1.07	
>10.15	703	3234	1.00	0.89-1.07	
Chlorinated hydrocarbon solvents (ppm)					

Unexposed	110500	553235	1.00	Reference	0.35
<27.58	1416	6746	1.00	0.92-1.09	
27.58 – 52.38	1119	5411	0.90	0.80-1.03	
>52.38	308	1323	0.97	0.80-1.17	
Other organic solvents (ppm)					
Unexposed	110320	552413	1.00	Reference	0.91
<105.55	1529	7137	1.02	0.96-1.09	
105.55 – 378.10	1180	5755	0.93	0.82-1.04	
>378.10	314	1410	0.86	0.70-1.05	
Cofactors					
Asbestos (f/cm^3)					
Unexposed	91112	461009	1.00	Reference	0.10
<2.28	11297	52700	1.07	1.04-1.10	
2.28 – 16.78	8684	42478	1.02	1.00-1.04	
>16.78	2250	10528	1.09	1.04-1.14	
Benzo[a]pyrere (µg/m3)					
Unexposed	103657	521657	1.00	Reference	0.59
<0.31	4846	22528	1.00	0.96-1.04	
0.31 – 7.25	3910	18042	1.01	1.00-1.06	
>7.25	930	4488	1.00	0.92-1.09	
Diesel engine exhaust (mg/m^3)					
Unexposed	96038	487969	1.00	Reference	0.11
<0.70	8973	40447	1.14	1.11-1.17	
0.70 – 2.27	6665	30393	1.21	1.09-1.16	
>2.27	1667	7906	1.05	1.00-1.12	
Sulphur dioxide (ppm)					
Unexposed	111109	556478	1.00	Reference	0.05
<8.35	1138	5106	1.08	1.01-1.15	
8.35 – 45.70	908	4072	1.10	1.01-1.20	
>45.70	188	1059	0.90	0.75-1.04	
Ionizing radiation (mSv)					
Unexposed	112736	563671	1.00	Reference	0.03
<4.08	288	1537	0.90	0.80-1.00	
4.08 – 8.91	241	1220	0.92	0.80-1.07	
>8.91	78	287	1.40	1.09-1.80	

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* In model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents and in model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.

**Occupationally unexposed individuals were used as a reference group.

***ppm, parts per million of agent; mg/m3, milligram of agent in a cubic meter of workroom air; f/cm3, fibers of asbestos in a cubic centimeter of workroom air; µg/m3, microgram of agent in a cubic meter of workroom air; mSv, annual equivalent radiation dose in millisieverts.

Table 4. Hazard ratios (HR) and 95% confidence intervals (95% CI) of bladder cancer associated with exposure to solvents, by age at diagnosis (ppm = parts per million)*

Agent****(**unit) Category (unit-years)	< 50 years					≥ 50 years				
	Cases	**Controls**	**HR**	**95% CI**	**P for trend**	**Cases**	**Controls**	**HR**	**95% CI**	**P for trend**
Trichloroethylene (ppm)										
Unexposed	54713	275139	1.00	Reference	0.44	51724	259857	1.00	Reference	0.40
<32.80	873	3858	1.11	1.02-1.22		2560	12026	1.04	1.00-1.10	
32.80– 129.50	1293	5868	1.12	1.03-1.21		1421	6870	1.01	0.94-1.09	
>129.50	569	2375	1.24	1.10-1.40		190	722	1.27	1.02-1.60	
Perchloroethylene (ppm)										
Unexposed	56843	284627	1.00	Reference	0.98	54934	275043	1.00	Reference	0.07
<13.60	200	896	1.02	0.90-1.21		547	2664	1.00	0.90-1.11	
13.60 – 87.55	337	1390	1.11	1.00-1.30		323	1393	1.13	1.00-1.30	
>87.55	68	327	0.90	0.60-1.30		91	375	1.00	0.70-1.38	
Aliphatic and alicyclic hydrocarbon solvents (ppm)										
Unexposed	54462	274116	1.00	Reference	0.50	51670	259994	1.00	Reference	0.06
<18.73	1262	5603	1.00	0.90-1.07		2386	10673	1.00	0.94-1.07	
18.73 – 337.40	1291	5685	1.12	1.00-1.27		1545	7390	1.00	0.90-1.10	
>337.40	433	1836	1.23	1.00-1.50		294	1418	1.00	0.81-1.16	
Aromatic hydrocarbon solvents (ppm)										
Unexposed	54732	274800	1.00	Reference	0.25	52549	262891	1.00	Reference	0.05
<11.15	1277	5955	1.03	0.95-1.11		1677	8635	0.95	0.90-1.01	
11.15 – 298.93	1102	5039	1.10	1.00-1.22		1367	6526	1.05	0.95-1.15	
>298.93	337	1446	1.09	0.83-1.42		302	1423	1.10	0.90-1.34	
Benzene (ppm)										
Unexposed	54040	272312	1.00	Reference	0.10	51323	258166	1.00	Reference	0.96
<5.68	1191	5297	1.00	0.90-1.20		2762	12870	1.00	0.90-1.09	

5.68 – 15.04	1568	7036	1.07	0.93-1.24		1604	7474	1.04	0.92-1.20	
>15.04	649	2595	1.22	1.03-1.44		206	965	1.04	0.90-1.26	
Toluene (ppm)										
Unexposed	53905	271682	1.00	Reference	0.84	51234	257762	1.00	Reference	0.26
<57.25	1341	5814	1.00	0.90-1.15		2799	12793	1.00	0.90-1.09	
57.25 – 707.50	1700	7575	1.00	0.90-1.11		1530	7377	1.00	0.90-1.10	
>707.50	502	2169	1.23	1.00-1.55		332	1543	1.11	0.90-1.41	
1, 1, 1- trichloroethane (ppm)										
Unexposed	54167	272587	1.00	Reference	0.12	51302	257856	1.00	Reference	0.06
<5.60	2897	12768	1.00	0.91-1.05		3114	15039	1.00	0.90-1.03	
5.60 – 10.15	283	1413	0.85	0.73-1.00		877	3818	1.08	1.00-1.20	
>10.15	101	472	0.90	0.70-1.11		602	2762	1.03	0.92-1.14	
Chlorinated hydrocarbon solvents (ppm)										
Unexposed	56234	281693	1.00	Reference	0.47	54266	279475	1.00	Reference	0.15
<27.58	453	1972	1.01	0.90-1.20		963	4774	1.01	0.91-1.12	
27.58 – 52.38	605	2877	0.83	0.70-1.01		514	2534	1.00	0.81-1.20	
>52.38	156	698	0.91	0.70-1.21		152	625	1.03	0.80-1.35	
Other organic solvents (ppm)										
Unexposed	56060	280904	1.00	Reference	0.79	54260	271509	1.00	Reference	0.36
<105.55	587	2644	1.05	0.94-1.16		942	4493	1.00	0.92-1.10	
105.55 – 378.10	570	2708	0.95	0.80-1.13		610	3047	0.90	0.76-1.04	
>378.10	231	984	0.90	0.64-1.20		83	426	0.80	0.60-1.09	

*HR estimates for aliphatic and alicyclic hydrocarbon solvents are from Model 2 and all the other HR are from model 1. In model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents and in model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.
**Occupationally unexposed individuals were used as a reference group in all analysis.

Table 5. Hazard ratios (HR) and 95% confidence intervals (95% CI) of bladder cancer associated with exposure to solvents, by sex (ppm = parts per million)*

Agent** (unit) Category (unit-years)	**Males**					**Females**				
	Cases	**Controls**	**HR**	**95% CI**	**P for trend**	**Cases**	**Controls**	**HR**	**95% CI**	**P for trend**
Trichloroethylene (ppm)										
Unexposed	78288	393919	1.00	Reference	0.03	28149	141077	1.00	Reference	0.67
<32.80	3090	14391	1.06	1.01-1.12		343	1493	1.01	0.83-1.23	
32.80– 129.50	2588	12179	1.07	1.02-1.14		126	559	0.96	0.71-1.30	
>129.50	663	2656	1.25	1.13-1.40		96	441	0.93	0.50-1.74	
Perchloroethylene (ppm)										
Unexposed	83408	417517	1.00	Reference	0.05	28369	142153	1.00	Reference	0.48
<13.60	639	3099	1.00	0.90-1.09		108	461	1.13	0.90-1.50	
13.60 – 87.55	516	2274	1.07	1.00-1.20		144	509	1.30	1.00-1.71	
>87.55	66	255	1.09	0.80-1.53		93	447	0.90	0.51-1.53	
Aliphatic and alicyclic hydrocarbon solvents (ppm)										
Unexposed	77843	392332	1.00	Reference	0.62	28289	141778	1.00	Reference	0.27
<18.73	3485	15623	1.00	0.94-1.05		163	653	1.03	0.83-1.28	
18.73 – 337.40	2589	12024	1.08	1.00-1.17		247	1051	0.90	0.70-1.20	
>337.40	712	3166	1.13	1.00-1.29		15	88	0.70	0.40-1.30	
Aromatic hydrocarbon solvents (ppm)										
Unexposed	79249	397066	1.00	Reference	0.01	28032	140625	1.00	Reference	0.59
<11.15	2598	13021	1.00	0.93-1.03		356	1569	1.00	0.80-1.30	
11.15 – 298.93	2169	10295	1.07	1.00-1.15		300	1270	1.03	0.80-1.31	
>298.93	613	2763	1.10	0.93-1.30		26	106	1.20	0.64-2.24	
Benzene (ppm)										
Unexposed	77200	389265	1.00	Reference	0.02	28163	141213	1.00	Reference	0.19
<5.68	3488	16210	1.00	0.90-1.05		465	1957	1.21	0.95-1.55	
5.68 – 15.04	3094	14178	1.03	0.94-1.13		78	332	1.14	0.80-1.70	
>15.04	847	3492	1.15	1.02-1.29		8	68	0.55	0.24-1.30	

Toluene (ppm)										
Unexposed	76767	387370	1.00	Reference	0.71	28372	142074	1.00	Reference	0.96
<57.25	3880	17474	1.02	0.94-1.11		260	1133	0.91	0.70-1.20	
57.25 – 707.50	3162	14644	1.03	0.95-1.12		68	308	0.80	0.53-1.15	
>707.50	820	3657	1.23	1.04-1.46		14	55	0.83	0.34-2.00	
1, 1, 1- trichloroethane (ppm)										
Unexposed	77107	388347	1.00	Reference	0.60	28362	142096	1.00	Reference	0.98
<5.60	5711	26544	1.00	0.92-1.01		300	1263	1.04	0.85-1.30	
5.60 – 10.15	1120	5078	1.00	0.91-1.07		40	153	1.15	0.80-1.70	
>10.15	691	3176	1.00	0.90-1.07		12	58	1.11	0.58-2.20	
Chlorinated hydrocarbon solvents (ppm)										
Unexposed	82184	411328	1.00	Reference	0.12	28316	141907	1.00	Reference	0.30
<27.58	1160	5718	1.00	0.90-1.08		256	1028	1.00	0.80-1.24	
27.58 – 52.38	1080	5249	0.90	0.80-1.04		39	162	0.90	0.60-1.44	
>52.38	205	850	1.00	0.81-1.21		103	473	1.02	0.50-2.08	
Other organic solvents (ppm)										
Unexposed	81842	409740	1.00	Reference	0.86	28478	142673	1.00	Reference	0.73
<105.55	1356	6455	1.00	0.93-1.07		173	682	1.30	1.05-1.50	
105.55 – 378.10	1129	5597	0.90	0.80-1.01		51	158	1.72	1.14-2.60	
>378.10	302	1353	0.84	0.70-1.03		12	57	1.23	0.50-3.14	

*HR estimates for aliphatic and alicyclic hydrocarbon solvents are from Model 2 and all the other HR are from Model 1. In model 1, we included benzene and toluene but excluded aliphatic and alicyclic hydrocarbon solvents and in model 2, we included aliphatic and alicyclic hydrocarbon solvents but excluded benzene and toluene. All other solvents were included in both multivariate models.

**Occupationally unexposed individuals were used as a reference group in all analysis.