Estimating the burden of occupational bladder cancer in Ontario using the CAREX Canada database: calculation and application of the population attributable risk

by

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Abstract

Objective: This study attempts to estimate the proportion of incident cases of bladder cancer in Ontario, Canada that is due to exposure to occupational carcinogens.

Methods: The population attributable risk approach is used to estimate the proportion of bladder cancer in Ontario that is due to occupation. Risk ratios were obtained from a review of epidemiologic literature using a priori inclusion and exclusion criteria. Summary risk estimates for each bladder carcinogen included were calculated using RevMan 4.2. The CAREX Canada database provided Ontario-specific estimates of the proportion of workers exposed to bladder carcinogens.

Results: In Ontario, the proportion of bladder cancer due to occupational exposure is approximately 5.6% (95% CI 0.2% to 14%). Based on the incident number of bladder cancer cases in 2001 in Ontario, it is estimated that approximately 52 new cases of bladder cancer were due to occupational exposure to polycyclic aromatic hydrocarbons (PAHs), diesel exhaust, aromatic amines and 2-naphthylamine. An alternate interpretation is if these occupational exposures were eliminated, 52 cases of bladder cancer per year in Ontario alone could be avoided.

Conclusion and Recommendations: The current study advances our knowledge of the extent to which specific occupational bladder carcinogens contribute to the overall bladder cancer burden in Ontario. The current study highlights the utility of the CAREX Canada database in advancing current knowledge on the burden of occupational cancer in Ontario. The methods used to estimate the proportion of bladder cancer attributable to occupational exposure in Ontario may be replicated to estimate the proportion of cancer in Ontario that is due to occupational exposure.

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Table of Contents

CHAPTER 5: DISCUSSION 77

List of tables

List of figures and illustrations

Chapter 1: Introduction

Studies in occupational epidemiology and occupational cancer contribute to the overall body of knowledge on the aetiology of human cancer. Almost half of all recognized human carcinogens are occupational carcinogens (Siemiatycki et al., 2004) and therefore are modifiable risk factors. Occupational cancer can be defined as cancers that are due to exposure to carcinogens in the workplace. Occupational bladder cancers, then, are bladder cancers that are due to exposure to carcinogens in the workplace. Cigarette smoking and certain occupational exposures, such as exposure to aromatic amines, are known modifiable risk factors for bladder cancer (Negri and La Vecchia, 2001; Silverman et al., 2006; van der Meijden, 1998; Tola, 1980; Cohen et al., 2000; Borden et al., 2003; Adami et al., 2002). Quantifying the number of workers who are exposed to bladder carcinogens is an important step in understanding the burden of occupational bladder cancer and identifying possible interventions. Most countries do not have good sources of data or adequate reporting systems in place with which to produce reliable statistics on occupational cancer (‘t Mannetje and Pearce, 2005). The assessment of the burden of occupational bladder cancer, therefore, requires the use of indirect methods from various data sources. This study will attempt to determine the magnitude or burden of occupational bladder cancer in Ontario by answering the question: What proportion of bladder cancers in Ontario is attributable to occupational factors, specifically occupational carcinogens? This quantification shows the degree to which the elimination of these occupational carcinogens would reduce the number of bladder cancer cases in Ontario each year.

Chapter 2: Literature Review

2.1 Bladder Cancer Statistics

In Ontario, bladder cancer is the fourth most commonly diagnosed cancer in men and the thirteenth among women (Cancer Care Ontario website, 2008). The age-adjusted incidence rate (using 1991 Canadian standard population) for all age groups from 1995 to 2004 in Ontario for bladder cancer is 22.09 per 100,000 men, and 5.86 per 100,000 women. The age-adjusted mortality rate (using 1991 Canadian standard population) for all age groups from 1995 to 2004 is 7.40 per 100,000 men and 2.08 per 100,000 women (Cancer Surveillance On-Line, 2008). Among Canadian males, the age-standardized incidence rate has been decreasing on average by 0.5 percent per year from 1995 to 2004 (Canadian Cancer Society, 2008). In this same time period there was also a corresponding decrease among males in the age-standardized mortality rate which decreased an average of 0.4 percent. Among Canadian females, however, while the incidence rate has been decreasing over time at an annual average of 0.4 percent, the mortality rate from 1995 to 2004 has been increasing by an average of 0.4 percent annually (Canadian Cancer Society, 2008). The male to female ratio is approximately 3 to 1 in Canada. The higher incidence among men is consistent with their more likely past exposure to occupational carcinogens, their earlier, long-term, and higher smoking rates.

The incidence and mortality of bladder cancer directly increase with age after age 50 years (Borden et al., 2003; Silverman et al., 2006). More than two-thirds of cases occur in people over 65 years of age. Bladder cancer incidence in Ontario by five-year age groups is presented in Table 1:

Table 1 – Bladder cancer incidence by five-year age group in Ontario 2004, age-standardized incidence rate per 100, 000

Age Group[1]	Rate/100, 000[2]
35-39	1.43
40-44	2.57
45-49	8.54
50-54	16.42
55-59	29.54
60-64	59.29
65-69	92.35
70-74	121.89
75-79	179.38
80-84	239.24
85+	235.61

The incidence of bladder cancer varies greatly internationally. The highest rates occur among men in Europe (southern, western and northern), North America and Oceania. Low rates are found in eastern Europe, Central America, South America and several areas of Asia. The five-year survival rate is about 80% (Adami et al., 2002).

2.2 General Disease Characteristics

About 95% of bladder cancers are transitional cell carcinomas (Cancer Surveillance On-line, 2008). Less than 5% develop as squamous cell carcinoma (found in 1-3% of cases) and even fewer as adenocarcinomas (found in less than 1% of patients) (Steineck, 2001; Droller, 2006). The development of the bladder cancer is associated with the excretion of carcinogenic metabolites in the urine (van der Meijden, 1998). Eighty percent of bladder tumours are superficial and are confined to the bladder mucosa. Twenty percent invade the muscle layer. A variable degree of reporting of bladder cancer may substantially influence descriptive data available (Adami et al., 2002). For example, in Ontario, the coding changed such that preinvasive lesions

[1] Bladder cancer incidence rate per 100, 000 in the age groups prior to 35-39 years is 0
[2] Incidence rate includes in situ carcinomas

(carcinoma in situ) were reported with invasive cancer up to 1989, but have been excluded since, resulting in an apparent drop in incidence in 1989 (Marrett et al., 1995). This continues to be the case in Ontario; however, other provinces have begun to report carcinoma in situ under bladder cancer again since 2006 resulting in variation in the age-standardized incidence rate among both males and females (Canadian Cancer Statistics, 2008). The variation in the estimated incidence rate due to this difference in reporting across the provinces can be seen in Table 2:

Table 2 – Estimated age-standardized incidence rate across Canada, 2008

	Rate per 100, 000										
	Canada	**NL**	**PE**	**NS**	**NB**	**QC**	**ON**	**MB**	**SK**	**AB**	**BC**
Males	27	26	32	35	33	37	19	30	28	29	28
Females	7	7	7	9	9	9	5	8	7	8	8

(Canadian Cancer Society, 2008)

Bladder cancer is considered a malignancy with a long latency period, the time between disease initiation and disease detection. This observation arose from that fact that most new cases of bladder cancer are found in those over 65 years of age. The average latent period for the development of bladder cancer has been estimated to be more than 15 years (van der Meijden, 1998) and has been speculated to range from 18 years to 44 years (Mantanoski and Elliot, 1981; Cohen and Johansson, 1992).

2.3 Bladder Cancer Risk Factors

Cigarette smoking is the most common and well-established risk factor for bladder cancer, contributing an estimated 35 to 50% of all bladder cancer in the United States (Borden et al., 2003). The proportion of bladder cancer attributable to ever smoking is 66% for men and 30% for women, according to the International Agency for

Research on Cancer (2004). Overall, smokers have two to three times the risk of developing bladder cancer compared to non-smokers (Silverman et al., 2006). However, the specific carcinogens involved in elevating the bladder cancer risk among smokers are unknown. There is suggestive evidence that aromatic amines are the bladder carcinogens in tobacco smoke, whereas tar and nicotine content in cigarettes have been shown to have little impact on cancer risk (Silverman et al., 2006). It has been demonstrated that cessation of smoking reduces the risk of bladder cancer (IARC, 2004). A recent review of 15 studies found inconclusive evidence of whether smoking status affects the recurrence or progression of disease (Borden et al., 2003).

In addition to smoking, a number of other non-occupational factors have also been suggested to be associated with bladder cancer risk such as: (1) genetic factors: race, family history and genetic polymorphisms; (2) dietary factors: consumption of fruits and vegetables, coffee, meat and fat, total fluid intake and consumption of drinking water containing arsenic and disinfection by-products ; (3) infections and inflammation of the bladder; (4) treatment-related factors such as the use of phenacetin-containing analgesics, chemotherapeutic agents and radiation therapy; and (5) physical activity (Gaertner et al., 2004).

The proportions of bladder cancer attributable to different risk factors would depend on the relative risk associated to each factor and on the frequency of exposure. The frequency of exposure varies according to geographic area and time period. In one Italian hospital-based case-control study, the investigators estimated that over 70% of bladder cancer cases could be explained by smoking, coffee consumption, low intake of vegetables, a history of cystitis, and occupation (D'Avanzo et al., 1995). Consistently, about half of bladder cancer cases can be accounted for by smoking, but the proportion of bladder cancer due to other factors remains unclear. This study aims to estimate the proportion bladder cancer due to occupational carcinogens in Ontario.

2.4 Bladder Cancer Occupational Risk Factors

Bladder cancer is strongly associated with occupational exposure to chemicals and has a well-established link with certain occupational exposures (van der Meijden, 1998; Steenland et al., 2003; ‘t Mannetje and Pearce, 2005). Occupational bladder cancer was first reported in 1895 by Rehn, who found four cases of bladder cancer in aniline workers (Tola, 1980). The study of occupational causes of bladder cancer began in the 1950s with the identification of bladder cancer in British dyestuffs and rubber industries (Silverman et al., 2006). Since then, many other occupations with potentially high risk for the development of bladder cancer have been suggested. However, much of the evidence on many of these occupational risks remains unclear due to inconsistent findings, small numbers of exposed subjects, or relatively small risk estimates.

The strongest evidence for the development of bladder cancer exists for occupational exposure to aromatic amines such as 2-naphthylamine, 4-aminodiphenyl, and benzidine to which dyestuffs workers, manufacturers of these chemicals, and rubber workers are exposed (Borden et al., 2003; Silverman et al., 2006). As such, their use in the workplace has been eliminated, particularly in developed countries. This leads to shifts in high-risk occupations, for example, reduced risks among rubber and leather workers and emerging risks among truck drivers and aluminum smelter workers (Carreon et al., 2006).

One problem encountered in the study of occupational bladder cancer is that there are occupational groups for which there have been consistently observed increased risks, but the bladder carcinogen responsible is unknown. Such is the case for increased risk of bladder cancer found among leather workers, painters, truck drivers (and other motor vehicles – buses, taxi cabs), and aluminum workers (Silverman et al., 2006).

2.5 Occupational Burden of Bladder Cancer

The measure used to determine the public health burden of a particular risk factor is the attributable fraction (AF) or the attributable risk (AR). These terms will be used interchangeably here. The attributable fraction may be calculated for an exposed group of individuals or for the population as a whole (Kelsey et al., 1996). It may be considered the proportion of the disease in the exposed group (or population) that would be eliminated if the exposure were eliminated. The population attributable risk combines the relative risk and the prevalence of exposure to measure the burden of disease and can be interpreted as the fraction of disease that would be avoided if exposure were eliminated.

For nearly three decades, several methods have been employed to estimate the burden of occupational disease. The most commonly cited figure of the proportion of cancers caused by occupational factors is 4% (Doll and Peto, 1981). These authors also estimated that the proportion of bladder cancer attributable to occupational exposures was 10% in males and 5% in females. Table 3 below outlines the estimates made and the methods used by some of the investigators who have attempted to determine the proportion of cancer due to occupational exposure.

Table 3 – Selected studies that have estimated the proportion of cancer due to occupational factors

Study (year) Country	Estimate – cancer overall	Estimate - bladder cancer	Methods
Doll and Peto (1981) United States	4 % of U.S cancer deaths	10% males 5% females	Classified individual cancers as definitely, possibly or not known occupational hazards. PAR estimates based on existing studies that have provided estimates of the proportions cases due to occupational exposure
Vineis and Simonato (1991) Multiple countries: United Kingdom, Italy, Germany, United States, Spain, Canada, Argentina, Denmark, Belgium, Finland	No estimate made	0-2% to 24%	Systematic review of case-control studies, including only studies that controlled for smoking

Study (year) Country	Estimate – cancer overall	Estimate - bladder cancer	Methods
Nurminen and Karjalainen (2001) Finland	8% 14% male 2% female	10.3% 14.2% male 0.7% female	Risk estimates obtained from epidemiologic literature with preference given to studies conducted in Finland and Scandinavia. Proportion of people exposed to occupational risk factors was obtained from census data and the use of a job-exposure matrix
Kogevinas et al. (2003) Western Europe: Germany, France, Spain, Greece, Italy, Denmark	No estimate made	4.2% to 7.4%	Pooled analysis of data from 11 case-control studies. Job-exposure matrix (FINJEM) used to evaluate prevalence of exposure and average levels of exposure
Steenland et al. (2003) United States	2.4% to 4.8% 3.3% to 7.3% males 0.8% to	5.6% to 19.0% 7% to 19% males 3% to 19%	AF calculated using epidemiologic studies, 1997 U.S mortality data and estimates of the proportion of the population exposed from two NIOSH surveys.

Study (year) Country	Estimate – cancer overall	Estimate - bladder cancer	Methods
	1.0% females	females	
‘t Mannetje and Pearce (2005) New Zealand	No estimate made	14.2% male 7.1% female	Relied on the estimates for gender-specific attributable fraction used in the report of Nurminen and Karjalainen (2001) which were based on the Finnish population and applied these to data from New Zealand
Deschamps et al. (2006) France	3.18% 5.67% males 0.22% females	2.1%	Descriptive study of incident cancer cases over 3 years. Occupational histories obtained. Diagnosis of work-related cancer based on systematic approach where there was potential exposure to carcinogens based on meeting 2 criteria.
Fritschi and Driscoll (2006) Australia	11% males 2% females	14.2% males 0.7% females	Estimates of risk from Nurminen and Karjalainen (2001). Used individual EU estimates for each industry and applied to Australian data.

From the table above, it has been estimated that occupational exposures may be responsible for 2% to 24% of bladder cancer, ranging from 7% to 19% among males and 0.7% to 19% among females. The estimates for cancer overall range from 2.5% to 8% for both males and females combined. The main determinant of the differences in these estimates is the prevalence of exposure to bladder carcinogens across the different populations, and the time periods under study.

The differing exposure circumstances to a range of carcinogens will vary from place to place. For example, using the CAREX International database, the two most common occupational carcinogen exposures across various European countries were consistently solar radiation and environmental tobacco smoke (Kauppinen et al., 1998). These are both fairly ubiquitous exposures. However, the differences in the exposure circumstances start to become apparent when the third, fourth and fifth most common occupational exposures are examined (Table 4)

Table 4 - Comparison of common occupational exposures across different European countries

Country	**3rd Most Common Occupational Carcinogen**	**4th Most Common Occupational Carcinogen**	**5th Most Common Occupational Carcinogen**
Denmark	Formaldehyde	Diesel exhaust	Crystalline silica
Finland	Crystalline silica	Wood dust	Radon
France	Radon	Diesel exhaust	Sulphuric acid mist
Italy	Asbestos	Diesel exhaust	PAHs
Netherlands	Crystalline silica	Diesel exhaust	Wood dust

(table generated from the results of Kauppinen et al., 1998)

The calculation of the population attributable risk involves not only the relative risk associated with a risk factor, but the frequency of the exposure in the population. Therefore, the population attributable risk will vary according to the geographical area and the calendar period in which the frequency of exposure was estimated. For these reasons, and to achieve the objective of this thesis, it is important to base the estimate of the proportion of bladder cancer due to occupational carcinogens using Ontario-specific data. It is important for occupational safety and health practitioners to have an understanding of the burden of occupational bladder cancer to identify the extent to which bladder cancer is avoidable and to be able to target the appropriate sub-groups for intervention. The aim of this study, then, is to estimate the proportion of bladder cancer in Ontario due to exposure to occupational carcinogens.

Chapter 3: Study Design and Methods

The purpose of this study is to estimate the burden of bladder cancer in Ontario that is attributable to occupational factors using the CAREX Canada database.

3.1 Objectives

I. Estimate the proportion of bladder cancer in Ontario that is due to exposure to occupational carcinogens through the calculation of the population attributable risk.

II. Conduct sensitivity analyses to determine the effect of varying the estimates of the "input data" on the attributable risk calculated.

III. Estimate the absolute number of occupational bladder cancer in Ontario by applying the population attributable fraction calculated above to Ontario bladder cancer statistics among the general population.

3.2 Methods

This study used a systematic approach to estimate the proportion of bladder cancer in Ontario that can be attributed to occupational exposures. The population attributable risk (PAR) was calculated to determine the burden of bladder cancer among workers in Ontario. These methods were based mainly on the methodology endorsed by the World Health Organization (WHO) for estimating the environmental burden of disease at the national and local levels by Driscoll et al. (2004), which includes:

i. The identification of known occupational bladder carcinogens

ii. The estimation of the proportion of the population with exposure to the carcinogen

iii. Ascertaining the relative risk for bladder cancer from the literature

iv. Calculation of the population attributable risk, by combining the information on the fraction of the population exposed with the data on the relative risks.

The first step in the calculation of the population attributable risk involved determining bladder carcinogens that are relevant in Ontario. The listing of occupational carcinogens by Siemiatycki et al. (2004) served as the main source of bladder carcinogen identification. This listing is based largely on the evaluations published by the International Agency for Research on Cancer (IARC).

The IARC Monograph Program evaluates the carcinogenic risk of chemicals to humans and publishes critical reviews evaluating the evidence on a wide range of exposures. The evaluations are conducted by an international working group of experts. Each monograph contains information on the extent of past and present human exposure to the agent(s) chosen for evaluation as well as information on the physical and chemical properties of the agent being reviewed. The overall evaluation of human carcinogenicity is based on epidemiologic studies, experimental evidence in animals, and other relevant evidence on genotoxicity, mutagenicity and metabolism. The IARC classifications are found in Table 5.

Table 5 – IARC Classifications

Group	Description of group
1	The agent, mixture, or exposure circumstance is carcinogenic to humans
2A	The agent, mixture, or exposure circumstance is probably carcinogenic to humans
2B	The agent, mixture, or exposure circumstance is possibly carcinogenic to humans
3	The agent, mixture, or exposure circumstance is not classsifiable as to its carcinogenicity to humans
4	The agent, mixture, or exposure circumstance is probably not carcinogenic to humans

(IARC, 2004)

The IARC Monographs are considered an authoritative source of information on the carcinogenicity of various human exposures (IARC 2004; Siemiatycki et al., 2004). Without such evaluations, it would be difficult for an individual investigator to assess causality, as this requires judgment which could be easily biased if based on the assessment of a single individual. It is important to have some understanding of how the IARC evaluations take place as this study relied on these authoritative assessments to determine which carcinogens would be included in the PAR calculation. Without the evaluations such as those of IARC and Siemiatycki et al. (2004) it would be difficult to compile an adequate list of occupational carcinogens related to bladder cancer.

From this list, a list specifically pertaining to bladder carcinogens was compiled. This list of carcinogens was then compared to the carcinogens listed on the CAREX Canada database to determine if they are relevant exposures in Ontario.

The second step in the PAR calculation was based entirely on the data contained in the Ontario-specific portion of the CAREX Canada database. To estimate the proportion of Ontario workers exposed to carcinogens related to bladder cancer, the number of workers in the industrial sector or occupations that are exposed to the carcinogens was obtained from the CAREX Canada database. Similar methodology was recently used in a global estimate of the burden of occupational disease (Ezzati et al., 2002; WHO, 2002; Concha-Barrientos et al.,2004).

The methods endorsed by the WHO assess the environmental burden of disease (Driscoll et al., 2004). This method for estimating the proportion of people exposed to occupational carcinogens requires the following information:

i. the proportion of the workforce employed in each sector
ii. the proportion of the workers exposed to individual carcinogens
iii. the likely turnover of workers
iv. the estimated level of exposure
v. the proportion of the population who are in the workforce.

The third step in the PAR calculation involved conducting a search of the scientific literature. The search was systematic in that the search terms were defined and *a priori* inclusion and exclusion criteria were outlined. Data from the studies included was consistently extracted and compiled in an evidence table, also known as a data extraction table. Part of this data extraction included an assessment of thoroughness of each study's exposure information. A summary risk estimate was calculated for each bladder carcinogen under study, as well as tests for heterogeneity conducted. Sensitivity analyses were conducted to explore any heterogeneity as well as to test the effects on the calculation of the PAR.

The final step in the PAR calculation was to combine the individual PAR's calculated for each carcinogen to obtain an overall PAR as per the methods of Nurminen and Karjalainen, 2001:

$PAR_{overall}$= 1-(1-PAR_a) X (1-PAR_b)….. where,

PAR_a is related to carcinogen a, PAR_b is related to carcinogen b and so on.

Alternatively, depending on the PAR values obtained, the $PAR_{overall}$ can be the sum of the exposure-specific PARs, if the values obtained are small (Steenland and Armstrong, 2006).

The data contained within the CAREX Canada database reflects the current exposure experience in Ontario. However, the methods proposed by Driscoll et al. (2004) involve estimating the proportion of the workforce ever exposed to occupational carcinogens so that a measure of the current burden of disease can be estimated. The final step in estimating the burden of bladder cancer was to apply the PAR to Ontario-specific incidence data.

3.3 Sources of Data

3.3.1 CAREX Canada Database

The CAREX database, International Information System on Occupational Exposure to Carcinogens, was developed by the Finnish Institute for Occupational Health (FIOH) as a tool to estimate the burden of occupational cancer in Europe. The CAREX database estimates the number of exposed workers by country, carcinogen and industry, and provides selected exposure data. The estimates were obtained using labour force and exposure estimates from two reference countries, Finland and the United States. It contains estimates of the number of workers exposed to 139 carcinogens as ranked by the International Agency for Research on Cancer: Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; and selected agents in Group 2B, possibly carcinogenic to humans are considered in the database. Industries are grouped in 55 categories using the International Standard Industry Codes,ISIC-2 (Kauppinen et al., 1998).

CAREX Canada is the Canadian version of the database containing information from British Columbia and Ontario. Preliminary exposure estimates in Ontario have been generated and added to the CAREX Canada database (Demers et al., 2007). Providing exposure estimates for hundreds of industrial sectors was beyond the resources available to CAREX Canada. However, detailed labour force estimates were added to the database. The ISIC-2 categories were converted into Census industry categories. Data from the Ontario portion of the 2001 Census of Canada were entered into the CAREX database to estimate the number of workers potentially exposed to carcinogens by industry. The preliminary data contained in the CAREX Canada database was based on proportions of workers in Finland and/or the United States. Recently, the estimates have been refined through the assessment of a team of Canadian occupational hygienists using available Ontario-specific exposure information, professional judgment and a review of the literature. Developing estimates within the CAREX Canada database involved multiple stages (Demers et al., unpublished).

Stage 1

Industry-specific prevalence estimates from Finland and the United States were used initially, because they were part of the original CAREX system. Prevalence estimates from Finland were based on two sources; the Finnish national register of workers exposed to carcinogens, held by FIOH since 1979, and a comprehensive estimation survey, SUTKEA, conducted by the hygiene staff of FIOH in the late

1980s/early 1990s based on industrial hygiene data collected for research projects or compliance testing. US prevalence estimates were based on the National Occupational Exposure Survey (NOES) carried out by NIOSH from 1981-83. The NOES used site visits to 4,490 establishments to gather data by occupational category within industry sector.

For each carcinogen/industry combination, a local expert in occupational exposure assessment determined whether conditions in Ontario were closer to those in that industry in Finland or in the US, or whether an average of the two was most applicable. Based on the Finnish and U.S data, the assessors generated initial estimated of the numbers of workers exposed to the carcinogens included in CAREX Canada.

Stage 2

The next stage involved improving these initial estimates to identify exposures that were overly underestimated or overestimated. These were identified as exposures that were not comparable between the reference country and Ontario due to industrial infrastructure, geology or major regulatory differences, as per the assessors' judgement. The most common carcinogens were prioritized for further evaluation to improve estimates.

Stage 3

Next, the specific exposure information underlying the Finnish and US prevalence data for each of these common carcinogens were reviewed by several Canadian occupational hygienists (each with training at either the masters or doctorate degree level) to assess whether similar conditions identified exist in Ontario and, where possible, to improve the estimates. The assessors used a combination of professional judgment and review of both the published and the grey literature regarding exposure.

Stage 4

Workplaced exposure measurement data were obtained from Ontario's Ministry of Labour, which maintains a database of air monitoring measurements collected in workplaces to measure compliance with regulatory exposure limits both personal (collected in the breathing zone of the worker) and area (collected at a stationary point in the workplace) measurements are included. Measurements made between 1981 and 1996 for nine carcinogens were obtained: asbestos (n=757), benzene (n=1,304), cadmium (n=924), ethylene dibromide (n=10), formaldehyde (n=7,607), lead (n=7,688), perchloroethylene (n=2,666), crystalline silica (n=4,592), and styrene (n=5,945). In addition, radiation exposure data from the National Dose Registry, operated by the Radiation Protection bureau of Health Canada were also obtained. The industry information on both data sources was recoded and the aggregated data was added to the CAREX system for easy retrieval. Members of the study team reviewed these data to identify potentially exposed groups that were not identified in the initial estimates.

Agents such as alcoholic beverages and betel quid with tobacco that are not useful for occupational surveillance in Canada were eliminated from the original CAREX database. As well, IARC has classified certain industries and occupations as carcinogenic. These exposure circumstances have also been eliminated from the CAREX Canada database since the underlying carcinogens have yet to be identified. Appendix A lists the carcinogens currently included in the CAREX Canada database.

The CAREX Canada database provides information through a number of screens in a Microsoft Access interface. The main screen contains information on exposure estimates by region, carcinogen and industry sector. Information is provided regarding the total number of workers by industry sector, as well as the number of workers exposed to a particular carcinogen within that industry sector. In addition to the exposure estimates, the CAREX Canada database contains information regarding the definitions of the industries and carcinogens included, the number of workers within occupational groups according to the 2001 Census, and information on subgroup exposures where the data are available. The CAREX Canada database is useful for on-going surveillance of occupational cancer in Ontario since it provides provincial estimates of the number of exposed workers using expertise of Canadian occupational hygienists and local labour force data where available. More information on the CAREX Canada database is available on the CAREX Canada website (http://www.carexcanada.ca/) and the Worksafe BC website (http://www.worksafebc.com/contact_us/research/research_results/res_60_10_340.asp).

3.3.2 2001 Canadian Census

The 2001 Census was used to calculate prevalence of exposure in Ontario workers that are potentially exposed to bladder carcinogens. To estimate the proportion of Ontario workers in the total population exposed to a given occupational bladder cancer carcinogen, the estimation was limited to those between the ages of 15 to 64 years to account for those of working age. Since the estimates of the number of workers exposed to carcinogens captured in the CAREX Canada database are based on the 2001 Census, the same data source will be used to calculate the prevalence of exposure: the number of workers exposed to bladder cancer carcinogens will serve as the numerator, and the Ontario population aged 15 to 64 years will serve as the denominator.

3.3.3 Identification of Bladder Carcinogens Through Existing Literature

There is no single source available to determine which bladder carcinogens affect Ontario workers. Thus an indirect method was utilized to determine occupations in Ontario where workers are at risk for bladder cancer. IARC Group 1, Group 2A and Group 2B served as the baseline for carcinogens that were considered in this study. This was further filtered to known and suspected bladder carcinogens as per the listing of occupational carcinogens by Siemiatycki et al. (2004). The final list of carcinogens were those carcinogens that are both listed by Siemiatycki et al. (2004) and for which data are available in the CAREX Canada database. IARC also identifies carcinogenic industries or occupations. In such cases the actual carcinogens are not easily identified, nor will such exposures be identifiable in the CAREX Canada database.

3.3.4 Cancer Surveillance On-Line

To determine the burden of occupational bladder cancer in Ontario the attributable fraction calculated was applied to the absolute number of incident cases of bladder cancer obtained through the Cancer Surveillance On-line website, http://dsol-smed.phac-aspc.gc.ca/dsol-smed/cancer/index_e.html.

Cancer Surveillance On-Line provides the most current publicly available cancer statistics in Canada. Trends in cancer incidence over time, by province/territory, and by age group for forty-five cancers, including bladder cancer, are available. The source of incidence data is the Canadian Council of Cancer Registries and population estimates are provided by Statistics Canada.

The age-range was restricted to those between the ages of 30 to 75 years. The lower age limit of 30 years was chosen to account for the latency period of bladder cancer and the likelihood that the potential exposure period before the age of 30 years is too short to produce a pathological effect. Although the incidence of bladder cancer increases with age, bladder cancer also has a relatively long latency, therefore the upper limit of 75 years was chosen.

3.4 Literature Review Search Terms and Inclusion Criteria

Once the carcinogens and occupations at risk for bladder cancer in Ontario were identified, a review of the literature for studies to be included in the attributable risk calculation was conducted on PubMed. Search terms included: bladder cancer, urinary bladder neoplasms, polycyclic aromatic hydrocarbons, 2-napthylamine, aromatic amines, vehicle emissions, automobile exhaust, and diesel exhaust. To ensure the comprehensiveness of the search, the search term “occupational exposure” was combined with “bladder cancer” and the reference lists of included articles were scanned to identify studies that may have been missed.

The literature review was conducted in two phases. The first phase was a title and abstract review, in which the inclusion criteria were be applied to the title and abstracts of the identified studies. The inclusion criteria were case-control and cohort studies on occupation and bladder cancer that have controlled for smoking, since smoking is a major confounder for bladder cancer. Studies based on populations in North America, Finland and Scandinavia and Western Europe were included to approximate risks for bladder cancer in Ontario from countries with similar industrial development. As well, the risks for bladder cancer vary geographically; therefore, counties with similar risks for bladder cancer were ideally included. Only when risk estimates were not available for these countries will populations from other countries be considered. Studies that have not controlled for smoking, studies that have used cancer controls, and studies with insufficient exposure information were excluded. In situations where it is unclear whether the inclusion criteria have been met, the assessment was made through information available in the entire article.

Studies included based on the assessment of the first phase were further assessed in the second phase of the literature review, which included a review of the entire study, data extraction of elements determined *a priori,* and an assessment of the exposure quality of each study. The elements extracted from each included study are available in the evidence tables presented in Appendix C.

The quality of the exposure assessment in each study was assessed on a scale of 1 to 5 by the student. Studies with exposure quality of 1 were not included in the calculation of the summary risk estimate. This allowed for sensitivity analysis by quality of exposure assessment. Each study was be rated as follows:

Table 6 - Exposure Quality Rating

Exposure Quality Rating	**Criteria**
1 – poor exposure information	Study includes occupations or industries where the carcinogen of interest may be present but occupational or industrial groupings are too broad to glean any information on the carcinogen(s) of interest.
2 – fair exposure information	Study includes occupational groups where the carcinogen of interest is prevalent but other exposures are possible and not accounted for.
3 – moderate exposure information	Study includes occupational groups where the carcinogen of interest is prevalent and other exposures have been accounted for.
4 – good exposure information	Study includes qualitative exposure information on the carcinogen(s) of interest.
5 – excellent exposure information	Study includes quantitative measures of exposure levels to carcinogen(s) of interest.

Figure 1 – Flow diagram of Overall Methods

1. Identify bladder carcinogens in Ontario

Source: IARC Group 1 and Group 2A, Siemiatycki et al (2004) & CAREX Canada

↓

2. Estimation of summary risk estimate for each bladder carcinogen identified to be used in calculation of population attributable risk (PAR)

Method: Systematic approach to literature, summary risk estimates calculated using RevMan

↓

3. Estimation of corresponding proportion of the population exposed to each carcinogen to be used in calculation of PAR

Source: CAREX Canada & 2001 Canadian Census

↓

4. Calculation of overall PAR based on component attributable fractions

Method: Nurimen et al., 2001, Steenland 2006 and Driscoll et al 2004

↓

5. Application of overall attributable fraction to Ontario bladder cancer statistics

Source: Cancer Surveillance On-Line

3.5 Calculating Summary Risk Estimates

Review Manager 4.2 was used to calculate the summary risk estimates used in the PAR calculation. The following steps were undertaken:

1. Define the studies to combine

Separate summary estimates were calculated for studies on incidence and mortality, provided the data were available. Studies were combined based on exposure to specific bladder carcinogens. The CAREX Canada database estimates the number of people exposed to carcinogens by industry for both men and women combined. It is not possible to obtain separate results by gender using the CAREX Canada database. Nor is it possible to obtain separate results by race. Therefore, a separate analysis by gender or race was not possible.

2. Evaluate the statistical heterogeneity of the data

Heterogeneity was evaluated using the I^2 statistic. The I^2 statistic measures the extent of inconsistency and is interpreted as the proportion of total variation in the study estimates that is due to heterogeneity between studies rather than sampling error (Higgins et al., 2003). A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity. Tests of heterogeneity statistically assess whether differing results from different studies could have come from the same population. However, tests for heterogeneity have notoriously weak power and should be complemented by sound judgment.

3. Estimate a common effect

4. Explore and explain any heterogeneity

Sensitivity analyses were conducted to explore any heterogeneity found.

5. Assess the potential for bias

Funnel plots were produced to assess the potential for publication bias.

Summary risk estimates were calculated using the generic inverse variance method. Standard errors were calculated from the 95% confidence intervals of the adjusted risk estimates using the following calculation:

Standard Error = log(upper limit) – log(lower limit)/2(1.96)

3.6 Population Attributable Risk Calculation

Calculation of the population attributable risk can answer the question: what proportion of bladder cancer in the population is due to occupational carcinogens?

Once the summary risk estimates were calculated through the pooled analysis, and the proportion of Ontario workers exposed to bladder carcinogens determined, the component population attributable risk (PAR) for each carcinogen identified was calculated as:

PAR= (P_e) (RR-1)/ (P_e (RR-1) + 1)

Where,

P_e = proportion of individuals exposed in the total population

RR = the relative risk of the disease in the exposed subjects

Given that there are multiple potential risk factors for bladder cancer in Ontario, the calculation of the attributable fraction due to all of the risk factors simultaneously will be required. According the to the methodology of Nurminen (2001), an overall attributable fraction for multiple risk factors in terms of the component attributable fractions can be calculated using the following formula:

$AF = 1-(1-AF_a) \times (1-AF_b)$…..,

under the assumption of statistical and biological independence between the factors. Alternatively, depending on the PAR values obtained, the $PAR_{overall}$ can be the sum of the exposure-specific PARs, if the values obtained are small (Steenland et al., 2006).

Chapter 4: Results

4.1 Identification of Known Occupational Bladder Carcinogens

Based largely on the International Agency for Research on Cancer Monograph Program, Siemiatycki et al. (2004) listed 28 definite human occupational carcinogens (IARC group 1), 27 probable human occupational carcinogens (IARC group 2A), 113 possible human occupational carcinogens (IARC group 2B) and 18 occupational and industries for which there is a possible, probable or definite excess risk of cancer.

Occupational bladder carcinogens and carcinogenic circumstances for which the evidence was deemed to be strong by Siemiatycki et al. (2004) were: aluminum production, 4-aminobiphenyl, auramine manufacture, benzidine, coal gasification, magenta manufacture, 2-naphthylamine and the rubber industry. Occupational bladder carcinogens and carcinogenic circumstances for which the evidence was deemed to be suggestive of increased bladder cancer risk were: ben[a]antracene, benzidine-based dyes, benzo[a]pyrene, boot and shoe manufacture and repair, 4-chloro-ortho-toluidine; coal tars and pitches, coke production, dibenz[a,h]antracene, diesel engine exhaust, hairdressers and barbers, 4,4'-methylenbe bis(2-chloroaniline), mineral oils untreated and mildly treated, ortho-toluidine, painters and petroleum refining.

Table 5 identifies which agents in the CAREX Canada database have also been included by Siemiatycki et al (2004) as bladder carcinogens.

Table 7 - Bladder Carcinogens (Strong and Suggestive Evidence)

Carcinogen (Siemiatycki et al 2004)	**Captured on CAREX Canada Database?**
*4-aminobiphenyl[3]	✓
*Benzidine	✓
*2-naphthylamine	✓
Mineral oils, untreated and mildly treated	✓
Benz[a]anthracene	✓
Benzo[a]pyrene	✓
Dibenz[a,h]anthracene	✓
Diesel engine exhaust	✓
4,4'-methylene bis(2-chloroaniline) (MOCA)	✓
Benzidine-based dyes	✓
4-chloro-ortho-toluidine	No
Ortho-toluidine	No

Ten carcinogens identified as bladder carcinogens by Siemiatycki et al. (2004) are also included in the CAREX Canada database. However, the CAREX Canada database groups the following exposures under the umbrella of polycyclic aromatic hydrocarbons (PAHs): mineral oils, untreated and mildly treated, dibenz(a,h)anthracene, soots,benz(a)anthracene, shale oils, benzo(a)pyrene, creosotes, coke production, PAHs excluding environmental tobacco smoke, coal-tars, coal gasification and coal tar pitches.

[3] Asterisk indicates that the evidence for an association with bladder cancer was strong. Otherwise, the evidence for the remaining agents was suggestive as per Siemiatycki 2004.

In addition to the carcinogens identified above, based on the IARC classifications Siemiatycki et al. (2004) also identified carcinogenic occupations and industries. These occupations and industries have been identified as such because the evidence has shown there to be increased risks for the development of cancer; however, the specific carcinogens involved have yet to be identified. This presents a problem in the estimation of the proportion of bladder cancer in Ontario that is due to occupational exposure since the CAREX Canada database provides information on the number of workers exposed by carcinogen. In their assessment of occupations and industries entailing a risk of cancer, Siemiatycki et al. (2004) tried to identify the suspected carcinogenic substances involved. The majority of identified carcinogens are already included in Table 5-1 above. The following occupations and industries have been identified by Siemiatycki et al (2004) as involving an excess risk of bladder cancer:

Table 8 - Industries and Occupations with Excess Risks for Bladder Cancer

Occupation or Industry	Suspected Substance (Siemiatycki et al., 2004)	Substance captured on CAREX Canada Database?
Aluminum production	Pitch volatiles	✓
	Aromatic amines	✓ - specific aromatic amines included
Auramine manufacture	2-naphthylamine	✓
	auramine	No
	Other chemicals	Too broad
	pigments	Too broad
Boot and shoe manufacture and repair	Leather dust	No
	benzene	✓
	Other solvents	Too broad
Coal gasification	Coal tar	✓
	Coal-tar fumes	✓
	PAHs	✓
Coke production	Coal-tar fumes	✓
Hairdressers and barbers	Dyes (aromatic amines, amino-phenols with hydrogen peroxide)	Too broad
	solvents	Too broad
	propellants	Too broad
	aerosols	Too broad
Magenta manufacture	magenta	No

Occupation or Industry	Suspected Substance (Siemiatycki et al., 2004)	Substance captured on CAREX Canada Database?
	Ortho-toluidine	No
	4,4'-methylene bis(2-methylaniline)	✓
	Ortho-nitrotoluene	No
Painters	No suspected substances identified	No
Petroleum refining	PAHs	✓
Rubber industry	Aromatic amines	✓
	solvents	Too broad

Based on a combination of the listing by Siemiatycki et al. (2004) and the carcinogens that are included in the CAREX Canada database using Ontario-specific estimates, the bladder carcinogens identified as hazards to Ontario workers and which will be included in this analysis are: polycyclic aromatic hydrocarbons (PAHs), diesel exhaust, beta-naphthylamine, 4-aminobiphenyl, benzidine, and benzidine-based dyes. Due to the small number of workers exposed in Ontario to the latter four agents, these agents have been grouped into a larger group known as aromatic amines.

Table 9 – Nature of evidence for bladder carcinogens included

Bladder carcinogen	Nature of evidence IARC	Nature of evidence Siemiatycki et al (2004)
PAHs		
coal tars and pitches	1	suggestive
mineral oils, untreated and mildly treated	1	suggestive
benz[a]anthracene	2B	suggestive
benzo[a]pyrene	1	suggestive
dibenz[a,h]anthracene	2A	suggestive
Aromatic amine dyes		
4-aminobiphenyl	1	strong
benzidine	1	strong
Beta-naphthylamine	1	strong
Diesel engine exhaust	2A	suggestive
4,4'-methylene bis(2-chloroaniline)	1	suggestive

The CAREX Canada database definition of occupational exposure to PAH includes the following scenarios (Demers et al. 2007):

"Inhalatory exposure at work to PAHs with at least four aromatic rings (eg, benzo(a)pyrene, benz(a)anthracene, dibenz[a,h]anthracene) likely to exceed significantly the nonoccupational levels in urban air (usually <0.005 ug/m3 of benzo(a)pyrene). Includes coal tar pitch, coal tars, soots, creosotes, shale oils, and untreated/mildly treated mineral oils. Excludes environmental tobacco smoke (assessed separately) and bus/truck/van/taxi drivers exposed to engine exhaust (low exposure)".

The CAREX Canada database defines occupational exposure to diesel as:

"Inhalatory exposure at work to diesel engine exhaust likely to exceed significantly the nonoccupational background level in urban air (usually <0.6 mg/m3, often <0.1 mg/m3, measured as nitrogen dioxide)".

4.2 Number and Proportions of Ontario Workers Exposed to Bladder Carcinogens

To determine the number and proportion of Ontario workers exposed to bladder carcinogens, the proportion of the Ontario workforce within each industry sector was obtained from the CAREX Canada database. The CAREX Canada database contains Ontario-specific information on the number of employed persons within each industry sector based on the 2001 Census. Table 8 below shows the number and proportion of Ontario workers in 52 industrial sectors. The CAREX Canada database provides information for specific manufacturing sectors, but for ease of presentation 24 manufacturing sectors have been collapsed into an overall combined manufacturing industry below.

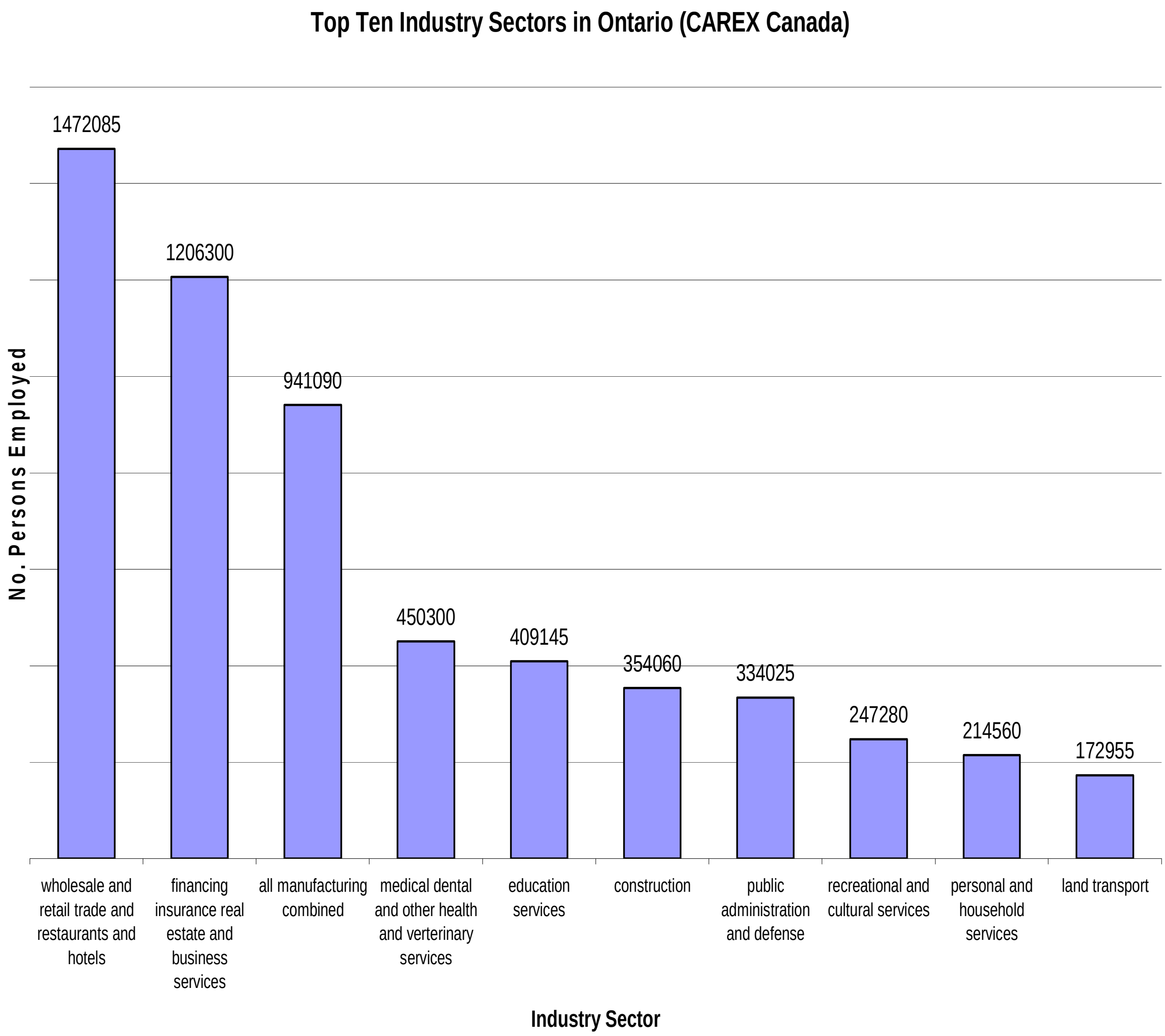
Table 10 – Proportion of Ontario workforce employed by industry sector

Industry	No. employed persons in Ontario (2001 Census)	Proportion of Ontario Workforce
Wholesale and retail trade and restaurants and hotels	1,472,085	0.226
Financing insurance real estate and business services	1,206,300	0.185
All manufacturing combined	941,090	0.144
Medical dental and other health and verterinary services	450,300	0.069
Education services	409,145	0.063
Construction	354,060	0.054
Public administration and defense	334,025	0.0513
Recreational and cultural services	247,280	0.038
Personal and household services	214,560	0.033
Land transport	172,955	0.026
Agriculture and hunting	121,810	0.019
Welfare institutions	121,560	0.019
Printing publishing and allied industries	94,370	0.014
Business professional and other organization	85,505	0.013
Communication	58,800	0.009

Industry	No. employed persons in Ontario (2001 Census)	Proportion of Ontario Workforce
Electricity gas and steam	43,360	0.007
Iron and steel basic industries	40,590	0.006
Services allied to transport	32,045	0.005
Air transport	31,090	0.005
Metal ore mining	13,265	0.002
Beverage industries	13,245	0.002
Forestry and logging	13,165	0.002
Non-ferrous metal basic industries	11,555	0.002
Sanitary and similar services	10,495	0.002
Other mining	8,700	0.001
Water works and supply	6,125	0.001
Water transport	2,855	<0.001
Fishing	1,110	<0.001
Crude pertoleum and natural gas production	915	<0.001
Coal mining	105	<0.001
TOTAL EMPLOYED PERSONS	6,512,465	1

Over half (55%) of Ontario's workforce is concentrated within three industry sectors: wholesale and retail trade and restaurants and hotels (23%), financing insurance real estate and business services (18%), and manufacturing (14%). Figure 2 below shows the ten industry sectors in Ontario with the greatest proportions of workers based on information compiled from the CAREX Canada database.

Figure 2 – Top Ten Ontario Industry Sectors (CAREX Canada)



The next step is to determine the proportion of workers in each industry sector potentially exposed to the selected bladder carcinogens. The CAREX Canada database contains Ontario-specific estimates based on the assessment of industrial hygienists and available Ontario-specific labour data. The following tables present the numbers and proportions of Ontario workers potentially exposed to PAHs, diesel exhaust and aromatic amines within each industry sector.

Table 11 – Number and proportion of Ontario workers potentially exposed to PAHs

Industry	**No. workers exposed to PAH**	**Proportion workers exposed within sector**
Wholesale and retail trade and restaurants and hotels	59,156	0.040
Personal and household services	14,942	0.070
Public administration and defense	11,254	0.034
Manufacture of transport equipment	5,109	0.026
Manufacture of fabricated metal products except machinery and equipment	4,963	0.049
Land transport	4,097	0.024
Manufacturing of machinery except electrical	2,784	0.037
Iron and steel basic industries	2,581	0.064
Medical dental and other health and verterinary services	1,973	0.004
Non-ferrous metal basic industries	1,515	0.131
Manufacture of plastic products not elsewhere classified	1,504	0.026
Financing insurance real estate and business services	1,391	0.001
Construction	1,334	0.004
Welfare institutions	696	0.006
Recreational and cultural services	597	0.002
Food manufacturing	559	0.006
Sanitary and similar services	536	0.051
Business professional and other organization	487	0.006
Air transport	454	0.015

Industry	No. workers exposed to PAH	Proportion workers exposed within sector
Metal ore mining	406	0.031
Manufacture of industrial chemicals	327	0.018
Education services	307	0.001
Agriculture and hunting	290	0.002
Manufacture of other non-metallic mineral products	273	0.018
Electricity gas and steam	247	0.006
Manufacture of glass and glass products	245	0.034
Forestry and logging	220	0.017
Other mining	160	0.018
Printing publishing and allied industries	155	0.002
Manufacture of wood and wood and cork products, except furniture	148	0.004
Manufacture of china pottery and earthenware	134	0.043
Communication	130	0.002
Manufacture of paper and paper products	129	0.004
Services allied to transport	118	0.004
Manufacture of electrical machinery apparatus appliances and supplies	103	0.001
Water transport	64	0.022
Manufacture of miscellaneous products of petroleum and coal	54	0.009
Manufacture of instruments photographic and optical goods	47	0.002
Manufacture of rubber products	44	0.004
Other manufacturing industries	41	0.001
Beverage industries	26	0.002
Manufacture of textiles	26	0.001
Manufacture of wearing apparel except footwear	23	0.001
Water works and supply	21	0.003
Crude pertoleum and natural gas production	12	0.013
Fishing	8	0.007
Manufacture of furniture and fixtures except primary metal	7	<0.001
TOTAL WORKERS EXPOSED to PAHs	119,779	**Total % ON Workers Exposed** ~ 0.02 **to PAHs**

According to the CAREX Canada database, the total number of workers potentially exposed to PAHs in Ontario is 119,779. The industries where the most workers are exposed to PAHs in Ontario are: wholesale and retail trade and restaurants and hotels (59,156 workers), all manufacturing industries combined (16,520 workers), personal and household services (14,942 workers), and public administration and defense (11,254 workers). The industry in which the greatest proportion of workers is exposed to PAHs is the basic non-ferrous metal industry with 13% of workers exposed.

Figure 3 – Ten Industry Sectors in Ontario with the most workers potentially exposed to PAHs

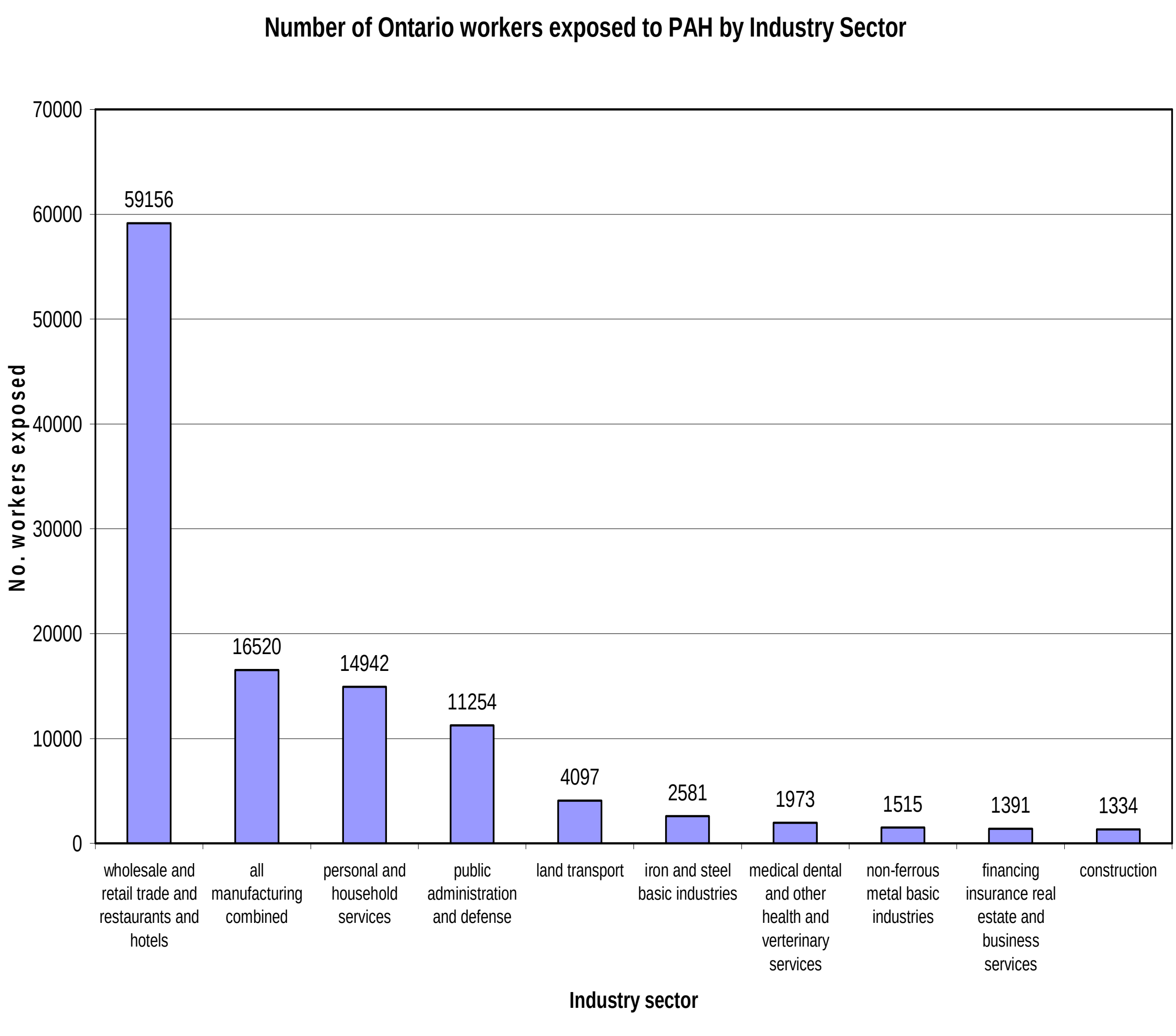


Table 12 - Number and proportion of Ontario workers potentially exposed to diesel exhaust

Industry	No. workers exposed to Diesel Exhaust	Proportion workers exposed
Land transport	94,652	0.547
Wholesale and retail trade and restaurants and hotels	26,124	0.018
Construction	24,247	0.068
Public administration and defense	15,215	0.046
Personal and household services	8,592	0.040
Communication	7,902	0.134
Financing insurance real estate and business services	7,532	0.006
Forestry and logging	6,203	0.471
Sanitary and similar services	3,439	0.328
Metal ore mining	3,001	0.226
Manufacture of transport equipment	2,571	0.013
Food manufacturing	2,560	0.028
Manufacture of other non-metallic mineral products	2,550	0.168
Other mining	2,512	0.289
Medical dental and other health and veterinary services	2,399	0.005
Manufacture of wood and wood and cork products, except furniture	2,120	0.060
Recreational and cultural services	1,584	0.006
Agriculture and hunting	1,551	0.013
Manufacture of fabricated metal products except machinery and equipment	1,422	0.014
Non-ferrous metal basic industries	1,322	0.114
Iron and steel basic industries	1,027	0.025
Beverage industries	995	0.075
Printing publishing and allied industries	979	0.010
Manufacturing of machinery except electrical	899	0.012
Manufacture of paper and paper products	882	0.024
Water works and supply	667	0.109
Services allied to transport	650	0.020
Education services	613	0.001
Water transport	489	0.171

Industry	No. workers exposed to Diesel Exhaust	Proportion workers exposed
Business professional and other organization	414	0.005
Manufacture of plastic products not elsewhere classified	385	0.007
Air transport	385	0.012
Manufacture of industrial chemicals	335	0.019
Manufacture of furniture and fixtures except primary metal	333	0.007
Welfare institutions	284	0.002
Other manufacturing industries	271	0.009
Electricity gas and steam	268	0.006
Manufacture of electrical machinery apparatus appliances and supplies	205	0.002
Manufacture of other chemical products	176	0.005
Manufacture of wearing apparel except footwear	143	0.004
Coal mining	139	undefined
Manufacture of glass and glass products	134	0.019
Manufacture of textiles	100	0.006
Manufacture of instruments photographic and optical goods	90	0.004
Manufacture of rubber products	72	0.006
Manufacture of china pottery and earthenware	50	0.016
Manufacture of miscellaneous products of petroleum and coal	45	0.007
Crude pertoleum and natural gas production	23	0.025
Tobacco manufacture	18	0.010
Fishing	10	0.009
Manufacture of footwear	10	0.004
TOTAL WORKERS EXPOSED to DIESEL EXHAUST	228,719	**Total % ON Workers Exposed** ~ 0.04 **to Diesel Exhaust**

The total number of workers potentially exposed to diesel exhaust in Ontario is 228,719. The industries where the most workers are exposed to diesel exhaust in Ontario are: land transport (94,652 workers), wholesale and retail trade and restaurants and hotels (26,124 workers), construction (24,247 workers), and all manufacturing sectors combined (15,371 workers). The industry in which the greatest proportion of workers is exposed to diesel exhaust is the land transport industry, with 55% of workers exposed.

Figure 4 – Ten Industry Sectors on Ontario with the most workers potentially exposed to diesel exhaust

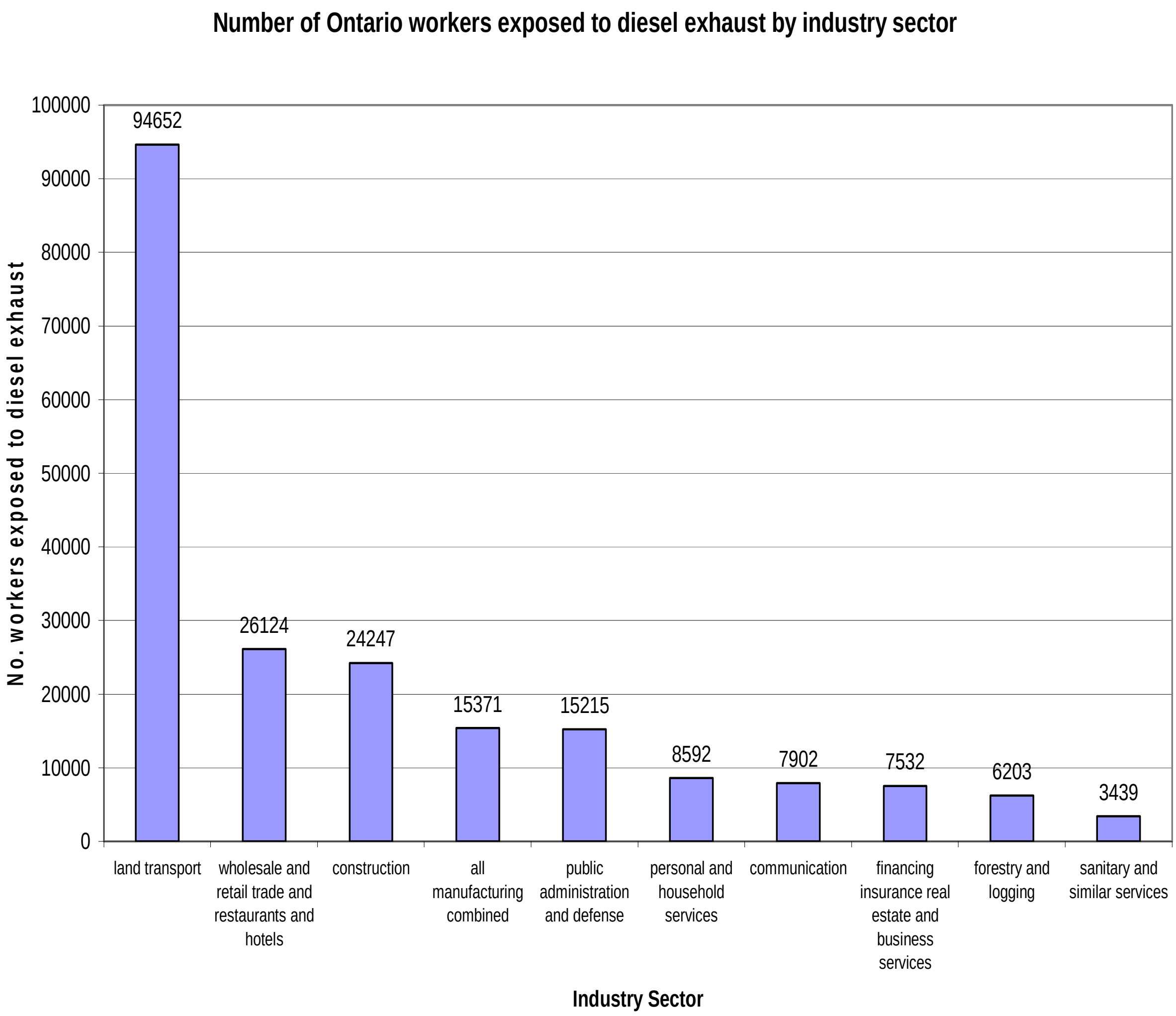


Table 13 shows the number and proportion of Ontario workers potentially exposed to aromatic amines.

Table 13 - Number and Proportion of Ontario Workers Potentially Exposed to Aromatic Amines

Carcinogen	No. workers exposed in Ontario	Proportion of Ontario workforce exposed
4-aminobiphenyl	20 (nominal estimate)	$3.07\ x10^{-6}$
Benzidine	10 (nominal estimate)	$1.50\ x10^{-6}$
2-naphthylamine	81 (Finland & United States)	$1.24\ x10^{-5}$
Benzidine-based dyes	10 (nominal estimate)	$1.50\ x10^{-6}$
4,4'-methylene bis(2-chloroaniline) (MOCA)	negligible	N/A

Very few workers were estimated to be exposed to 4-aminobiophenyl, benzidine, and benzidine-based dyes. The estimate for exposure to beta-naphtylamine was based on Finnish and US estimates. The estimates for workers exposed to PAHs and diesel exhaust were based on Ontario data. For 4-aminobiphenyl, a nominal estimate was made. The hygienists assessing this exposure in Ontario were unaware of any data specifically on 4-aminobiphenyl. Industry Canada's Trade Data Online database groups 4-aminobiphenyl under aromatic monoamines not elsewhere specified. Therefore, it is feasible that 4-aminbiohenyl is used in commercial and non-commercial research settings in Ontario, and a nominal estimate of 20 exposed persons was made.

A nominal estimate was also made for benzidine and benzidine-based dyes. Benzidine and benzidine dihydrochloride are listed on the List of Prohibited Toxic Substances under the Canadian Environmental Protection Act, 1999. However, there are potential exposure scenarios permitting limited use in Canada, such as in a laboratory for scientific research. The Chemical Control Branch of Environment Canada, which does not currently collect emissions data for these agents, states that for benzidine and benzidine dihydrochloride emission data should be collected for the National Pollutant Release Inventory database. Therefore, it may be possible for some workers to be exposed to emissions, and a nominal estimate of 10 exposed workers in Ontario was made.

To estimate the proportion of the Ontario workforce that is exposed to bladder carcinogens, the proportion of the workforce in each industry sector is multiplied by the proportion of workers in that sector who are exposed to the carcinogen. Table 14 below shows the proportion of the workforce exposed to bladder carcinogens. All the proportions are summed to estimate the proportion of the total workforce exposed to bladder carcinogens.

Table 14 – Number and Proportion of Ontario workforce exposed to bladder carcinogens

Bladder carcinogen	No. ON workers exposed	Proportion ON workforce exposed
PAH	119,848	0.018
diesel exhaust	228,719	0.035
4-aminobiphenyl	20	$3.07 x 10^{-6}$
benzidine	10	$1.50 x 10^{-6}$
benzidine-based dyes	10	$1.50 x 10^{-6}$
2-naphthylamine	81	$1.24 x 10^{-5}$
4,4'methylense bis(2-chloroaniline) (MOCA)	negligible	N/A
TOTAL	348,688	0.054

In Ontario, an estimated 348, 688 workers are exposed to bladder carcinogens. The proportion of the workforce currently exposed to “above background” levels of bladder carcinogens is approximately 5.4%.

Using the method endorsed by the World Health Organization (Driscoll et al., 2004), the proportion of the workforce ever exposed to bladder carcinogens was calculated. A workforce turnover factor of four and a partitioning factor of 0.1 (high-level exposure) and 0.9 (low-level exposure) was used to estimate the proportion of Ontario workers who are exposed to high-levels and low-levels of bladder carcinogens.

Table 15 – Proportion of Ontario workforce and population ever/never exposed to bladder carcinogens

Bladder carcinogen	Proportion of workforce ever exposed	Proportion of population never exposed
PAH	0.074	0.938
diesel exhaust	0.140	0.882
2-naphthylamine	4.98E-05	0.999
aromatic amines	2.46E-05	0.999

Table 16 – Proportion of Ontario workforce and population exposed to high levels of bladder carcinogens

Bladder carcinogen	Proportion of workforce ever exposed high level	Proportion of population ever exposed high level
PAH	0.007	0.006
diesel exhaust	0.014	0.012
2-naphthylamine	4.98E-06	4.18E-06
aromatic amines	2.46E-06	2.06E-06

Table 17 - Proportion of Ontario workforce and population exposed to low levels of bladder carcinogens

Bladder carcinogen	Proportion of workforce ever exposed low level	Proportion of population ever exposed low level
PAH	0.066	0.056
diesel exhaust	0.126	0.106
2-naphthylamine	4.48E-05	3.76E-05
aromatic amines	2.21E-05	1.86E-05

The economically active population (0.84) was calculated as the number of employed persons in Ontario according to the CAREX Canada database (6, 512, 465) divided by the number of working-aged people in Ontario aged 15 to 64 years according to the 2001 Census (7, 705, 140). Multiplying the economically active population with the proportion of the workforce ever exposed to bladder carcinogens at high- and low-levels yields an estimate of the proportion of the Ontario population ever exposed at high- and low-levels.

4.3 Risk estimates to be used in PAR calculation

4.3.1 Pooled risk estimates

Bladder cancer and occupational exposure to PAH

In the literature search, seven studies met the inclusion/exclusion criteria and reported results for bladder cancer incidence or mortality and exposure to PAHs. Results of these studies are shown in the tables found in Appendix C and results of the pooled analysis are shown in Figure 5. Of the seven studies only Moulin et al. (2000) reported on bladder cancer mortality (SMR 1.77, 95% CI 0.71 to 3.64). Since there was only a single study reporting on bladder cancer mortality associated with exposure to PAHs, this SMR is the estimate that will be used in the calculation of PAR for bladder cancer mortality.

Of the six studies reporting on bladder cancer incidence after PAH exposure, two case-control studies reported statistically significant increased risks of 1.97 (95% CI 1.10 to 3.51) (Tremblay et al., 1995) and 1.6 (95% CI 1.1 to 2.3) (Pesch et al., 2000). The remaining four studies (3 cohort studies, 1 case-control study) (Zeegers et al., 2001; Romundstad et al., 2000a; Romundstad et al., 2000b; Clavel et al., 1994) reported slightly increased risks that were not statistically significant ranging from 1.18 (95% CI 0.62 to 2.24) to 1.37 (95% CI 0.96 to 1.90). The summary risk estimate calculated was statistically significant at 1.40 (95% CI 1.19 to 1.63) and did not show evidence of heterogeneity.

The study by Zeegers et al. (2001) was a population based case cohort study in the Netherlands which was conducted among 58, 279 men. A case-cohort was assembled consisting of 532 cases and 1, 630 subcohort members. The overall cohort of men followed was large. However, the number of cases of bladder cancer ascertained was small. To increase the precision of the measurement, a larger number of subcohort members were included. A strength of this study was the exposure assessment, in which the probability of exposure to PAHs was assessed by experts in occupational epidemiology and hygiene. However, the assessment was based on occupational titles and no quantitative measurements were available. No dose-response trend was found for increasing levels of PAH exposure.

The study by Romundstad et al. (2000a) investigated the association between bladder cancer and exposure to PAHs in a cohort of 1790 aluminum production workers. A quantitative estimate of PAH exposure was based on personal measurements, stationary measurements and descriptions of processes over time. An attempt was made to account for the confounding effects of smoking through information obtained from company medical files and the recollection of three long-term employees. Thus, the smoking data was subject to recall bias. This study may have been too small to detect statistically significant increased risk for bladder cancer. Although no test for trend was reported, there did not appear to be increased risk for bladder cancer with increasing cumulative exposure to PAHs.

Clavel et al. (1994) conducted a hospital based case-control study in France. The controls were patients admitted to the hospitals for diseases other than cancer, haematuria and work accidents. By excluding potential “work-related” diseases, the control subjects’ diseases were less likely to be associated with occupational exposure to PAHs and the comparison group was more likely to be representative of the healthy population with respect to occupational exposures. Only a small number of cases and controls were included and this was further restricted to males, further reducing the sample size. Due to the small sample size, it is possible that this study did not have enough power to detect an effect. A strength of this study was the exposure assessment in which occupational exposures were evaluated by industrial health experts who were blind to case and control status of the patients. The investigators reported a statistically significant dose-response trend for increasing levels of PAH exposure, which remained statistically significant after adjustment for smoking.

Romundstad et al. (2000b) conducted a cohort study of 5,627 men employed in two Norwegian aluminum reduction plants. Quantitative estimates of exposure to PAHs were based on statistical modeling of personal measurements, stationary measurements and process data. This was a strength of the study. The workers’ age distribution was not provided. If the majority of the workers were less than 55 years, it is possible that the length of follow-up was not long enough to account for the long latency of bladder cancer. However, this is impossible to state with any certainty since the age distribution of the cohort was not provided. This is a study weakness. No clear dose-response trend was present.

Pesch et al. (2000) conducted a population based case-control study. This was a large multicentre study which identified 1035 cases of bladder cancer. To increase the precision of the estimate 4298 population controls were included. Exposure assessment was based on job titles and job tasks obtained in a structured questionnaire. The workers were asked to self-assess exposure by estimating the average working hours per day per exposure. The exposure assessment was prone to recall bias. A job-exposure matrix and a job task-exposure matrix were used to assess the probability and intensity of exposure to PAHs. No dose-response trends were included in this study

A nested case-control study was conducted by Tremblay et al. (1995). From a cohort of 16, 0000 males employed at an aluminum plant in Quebec, 123 cases of bladder cancer were found and matched to 414 controls obtained from a random sample of cohort members. The sample size was small and the investigators attempted to address this by matching three controls per case. Detailed occupational histories were available from company records for all subjects. A job-exposure matrix was constructed by a company industrial hygienist. The estimation of exposure was also based on personal sampling carried out since 1972 and stationary sampling which was carried out since the 1950s. This exposure assessment was a strength of the study as it was not prone to recall bias. Furthermore, smoking status was obtained from company medical records and abstracted by a medical record technician who was blind to the disease status of the worker. Although tests for trend were not reported, there was evidence of increasing risk for bladder cancer associated with increasing cumulative exposure to coal tar pitch volatiles.

Figure 5 – Forest Plot: PAH exposure

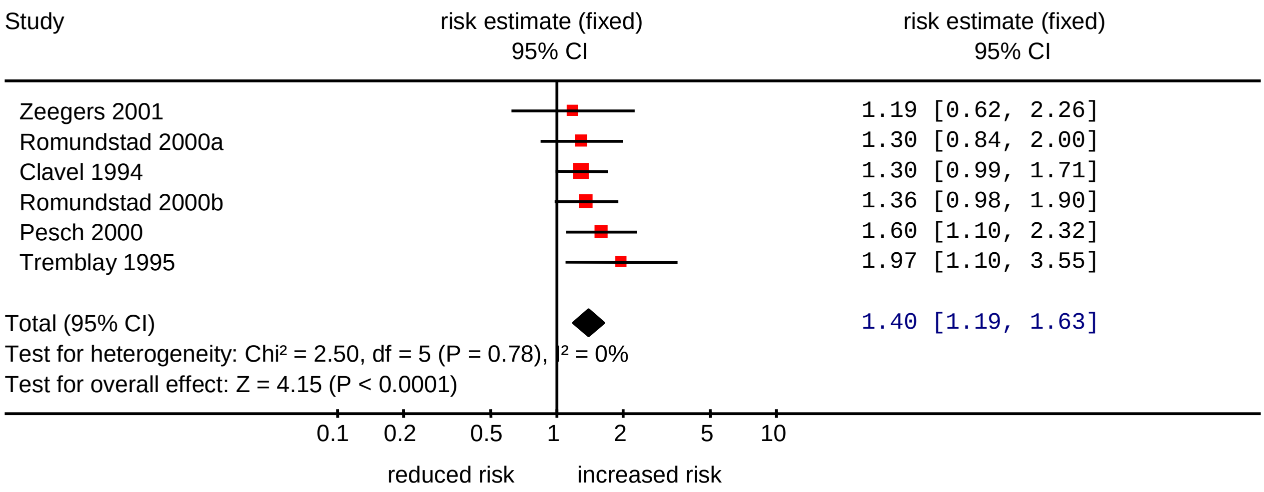
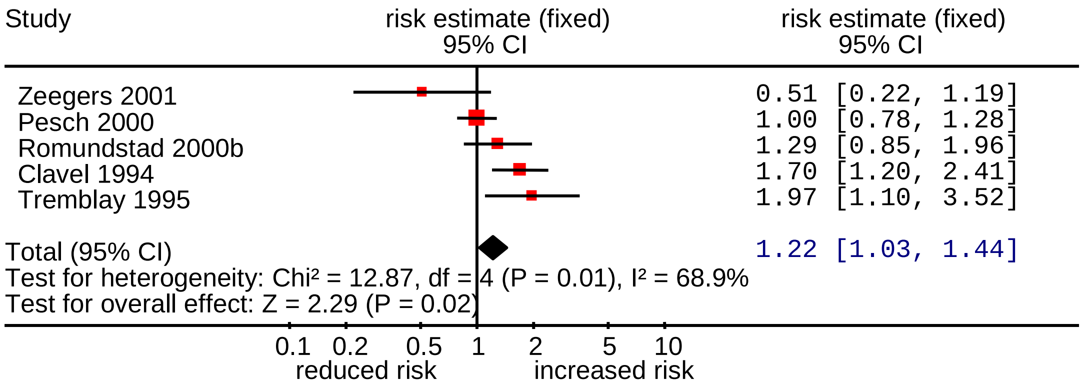


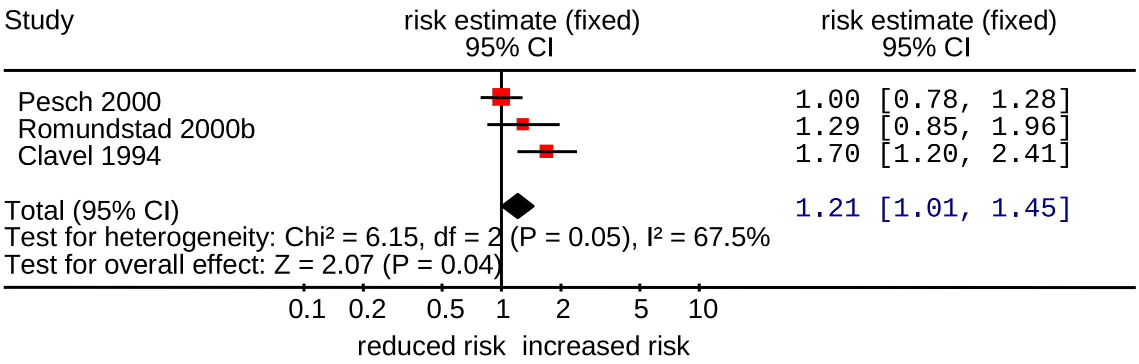
Figure 6 – Forest Plot: Low-level PAH exposure



Five of the seven studies on bladder cancer and occupational exposure to PAH reported qualitative or quantitative values for low PAH exposure. Two studies did not find increased risks of bladder cancer after low-level exposure to PAH (Zeegers et al., 2001; Pesch et al., 2000). The three remaining studies did find increased risks for bladder cancer after low-level PAH exposure. Two case-control studies reported statistically significant increased risks of 1.70 (95% CI 1.20 to 2.41) (Clavel et al., 1994) and 1.97 (95% CI 1.10 to 3.52) (Tremblay et al., 1995). The remaining study reported a non-significant increased risk of 1.29 (95% CI 0.85 to 1.96) (Romundstad et al., 2000b). The summary risk estimate calculated was statistically significant 1.22 (95% CI 1.03 to 1.44). However, the studies were identified as heterogeneous by the test of heterogeneity.

To account for the heterogeneity, the studies with the highest (Tremblay et al., 1995) and lowest (Zeegers et al., 2001) risk estimates were deleted. However, the studies were still heterogeneous. It is not, therefore, appropriate to pool the results of these studies. The decision was made to use the risk estimate (1.97, 95% CI 1.10 to 3.51) from the study with the highest exposure quality rating (EQ=5) and having the greatest number of subjects included in the analysis (16,000) (Tremblay et al., 1995) among the studies that included levels of exposure to PAH in their analyses.

Figure 7 – Forest Plot: Low-level PAH exposure – deletion of highest and lowest risk estimates



Bladder cancer and occupational exposure to Diesel Exhaust

In the literature search, seven studies met the inclusion/exclusion criteria and reported results for bladder cancer incidence associated with exposure to diesel exhaust. Results of these studies are shown in the tables in Appendix C and results of the pooled analysis are shown in Figure 8. None of the seven studies reported on bladder cancer mortality: all seven reported on bladder cancer incidence.

Of the seven studies reporting on bladder cancer incidence associated with diesel exhaust exposure, one case-control study reported a statistically significant increased risk of 1.5 (95% CI 1.10 to 2.0) (Silverman et al., 1986). Five studies (1 cohort studies, 4 case-control studies) (Zeegers et al., 2001; Kellen et al., 2007; Soll-Johanning et al., 2003; Steineck et al., 1990; Smith et al., 1985) reported increased risks that were not statistically significant ranging from 1.17 (95% CI 0.74 to 1.84) to 1.70 (95% CI 0.90 to 3.30). One cohort study reported a risk approaching unity: 0.97 (95% CI 0.77 to 1.21) (Guo et al., 2004). The summary risk estimate calculated was 1.21 (95% CI 1.05 to 1.39) and demonstrated very little heterogeneity.

Guo et al. (2004) conducted a cohort study of all economically active Finns born between 1906 and 1945 who were followed-up from 1971 to 1995. The sample size was large and comprised of 667, 121 males and 513, 110 females. Exposure estimates were derived from a Finnish job-exposure matrix (FINJEM), which was developed based on exposure measurements, hazard surveys and the judgment of 20 Finnish occupational hygienists. A limitation of this study is that the average level of exposure to diesel exhaust captured in FINJEM was based on the concentration of nitrogen dioxide in the air as an indicator of diesel exhaust exposure. Diesel exhaust is a complex mixture of gaseous and particulate matter and basing exposure estimates on a single indicator may underestimate levels of exposure. There was no evidence for increasing risk of bladder cancer associated with increasing levels of diesel exhaust exposure.

The study by Zeegers et al. (2001) was a population based case cohort study in the Netherlands which was conducted among 58, 279 men. The details of this study are described in the section above on exposure to PAHs. Since bladder cancer risk estimates were also provided for diesel exhaust exposure, this study was included in this section as well.

Smith et al. (1985) conducted a population based case-control study in the United States. The sample size was relatively large, with 2,108 cases and 4,046 controls. Exposure data was obtained through face-to-face interviews using a structured questionnaire which captured information on lifetime history of artificial sweeteners, smoking, caffeine intake, and occupation. A limitation of this study is that occupation as an auto or truck mechanic for at least six months in their lifetime was considered the "exposed" group. The subjects were also grouped in a "chemically related" exposure group if they worked in occupations or industries with similar chemical exposures as auto and truck mechanics. This presents problem in exposure misclassification, as it is possible that those classified as "exposed" using such a broad definition of exposure may not be in fact exposed to any of the suspected chemicals being studied, resulting in an overestimation of the relevant exposure.

Soll-Johanning et al. (2003) conducted a nested case-control study of 84 bladder cancer cases, and 255 controls among a cohort of 18, 174 bus drivers and tramway employees. This represents a small sample size, one which may not have the power to detect a statistically significant effect. A strength of this study is that exposure information was obtained from employment records in addition to structured interviews, thus reducing the occurrence of recall bias. The investigators also took into account exposure to air pollution on the various bus routes. There was some evidence of an increased risk for bladder cancer with increasing time as a bus driver; however no tests for trend were reported.

A population based case-control study was conducted by Silverman et al. (1986), which included 1, 909 cases and 3, 569 controls. This is a relatively large sample size. The authors frequency matched approximately two controls per case to increase the precision of their measurement. A limitation in the study methods is that exposure was assessed based on “ever’ or “usually” employed in various motor exhaust-related occupations. This is a broad definition of exposure that may lead to misclassification of exposure, leading to an overestimated risk of bladder cancer. A statistically significant dose-response trend was observed for truck drivers and deliverymen with increasing duration of employment.

Kellen et al. (2007) conducted a population based case-control study which included 200 cases and 385 controls. This small sample size may not have the power to detect statistically significant risks for bladder cancer. A strength in study methodology was the way in which exposure data was collected. Trained interviewers conducted face-to-face interviews collecting information on medical history, lifetime smoking history, family history of bladder cancer, 20-year residential history, food frequency, and lifetime occupational history. Occupational exposure to diesel exhaust was blindly coded by two occupational hygienists. Tests for trend were conducted and no dose-response trend was evident for increasing levels of diesel exposure.

Steineck et al. (1990) conducted a population based case-control study which included 256 cases and 287 controls. This is a small sample size, which may not have the power to detect statistically significant effects. A strength of this study was the exposure assessment. Questionnaires were mailed out and collected information on occupational history. An occupational hygienist, who was unaware of case-control status, classified subjects as exposed or unexposed to 38 different agents. There was evidence of increased bladder cancer risk associated with increasing levels of annual does, although no test for trend was reported.

Figure 8 – Forest Plot: Diesel exposure

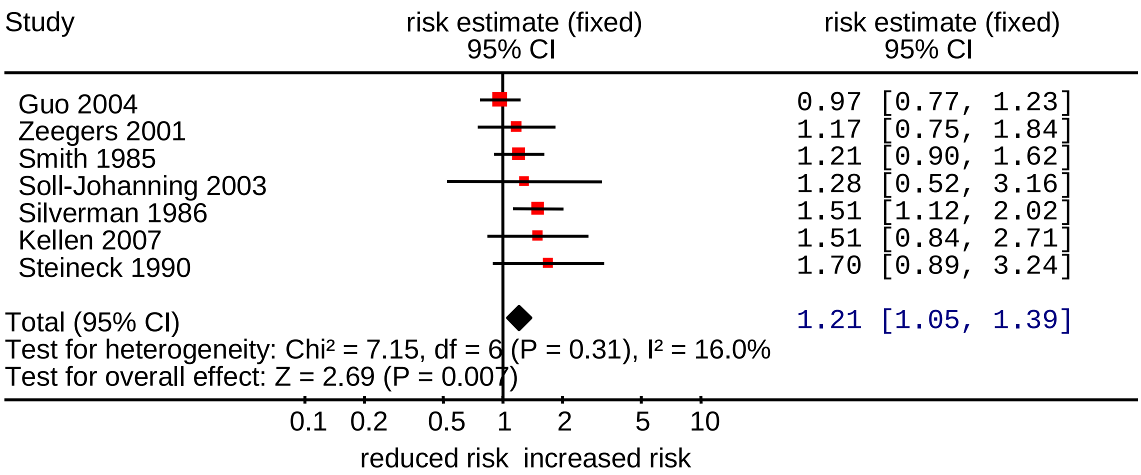
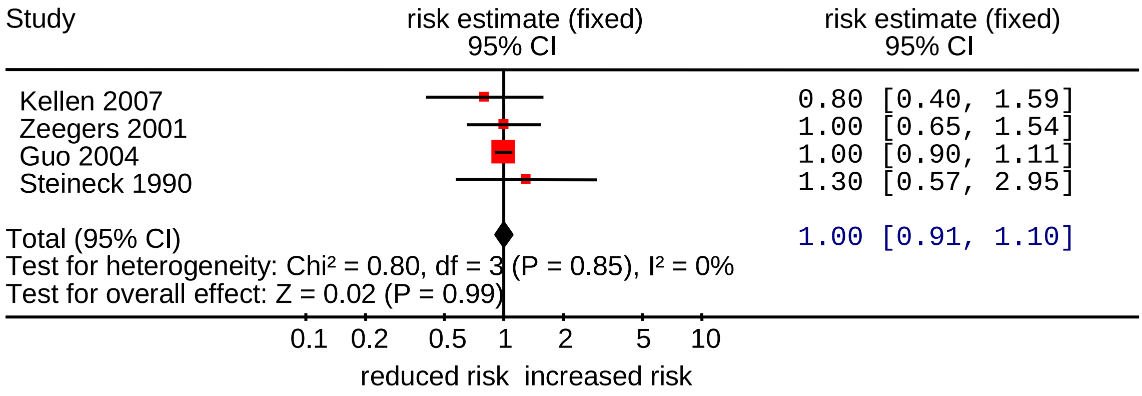


Figure 9 – Forest Plot: Low-level diesel exposure



Four of the seven studies on bladder cancer and occupational exposure to diesel exhaust included qualitative or quantitative analyses by level of diesel exhaust exposure. Only one of the four studies found an increased risk for bladder cancer associated with low-level diesel exhaust exposure, and this lacked statistical significance. The summary risk estimate was 1.00 (95% CI 0.91 to 1.10).

Bladder cancer and occupational exposure to Aromatic Amines

In the literature search, seven studies met the inclusion/exclusion criteria and reported results for bladder cancer incidence associated with exposure to aromatic amines as a group of exposures. Results of these studies are shown in the tables in Appendix C and results of the pooled analysis are shown in Figure 10. None of the seven studies reported on bladder cancer mortality: all reported on bladder cancer incidence.

Of the seven studies reporting on bladder cancer incidence associated with aromatic amine exposure, all studies with the exception of one cohort study reported statistically significant increased risks ranging from 2.60 (95% CI 1.84 to 3.66) to 8.8 (95% CI 3.3 to 17.1) (Outellet-Hellstron et al., 1996; Bonassi et al., 1989; Boyko et al., 1985; Kellen et al., 2007; Schulte et al., 1986; Vineis et al., 1987). The remaining study reported a non-statistically significant increased risk of 1.36 (95% CI 0.42 to 4.35). The summary risk estimate calculated was 3.21 (95% CI 2.52 to 4.09). However, the studies were determined to be heterogeneous.

The study by Zeegers et al. (2001) also included the risk for bladder cancer associated with exposure to aromatic amines. A description of study strengths and limitations can be found in the section on bladder cancer and occupational exposure to PAHs.

Boyko et al. (1985) conducted a hospital based case-control study, 932 cases and 1457 controls were included. Subjects were classified as chemical dye workers or non-chemical dye workers based on information collected in a face-to-face interview. A limitation of this study was that although aromatic amine exposure is highly prevalent in dye manufacturing, exposures were only assessed at the level of occupation, and no exposure measurements were estimated or obtained.

A hospital based case-control study with 461 male cases and 566 controls was carried out by Vineis and Esteve (1987). Exposure data was obtained by a trained interviewer using a standard questionnaire. Information was collected on history of smoking and lifetime occupational history. A limitation of this study is that only exposure to cigarette smoke and occupational exposure in the rubber industry or in the dyestuff production was considered. Other bladder cancer risk factors were not accounted for, thus it is impossible to assess whether the increased risk for bladder cancer observed is due to exposure to aromatic amines or confounded by other bladder cancer risk factors such as genetic or dietary factors.

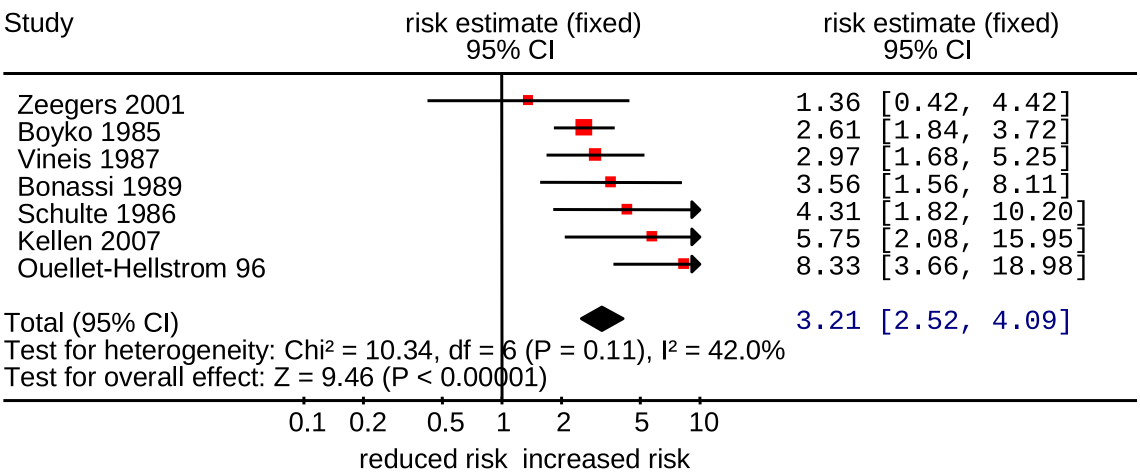
Bonassi et al. (1989) conducted a population based case-control study between 1972 and 1982. 121 cases and 342 controls were included. This is a small sample size and the study may not have enough power to detect a statistically significant effect. Exposure data was obtained through a standard questionnaire administered by trained interviewers. Subjects were classified into occupational categories which were identified *a priori*. In addition, a job-exposure matrix was constructed to assess potential lifetime exposure to aromatic amines.

Schulte et al. (1986) conducted a nested case-control study among a cohort of workers 1, 385 occupationally exposed to aromatic amines in a dye-intermediary production plant. There were 13 cases of bladder cancer and the remaining 1372 workers in the cohort comprised the control group. It is possible that the control group or the "non-cases" experienced the same occupational exposures as the cases, and therefore was not a good comparison group.

The study by Kellen et al. (2007) also included the risk for bladder cancer associated with exposure to aromatic amines. A description of study strengths and limitations can be found in the section on bladder cancer and occupational exposure to diesel exhaust.

A cohort study on the incidence of bladder cancer in a cohort of 700 chemical plant workers was undertaken by Ouellet-Hellstrom et al. (1996). Work histories and exposure data was obtained form a corporate database and personnel records. A strength of this study was that an exposure assessment committee of former and current workers who were knowledgeable about work processes developed an exposure score for each job title. Work histories were also obtained through a mailed survey.

Figure 10 – Forest Plot: Aromatic Amine Exposure



To account for the heterogeneity, the studies with the highest (Ouellet-Hellstrom et al., 1996) and lowest (Zeegers et al., 2001) risk estimates were deleted, thus reducing the I^2 statistic to 0%. The studies with the highest and lowest risk estimates were both cohort studies, leaving only case-control studies as contributing to the pooled risk estimate. The resulting summary risk estimate was statistically significant at 3.05 (95% CI 2.35 to 3.95).

Figure 11 – Forest Plot: Aromatic amine exposure – deletion of highest and lowest risk estimates

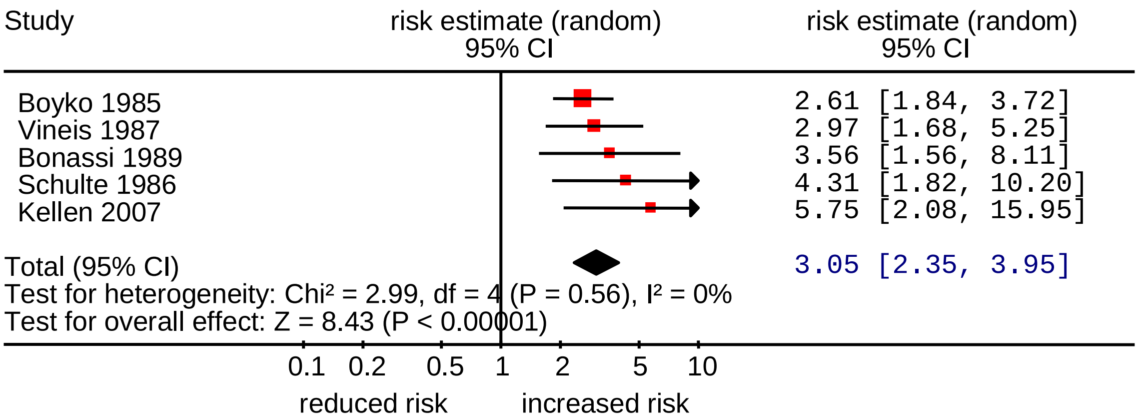


Figure 12 – Forest Plot: Low-level aromatic amine exposure

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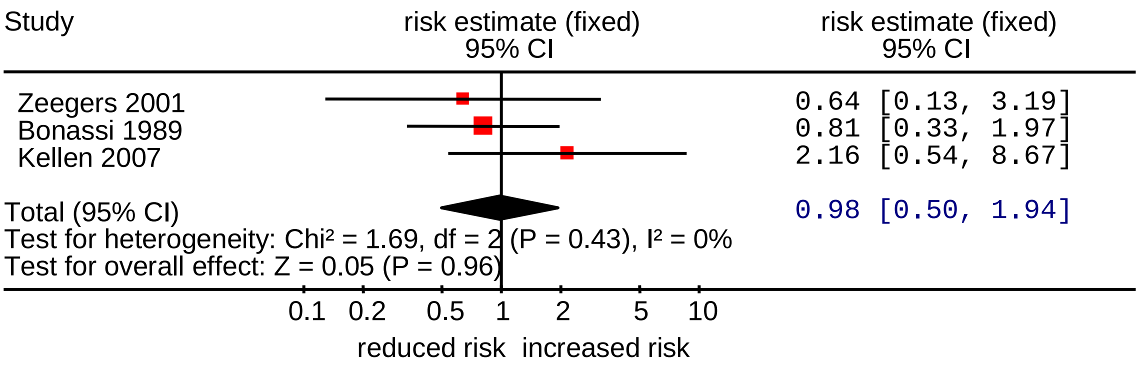
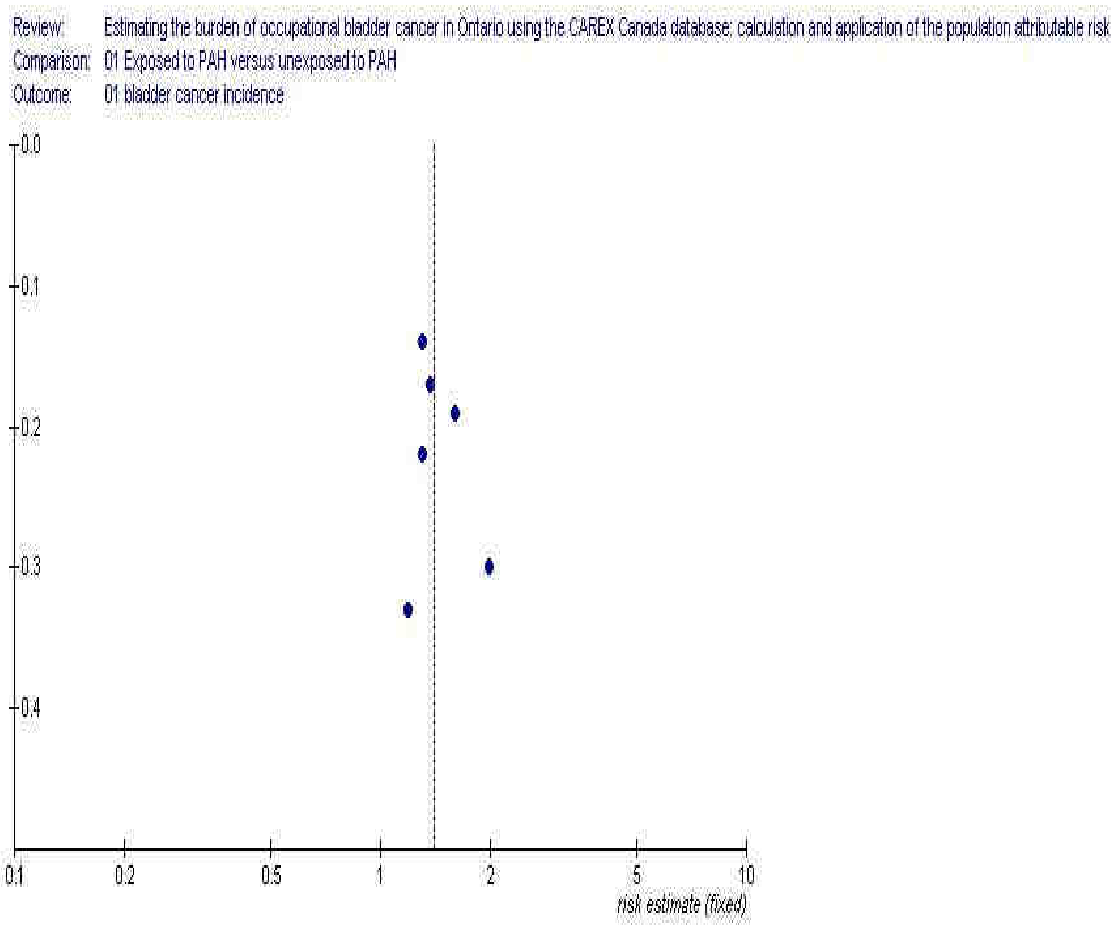


Three of the seven studies on bladder cancer and occupational aromatic amine exposure included analyses by level of exposure. Only one study found an increased risk for bladder cancer after low aromatic amine exposure lacking statistical significance. The summary risk estimate for low-level exposure to aromatic amines was 0.98 (95% CI 0.50 to 1.94).

Publication Bias

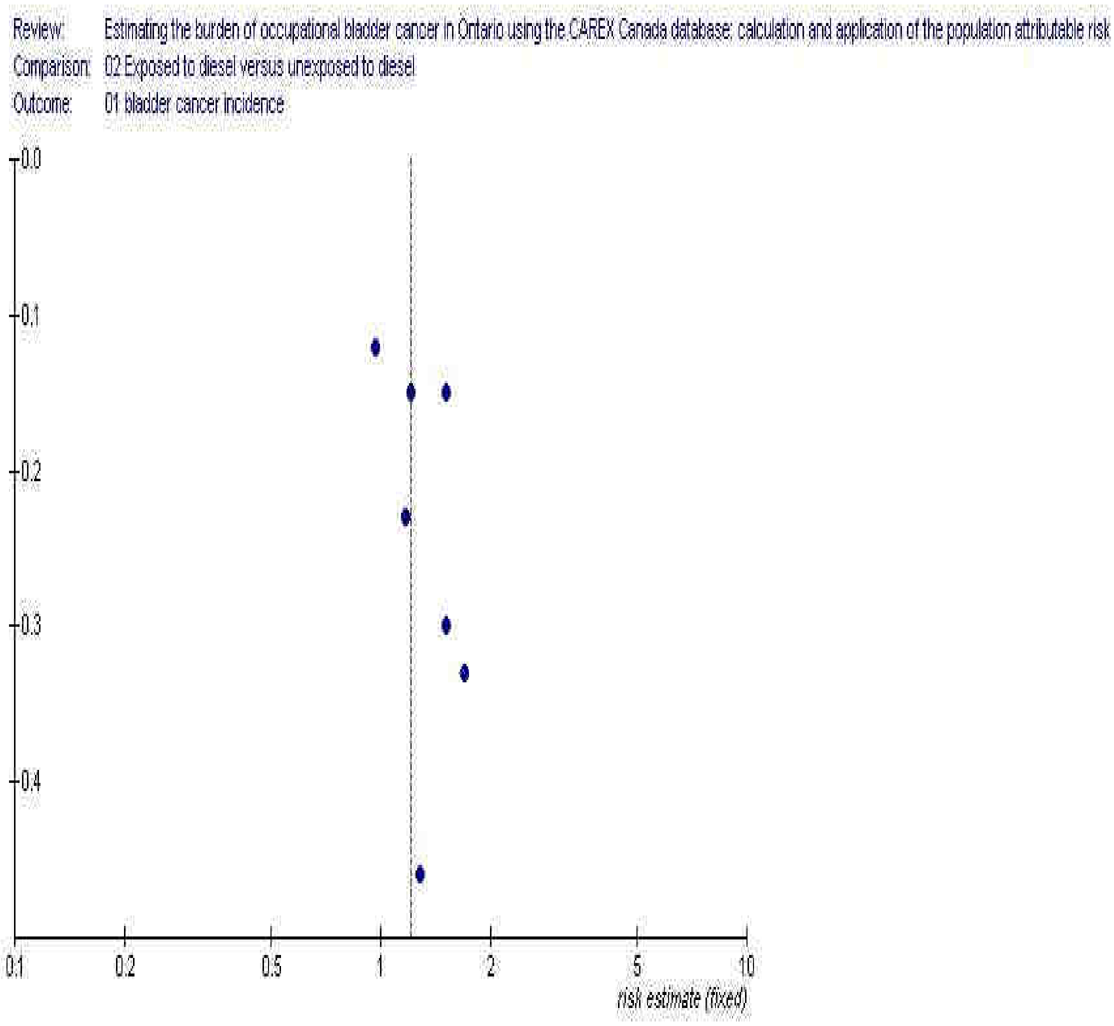
The funnel plot for the studies included on the risk of bladder cancer and occupational exposure to PAH appears to be fairly symmetrical, an indication that publication bias is not present. Although the funnel plot is missing the wide scatter of points toward the bottom of the funnel, this is due to the *a priori* inclusion criteria that excluded any studies with a low exposure quality rating. The smaller studies with poor methodological design were purposely excluded from the calculation of the summary risk estimate.

Figure 13 – Funnel Plot: PAH exposure



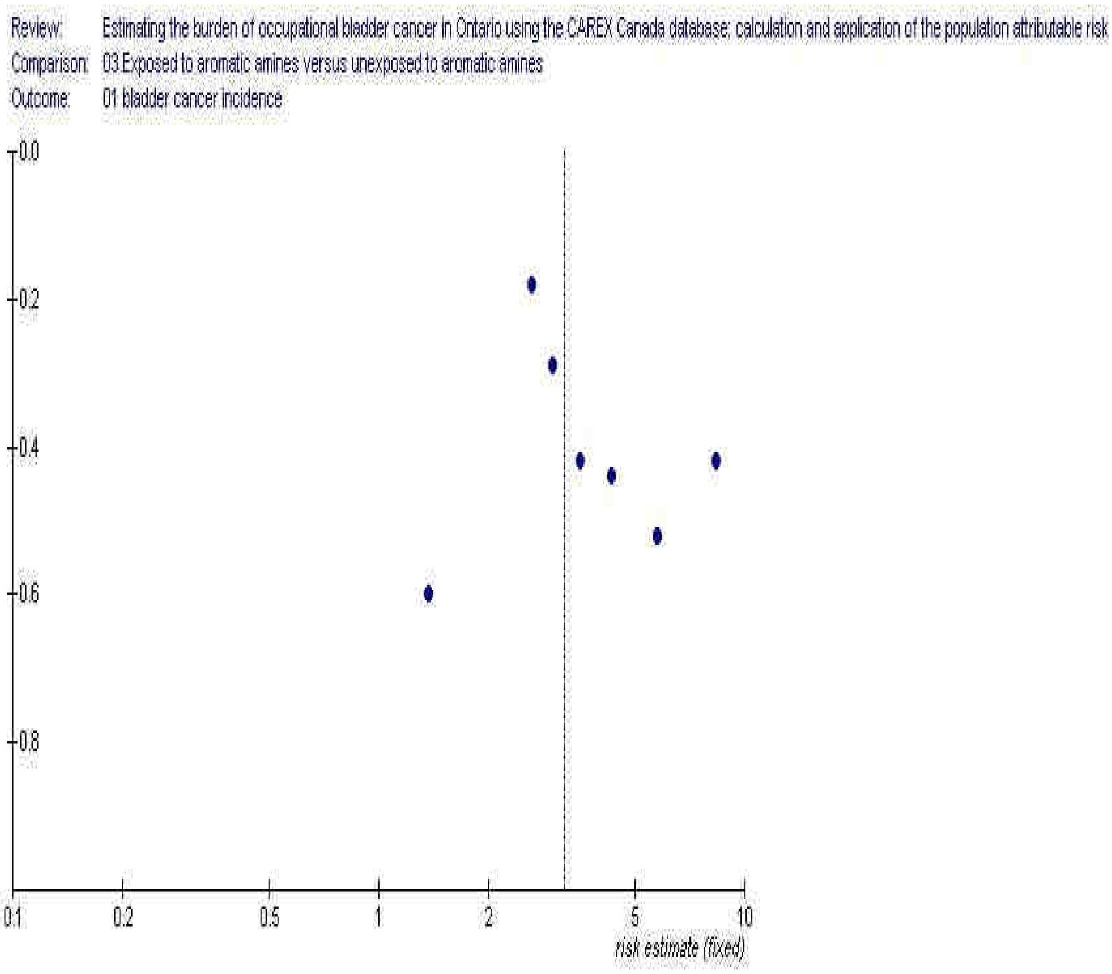
The funnel plot for the studies on bladder cancer and occupational exposure to diesel exhaust appears to be asymmetrical, with points missing on the left side of the funnel, indicating that smaller studies with negative findings may not have been published. With seven points on the plot, it is difficult to assess the degree of bias present. With this type of asymmetry, it is possible that the summary risk estimate found may be an overestimate. As with the funnel plot above, the wide area of the funnel is missing due to the *a priori* inclusion criteria used.

Figure 14 – Funnel Plot: diesel exposure



The funnel plot below represents the studies included on bladder cancer associated with occupational exposure to aromatic amines. Upon initial assessment, this funnel plot does appear to be asymmetrical. Again, for the same reasons cited above, the scatter of points along the bottom of the plot (or the wide end of the funnel) is missing due to the *a priori* inclusion criteria which prevented smaller, less methodologically sound studies from being excluded. It is possible that the asymmetry presented here is due to a true heterogeneity among the studies. This is further supported by the high I^2= 42%.

Figure 15 – Funnel Plot: aromatic amine exposure



The table below summarizes the summary risk estimates obtained from the pooled analyses. These summary risk estimates will be used in the calculation of the population attributable fraction for the incidence of bladder cancer due to occupational exposures. A separate calculation for mortality will not be conducted as only one study on mortality associated with PAH exposure met the inclusion criteria, while no studies met the inclusion criteria for mortality associated with diesel exhaust, and aromatic amine exposure.

Table 18 – Summary risk estimates for selected bladder carcinogens

Exposure Level	**Summary risk estimate (SRE)**			
	PAH	Diesel Exhaust	2-naphthylamine	aromatic amines
unexposed	1.00	1.00	1.00	1.00
low	1.97	1.00	1.00	0.98
high	1.40	1.21	16.83	3.21

4.4 Calculation of population attributable fraction (PAR)

Tables 19 to 22 contain the population attributable fraction calculated for each occupational bladder carcinogen under consideration.

Table 19 – Population Attributable Fraction Calculation – PAH Exposure

PAH Exposure Level	Proportion of population ever exposed by level	SRE	Pi x RRi
Unexposed	0.938	1.00	0.938
Low	0.056	1.97	0.110
High	0.006	1.40	0.009
Σ Pi x RRi			1.057
PAR			**0.054**

Table 20 – PopulationAttributable Fraction Calculation – Diesel Exhaust Exposure

Diesel Exposure Level	Proportion of population ever exposed by level	SRE	Pi x RRi
Unexposed	0.882	1.00	0.882
Low	0.106	1.00	0.106
High	0.012	1.21	0.014
Σ Pi x RRi			1.002
PAR			**0.002**

Table 21 – Population Attributable Fraction Calculation – 2-naphthylamine

BNAP Exposure Level	Proportion of population ever exposed by level	SRE	Pi x RRi
Unexposed	0.999	1.00	0.999
Low	3.76E-05	1.00	3.76E-05
High	4.18E-06	16.83	7.03E-05
Σ Pi x RRi			1.000066155
PAR			**6.62E-05**

Table 22 – Population Attributable Fraction Calculation – Aromatic Amines

Aromatic Amine Exposure Level	Proportion of population ever exposed by level	SRE	Pi x RRi
Unexposed	0.999	1.00	0.999
Low	1.86E-05	0.98	1.82E-05
High	2.06E-06	3.21	6.62E-06
Σ Pi x RRi			1.000004189
PAR			**4.19E-06**

Table 23 – Overall Population Attributable Fraction/ Population Attributable Fraction

Carcinogen	PAR
2-naphthylamine	6.62E-05
aromatic amines	4.19E-06
diesel exhaust	0.002
PAH	0.054
PAR Overall	**0.056**

Since the exposure-specific attributable fractions are small, the overall attributable fraction for bladder cancer due to exposure to beta-naphtylamine, aromatic amines, polycyclic aromatic hydrocarbons and diesel exhaust can simply be summed to approximate the overall population attributable fraction (Steenland et al., 2006). Therefore, the proportion of bladder cancer in Ontario due to occupational exposures is approximately 0.056 (95% CI 0.002 to 0.140). By far, the majority of this is due to occupational exposure to PAHs.

4.5 Sensitivity Analysis

The attributable fraction calculated depends on both the relative risk due to exposure and the proportion of the population exposed. Tables 22 to 36 illustrate changes to the overall PAR based on various sensitivity analyses conducted.

The decision was made not to use the pooled risk estimate for low-level PAH exposure due to the heterogeneous nature of the studies. The pooled risk estimate for low-level

PAH exposure was 1.21 (95% CI 1.01 to 1.45), I^2=67.5%. Had this pooled risk estimate been used, the resulting attributable fraction would have been 0.017.

Table 24 – Population Attributable fraction calculated using pooled risk estimate for low-level PAH exposure

Carcinogen	PAR (low-level PAH pooled)
PAH	0.014493191
Diesel exhaust	0.002470553
BNAP	6.61502E-05
Aromatic amines	4.18936E-06
Total	0.017034084

All pooled risk estimates were calculated using the fixed effects model. Calculation of the pooled risk estimates under the random effects model was conducted twice: once using a pooled risk estimate for low-level PAH exposure (even though the summary risk estimate was heterogeneous) and again using a single risk estimate for low-level PAH exposure based on the study with the highest exposure quality rating and the greatest number of subjects.

Table 25 – Population Attributable fraction calculated based on the random effects model (using pooled risk estimate for low-level PAH exposure)

Carcinogen	PAR (random effects)
PAH	0.017723281
Diesel exhaust	0.002705208
BNAP	6.61502E-05
Aromatic amines	3.85917E-06
Total	0.020498498

Table 26 – Population Attributable fraction calculated based on the random effects model (using non-pooled risk estimate for low-level PAH exposure)

Carcinogen	PAR (random effects)
PAH	0.053402728
Diesel exhaust	0.002705208
BNAP	6.61502E-05
Aromatic amines	3.85917E-06
Total	0.056177945

The PAR was recalculated using only the studies that included either qualitative or quantitative measures of level of exposure to the carcinogens, exposure quality rating 4 and 5. Using studies that were deemed to have better exposure assessment quality, the overall PAR was 0.035.

Table 27 – Attributable fraction calculated using studies with exposure quality 4 and 5

Bladder carcinogen	PAR (EQ = 4/5)
PAH	0.033849726
Diesel exhaust	0.001177978
BNAP	6.61502E-05
Aromatic amines	1.32903E-05
Total	0.035107145

Upon closer examination of the bladder carcinogens included for analysis, the inclusion of diesel exhaust as a bladder carcinogen can come under closer scrutiny. Although IARC has classified diesel exhaust as “probably carcinogenic to humans” and Siemiatycki et al. (2004) have concluded that there is suggestive evidence linking diesel exhaust to bladder cancer, the SRE found here is considerably low at 1.21 (95% CI 1.05 to 1.39). This calls into question whether diesel exhaust should be included here as a bladder carcinogen. The resulting PAR without diesel included in the analysis is 0.053, thus in fact it makes very little difference if diesel exhaust is included or not.

Table 28 – Population Attributable fraction calculated with the exclusion of diesel exhaust exposure

Carcinogen	PAR
2-naphthylamine	6.61502E-05
aromatic amines	4.18936E-06
PAH	0.053402728
Total	0.053473068

A common exercise when calculating summary risk estimates is to reanalyze the data by study type. This was also done here. Tables 29 to 38 present changes to the PAR when the summary risk estimates used are based on cohort studies and case-control studies separately. The PAR recalculated using only cohort studies was 0.006 and 0.020 using only case-control studies.

Table 29 – Population Attributable fraction for PAH exposure based on cohort studies only

PAH Exposure Level	Proportion of population ever exposed by level	SRE (cohort studies only)	Pi x RRi
Unexposed	0.938208687	1.00	0.938208687
Low	0.055612181	1.07	0.059505034
High	0.006179131	1.32	0.008156453
Σ Pi x RRi			1.005870175
PAR			0.005835917

Table 30 – Attributable fraction for diesel exhaust exposure based on cohort studies only

Diesel Exposure Level	Proportion of population ever exposed by level	SRE (cohort only)	Pi x RRi
Unexposed	0.882063237	1.00	0.882063237
Low	0.106143087	1.00	0.106143087
High	0.011793676	1.01	0.011911613
Σ Pi x RRi			1.000117937
PAR			0.000117923

Table 31 – Population Attributable fraction for 2-naphthylamine exposure based on cohort studies only

BNAP Exposure Level	Proportion of population ever exposed by level	SRE	Pi x RRi
Unexposed	0.999958209	1.00	0.999958209
Low	3.76116E-05	1.00	3.76116E-05
High	4.17906E-06	16.83	7.03336E-05
Σ Pi x RRi			1.000066155
PAR			6.61502E-05

Table 32 – Population Attributable fraction for aromatic amine exposure based on cohort studies only

Aromatic Amine Exposure Level	Proportion of population ever exposed by level	SRE (cohort only)	Pi x RRi
Unexposed	0.999979363	1.00	0.999979363
Low	1.85736E-05	0.64	1.18871E-05
High	2.06373E-06	4.59	9.47254E-06
Σ Pi x RRi			1.000000722
PAR			7.22307E-07

Table 33 – Population attributable fraction calculation based on cohort studies only

Bladder carcinogen	PAR (cohort only)
PAH	0.005835917
Diesel exhaust	0.000117923
BNAP	6.61502E-05
Aromatic amines	7.22307E-07
Total	0.006020712

Table 34 – Population Attributable fraction for PAH exposure based on case-control studies only

PAH Exposure Level	Proportion of population ever exposed by level	SRE (case-control studies only)	Pi x RRi
Unexposed	0.938208687	1.00	0.938208687
Low	0.055612181	1.26	0.070071348
High	0.006179131	1.46	0.009021532
Σ Pi x RRi			1.017301568
PAR			0.017007314

Table 35 – PopulationAttributable fraction for diesel exposure based on case-control studies only

Diesel Exposure Level	Proportion of population ever exposed by level	SRE (case-control only)	Pi x RRi
Unexposed	0.882063237	1.00	0.882063237
Low	0.106143087	0.98	0.104020225
High	0.011793676	1.39	0.01639321
Σ Pi x RRi			1.002476672
PAR			0.002470553

Table 36 – Population Attributable fraction for 2-naphthyamine exposure based on case-control studies only

BNAP Exposure Level	Proportion of population ever exposed by level	SRE	Pi x RRi
Unexposed	0.999958209	1.00	0.999958209
Low	3.76116E-05	1.00	3.76116E-05
High	4.17906E-06	16.83	7.03336E-05
Σ Pi x RRi			1.000066155
PAR			6.61502E-05

Table 37 – Population Attributable fraction for aromatic amine exposure based on case-control studies only

Aromatic Amine Exposure Level	Proportion of population ever exposed by level	SRE (case-control only)	Pi x RRi
Unexposed	0.999979363	1.00	0.999979363
Low	1.85736E-05	1.08	2.00595E-05
High	2.06373E-06	3.05	6.29439E-06
Σ Pi x RRi			1.000005717
PAR			5.71651E-06

Table 38 – Population Attributable fraction calculation based on case-control studies only

Bladder carcinogen	PAR (case control only)
PAH	0.017007314
Diesel exhaust	0.002470553
BNAP	6.61502E-05
Aromatic amines	5.71651E-06
Total	0.019549734

4.6 Application of PAR to Ontario Bladder Statistics

In Ontario, the total number of new cases of bladder cancer in the year 2001 in the population aged 25 to 75 years was 929 cases (Cancer Surveillance On-line). To estimate the number of these cases that are due to occupational exposure to the carcinogens included here, the total number of new cases of bladder cancer in the population aged 25 to 75 years is multiplied by the PAR calculated above (0.056) for bladder cancer due to occupational carcinogens. It is estimated that in 2001, there were approximately 52 new cases of bladder cancer due to occupational exposure to PAH, diesel exhaust, aromatic amines and 2-naphthylamine.

Chapter 5: Discussion

5.1 PAR Estimates

Using the Ontario-specific estimates contained in the CAREX Canada database, 348, 688 workers, approximately 5.3% of the workforce in Ontario are potentially exposed to bladder carcinogens at greater than background levels. The overall proportion of bladder cancer due to occupational exposures is approximately 5.6% (95% CI 0.2% to 14%).

A number of sensitivity analyses were conducted to observe the effect of excluding studies with weaker exposure assessments; using the random effects model; excluding carcinogens for which the strength of evidence may be weaker; and regrouping the studies according to study type to observe the effect on the PAR estimate.

By including only studies with an exposure quality rating of 4 or 5, the PAR estimate was reduced to 3.5%. The effect of including studies based on highly conservative inclusion criteria is to underestimate the population attributable risk.

Recalculating the summary risk estimates using the random effects model resulted in the PAR decreasing to 2.0%. This reduction was due to the summary risk estimate used for low-level PAH exposure. It was not deemed appropriate to group the studies to calculate a summary risk estimate for low-level PAH exposure due to heterogeneity among the studies. Instead, the risk estimate from the study with the highest exposure quality and the most number of subjects was chosen. Including this estimate resulted in no change to the overall PAR of 5.6% using the random effects model.

Since the strength of association for the risk of bladder cancer due to exposure to diesel exhaust (SRE 1.21) was not as strong as the summary risk estimates for the other carcinogens included in the PAR estimate, the PAR was recalculated without diesel exhaust. This had a negligible effect on the PAR, as it was only slightly reduced to 5.3%. This is a logical reduction since the summary risk estimate was relatively low, the prevalence of exposure in Ontario to diesel exhaust would have to be much greater for there to be a significant effect on the overall PAR.

By grouping the studies according to study type, the PAR changed drastically: 0.6% and 2.0% for cohort studies and case-control studies, respectively. The PAR estimates would justifiably be so divergent from the overall PAR estimate due to the regrouping of the studies themselves. The estimate for the overall PAR was based on 21 studies for high exposure and 12 studies for low exposure. When these studies were combined by carcinogen this resulted in three or more studies being grouped together to calculate the summary risk estimates. By limiting the results by study type, the studies were further parsed resulting in some groups of no more than two studies. This resulted in very unstable SREs. It was no longer appropriate to group the studies, resulting in the highly divergent PAR estimates.

5.2 Sample Size Calculation

The PAR estimate relies on the prevalence of exposure in the population under study as well as the relative risk of disease. A summary risk estimate was calculated and used in the PAR estimate for each carcinogen included. Did the studies included in the summary risk estimate calculation include enough subjects to detect a statistically significant effect? To answer this question, the sample size in case-control studies was calculated using the following formula:

$$n \text{ (each group)} = (p_0q_0 + p_1q_1)(z_{1-\alpha/2} + z_{1-\beta})^2 / (p_1 - p_0)^2$$

The sample size required for PAHs was calculated since this exposure contributed the most by far to the overall PAR estimate. Data from the CAREX Canada database indicated that the proportion of Ontario workers exposed to PAHs is 0.02. The SRE calculated for PAH exposure is 1.40. Using the conventional alpha level of 0.05 and beta level of 0.20 (80% power), the required sample size calculated was approximately 5735 per group. None of the studies which contributed to the SRE included this many control subjects. Because both the proportion of exposure among Ontario workers and the SRE are both relatively low, a large number of subjects is needed to detect a relative risk of 1.40. The SRE calculated is a best estimate of the risk of bladder cancer associated with occupational PAH exposure. If the "true" relative risk were higher, the required sample size would decrease (Table 39). Similarly, if the proportion of exposure among the controls was higher, the required sample size would also decrease (Table 40).

Table 39 – Sample Size Estimates for Postulated Relative Risks of Bladder Cancer Associated with PAH exposure

Postulated Relative Risks	Required Sample Size in Each Group
1.40	5735
1.80	1663
2.00	1137
2.50	584

Table 40 – Sample Size Estimates for Various Proportions of Exposure to PAHs Among Controls

Estimated Proportion of Exposure among Controls	Required Sample Size in Each Group
0.02	5735
0.04	2795
0.10	1031
0.20	443

Using the CAREX Canada database provided the best estimate of PAH exposure among Ontario workers, as no other sources data are readily available. The assessors deemed workers exposed to PAHs for exposures above non-occupational levels of exposure in urban air (i.e. above background levels). Due to the broad definition of occupational exposure, it is unlikely that the estimate of 0.02 workers exposed to PAHs in Ontario is an underestimate. However, the SRE calculated for exposure to PAHs, 1.40, may be an underestimate of the risk of bladder cancer associated with PAH exposure. Given that the sample sizes of the studies included in the calculation of the SRE for exposure to PAHs may not have have been large enough to detect such a relatively small risk, it is possible that the PAR calculated here is an underestimate of the risk of bladder cancer in Ontario that may be preventable should PAH exposure be eliminated.

5.3 Occupations Potentially at Risk for Bladder Cancer in Ontario

Polycyclic aromatic hydrocarbons (excluding environmental tobacco smoke), diesel exhaust, beta-naphthylamine and aromatic amines have been identified as bladder carcinogens in Ontario workplaces, with the greatest contribution coming from exposure to PAHs.

The two industry sectors in Ontario with the most workers exposed to PAHs are wholesale and retail trade and restaurants and hotels and manufacturing. The assessors defined exposure to PAHs as:

“Inhalatory exposure at work to PAHs with at least four aromatic rings (eg, benzo(a)pyrene, benz(a)anthracene, dibenz[a,h]anthracene) likely to exceed significantly the nonoccupational levels in urban air (usually <0.005 ug/m3 of benzo(a)pyrene). Includes coal tar pitch, coal tars, soots, creosotes, shale oils, and untreated/mildly treated mineral oils. Excludes environmental tobacco smoke (assessed separately) and bus/truck/van/taxi drivers exposed to engine exhaust (low exposure)”

The CAREX Canada database provides additional information on subgroups exposed to the carcinogens included in the database, thus providing information on potential subgroups to target prevention efforts.

The majority of PAH exposure occurring in the wholesale and retail trade and restaurants and hotels sector occurs in occupations in food and beverage service, and among chefs and cooks. Exposure in these occupational groups occurs when working in the vicinity of a grill or barbeque or cooking over a grill/barbeque. The assessors have deemed these exposures to be low. It is most likely that exposure to PAH in these occupations will never be completely eliminated. However, due to the large numbers of workers potentially exposed it is important that workers understand the hazards in the workplace and that employers ensure that proper ventilation of the workplace to avoid unnecessary peaks in exposure. The next subgroup within the wholesale and retail trade and restaurants and hotel sector at potential risk for PAH exposure are automotive service technicians, truck mechanics and mechanical repairers; heavy-duty equipment mechanics; and other small engine and equipment mechanics. Exposure in these occupational groups occurs during maintenance and repair of diesel powered vehicles and equipment. There appears to be some overlap between PAH exposure and diesel exhaust exposure in the CAREX Canada database. The main distinction being that workers identified as being exposed to diesel exhaust are diesel vehicle drivers who are exposed to diesel exhaust; whereas, workers exposed to combustion by-products while repairing diesel-powered vehicles/equipment are considered exposed to PAHs.

Manufacturing was identified as the next industry sector with the most workers potentially exposed to PAHs. The majority of workers are employed in the manufacture of transport equipment, the manufacture of fabricated metal products and the manufacture of machinery (excluding electrical machinery). The occupations at risk of PAH exposure in these manufacturing sectors include: welders and related machine operators; foundry workers; metalworking machine operators; machining tool operators; machinists and machining and tooling inspectors; tool and die makers; and structural metal and platework fabricators and fitters. This is not an exhaustive list of occupations within these sectors. Exposure scenarios in which PAH exposure may occur include: the operation, cleaning and maintenance of ovens and furnaces in nonferrous metal mills and foundries; the hardening of metals, forging, founding and other related metal working tasks; metal machining and tool manufacturing; and welding of painted steel in confined spaces. Again, this is not an exhaustive list of exposure scenarios in which exposure to PAHs may occur.

5.4 Strengths

A major strength of the current study is the PAR was calculated using local level exposure prevalence and proportions of workers employed in each industry sector. Past studies assumed the occupational exposure prevalences of other countries were similar to their own and applied them to their own workforce statistics. Had the Finnish and U.S prevalence estimates been used to estimate the total number of workers exposed to diesel exhaust and PAH, the Ontario estimates would have been 109, 939 and 27, 908 workers respectively. When the prevalence estimates were improved by occupational hygienists using local data sources the number of workers increased to 228, 719 Ontario workers exposed to diesel exhaust and 119, 779 workers exposed to PAH. The CAREX Canada database contains comprehensive information on the type of occupational exposures to known and suspected human carcinogens, IARC groups 1 and 2A, in Ontario. As well, the CAREX Canada database provides estimates of the number of workers exposed to known and suspected occupational carcinogens in Ontario by industry sector, which in itself is another way to assess the potential magnitude of occupational cancer.

In addition to using Ontario-based estimates for the proportions of workers exposed to occupational bladder carcinogens, this study also attempted to account for level of exposure by applying a partitioning factor for high and low exposures. The partitioning factor was used because Ontario-specific data on the level of exposure within the industry sectors is not available. Other studies simply classified exposure as present or absent. Summary risk estimates were included for both high and low levels of exposure to the bladder carcinogens of interest.

Another strength of the present study is the timeframe covered by the studies included in when calculating the summary risk estimates. Exposures and working conditions from 1900 to 2004 were included and the studies were published between 1985 and 2007. This represents a much broader and recent study period compared to past calculations of the PAR were derived.

Unlike other studies that have calculated the PAR for occupational cancer using a risk estimate from a single study, the current study reviewed original studies and calculated a summary risk estimate to be used in the PAR calculation.

The a priori inclusion criteria were developed to ensure smoking, a major confounder, was accounted for, to include countries with industrial development similar to that of Ontario and to ensure studies included sufficient exposure information. The studies were further rated by the quality of the exposure information to exclude studies with poor exposure assessments.

5.5 Limitations

To make appropriate recommendations and summary statements regarding the magnitude of occupational bladder cancer in Ontario, it is important to understand the limitations in the current methodology and the estimates obtained. There are several sources of uncertainty in the estimation of the proportion of bladder cancer attributable to occupational exposures in Ontario. As demonstrated from the different sensitivity analyses conducted, the PAR calculated is heavily dependent on the risk estimate used in the calculation. The cohorts of workers in the studies included in the pooled analyses are, therefore, probably not representative of the entire exposed workforce in Ontario. However, in the absence of Ontario-specific risk estimates for occupational bladder cancer, the summary risk estimates calculated were a best estimate of an overall relative risk for exposure to the carcinogens of interest. When calculating the summary risk estimates used in the PAR calculation, a priori criteria were set to be able to include studies with the best methods and exposure assessments and to control for such confounders such as smoking, which is strongly associated with the risk of bladder cancer.

The CAREX Canada database estimates the current exposure circumstance for workers in Ontario. Although the PAR estimated here accounts for past numbers of workers by applying a turnover factor to estimate the number of workers “ever” exposed to bladder carcinogens, the current exposure circumstance is still used. Based on the CAREX Canada database it would be more accurate to estimate the future burden of occupational bladder cancer. However, recognizing this limitation helps to place the current estimate into context as past exposures can be assumed to be much more prevalent. The current estimate, therefore, underestimates the prevalence of exposure.

The exposure assessment methods used to populate the CAREX Canada database were unclear, and mostly based on the Finnish and U.S data. Although detailed labour force statistics have been entered into the CAREX Canada database and Ontario-specific measurement data was made available by the Ministry of Labour, there are still limitations regarding the broadness of exposure categories, the issue of overlap between exposures (i.e between PAHs and diesel exhaust) and issues in possible double-counting of workers that have yet to be resolved, all leading to crude estimates. However, the version available at the time this study took place was a preliminary version of the database and further improvements have been made. In addition, the lead investigator for CAREX Canada has received funding to continue to further refine the estimates contained in the database. This being the case the CAREX Canada database does have the potential to be a useful tool in occupational cancer surveillance in Ontario and Canada overall once information from the remaining provinces and territories has been included.

Another limitation of the current study was that there was a single quality assessor to rate the exposure quality of the studies included in the summary risk estimate calculations. There is no way to test whether the exposure rating criteria are reliable, as there was no opportunity to verify inter-rater reliability. It is possible, then, that the exposure criteria chosen were quite arbritrary and not indicative of study quality at all.

The PAR estimates calculated here were applied to the number of incident bladder cancer cases in Ontario for both male and females combined. The CAREX Canada database does not provide estimates for the number of workers exposed to workplace carcinogens by gender, but provides an overall estimate for the number of workers exposed within each industry sector. Due to a lack of data, no attempt was made to account for gender-based differences in exposure. The decision was made not to apply the PAR calculated to the number of incident cases of bladder cancer among males and females separately as this would have been an inappropriate application of the estimate.

No definitive list of all carcinogens used in Ontario presently exists. As such, other documents and reliable lists of occupational carcinogens were sought. Inevitably bladder carcinogens may have been overlooked in the present study, either because exposure levels to the carcinogen are too low within the industry sector and therefore did not meet the exposure threshold hold to be included in the CAREX Canada database, or simply because the exposure was not included in the CAREX Canada database at all. Another factor related to this point are unidentified carcinogens in processes or occupations that have been listed as human carcinogens by IARC such as painters, shoe repair, and the rubber industry. The PAR calculated will vary according to the carcinogens included. However, this also depends on the prevalence of exposure within the population and the risk associated with the particular carcinogen. It is up to the discretion of the investigators to determine which carcinogens are going to be included in the estimate, for example Nurminen and Karjalainen (2001) included exposure to lead and chlorinated hydrocarbon solvents as occupational bladder carcinogens in their estimate of the attributable fraction. The CAREX Canada database does provide estimates for the number of workers in Ontario who are exposed to these substances. 73, 569 Ontario workers are exposed to lead and 13, 639 workers are exposed to perchloroethylene and trichloroethylene combined. However, the decision was made not to include these substances as bladder carcinogens since they were not identified as such by Siemiatycki et al. (2004). The present estimate, then, may underestimate the proportion of the bladder cancers in Ontario due to occupation.

Another issue to consider when determining which bladder carcinogens to include in the PAR calculation is the strength of evidence for carcinogenic potency. An underlying assumption when calculating the PAR is that of causality. Causality is assessed differently by different investigators leading to differing lists of carcinogens included in PAR estimates.

One of the limitations of using the CAREX Canada database was that exposure was defined broadly. The criterion for exposure was defined to include all exposures above background levels for each carcinogen. The CAREX Canada database does not contain exposure information by level of exposure

The two bladder carcinogens with the greatest prevalence in Ontario, PAH and diesel exhaust, are both ubiquitous exposures that are also found outside of the workplace. In addition, they are considered complex mixtures and assessing exposure to a single PAH is difficult. Although diesel exhaust is also recognized as a complex mixture containing PAH, it was assessed separately in the CAREX Canada database. This calls into question the feasibility and utility of preventing occupational exposure when exposure outside of the workplace will also occur.

Conclusion and Recommendations

The Cancer 2020 Action Plan found that there was a lack of well-documented data on factors associated with occupational carcinogens (Canadian Cancer Society, 2006). The 2006 Cancer 2020 Report found that there is very little information in Ontario on the burden of occupational cancer. The current study advances our knowledge of the extent to which specific occupational bladder carcinogens contribute to the overall bladder cancer burden in Ontario. The proportion of bladder cancer in Ontario due to exposure to occupational carcinogens is approximately 5.6% (95% CI 0.002 to 0.140). Including only the studies with the best exposure quality, the proportion is reduced to

3.5%. In Ontario, it is estimated that in 2001, there were between 33 to 52 incident cases of bladder cancer due to occupational exposure to PAH, diesel exhaust, aromatic amines and 2-naphthylamine. Based on the strengths and limitations identified above the present PAR calculation may be an underestimation of the actual proportion of bladder cancer that may be avoided by eliminating occupational exposures.

In addition to estimating the proportion of bladder cancer due to occupational exposures in Ontario, the present study helps to inform strategies for primary cancer prevention through the identification of priority areas on which to focus efforts. Through the CAREX Canada database, Ontario-specific exposure estimates were available. These estimates were necessary for the calculation of the PAR but are also useful in themselves since knowledge of the numbers of exposed workers and the prevalence of exposure within industry sectors allow focused prevention efforts on priority areas. Large numbers of Ontario workers are exposed to PAHs and diesel exhaust, 119, 779 workers and 228, 719 workers, respectively. One consideration is to screen identified high-risk groups for bladder cancer. However, due to the broad classification of both exposure and industry sectors in the CAREX Canada database, the identification of such high-risk groups is not yet possible.

Several studies in the past have attempted to quantify the proportion of cancer due to occupational exposures. Other studies have also estimated the proportion of bladder cancer attributable to occupational exposures. The estimates range from 2.0% to 14% of cancer is due to occupation and specifically 2.0% to 24% of bladder cancer is attributable to exposure to bladder carcinogens at work. Given the broad range of estimates, why then was it necessary to calculate the PAR specifically for Ontario?

Although the present estimate of 5.6% is lower than estimates from past studies from other countries, see Table 1, the present estimate is a much more valid one since it accounts for the local prevalence of exposure and the effects of historical risks over time by using risk estimates that are more reflective of present day exposure scenarios. Studies that have assumed the exposure prevalence of another country is similar to their own have produced the exact PAR estimates to those of the country whose exposure prevalence was utilized (Fritschi and Driscoll, 2006;'t Mannetje and Pearce, 2005; Nurminen and Karjalainen, 2001). Had resources been available to estimate local exposure prevalence, it is feasible that the PAR estimates calculated in those studies may have differed.

The present study also has the added benefit of identifying a changing pattern of risk over time. For example, as bladder carcinogens are eliminated from the workplace new carcinogens are emerging. The highest risks for bladder cancer were found for 2-naphthylamine and for the overall group of aromatic amines, with risks ranging from 3.21 to 16.83 at high exposure levels. These represent historic exposures as the data contained in the CAREX Canada database identified that current exposure to these carcinogens in Ontario was very minimal. The emerging carcinogens that are of concern are those affecting a large proportion of workers, namely exposure to PAHs and diesel exhaust. This also highlights the issue of regulation of carcinogenic agents. The purpose of the Ontario Occupational Health and Safety Act and the regulations under this act is to protect Ontario workers against health and safety hazards on the job. The legislation outlines the workers' and employers' rights and duties under the Act. Regulation 833, Control of Exposure to Biological or Chemical Agents, sets limits for approximately 600 toxic substances in workplace air. Under Part 10 of Regulation 833, benzidine and 2-naphthylamine have been listed as known toxic agents for which exposure values have not been established and to which any exposure should be avoided. The results of the PAR calculation show the effectiveness of current legislation as the aromatic amines contribute very little to the burden of bladder cancer in Ontario. Interestingly, benzo(a)pyrene, a specifc PAH is also on this same list of exposures which should be avoided. However, the current results show that of the bladder carcinogens under study, PAHs contribute the most to the burden of bladder cancer in Ontario. This is in part because PAHs are complex mixtures and very rarely can exposure to a single PAH, such as benzo(a)pyrene, be isolated. In addition, due to the ubiquitous nature of PAHs, exposure to PAHs may be reduced but in reality never eliminated. This highlights a dilemma for occupational health professionals and the need for increased attention to prevention efforts in the area of PAHs.

The current study highlights the utility of the CAREX Canada database in advancing current knowledge on the burden of occupational cancer in Ontario. The methods used to estimate the proportion of bladder cancer attributable to occupational exposure in Ontario may be replicated to estimate the proportion of cancer in Ontario that is due to occupational exposure. There is also the opportunity through the periodic updating of the CAREX Canada database to identify changing exposure and therefore risk patterns in Ontario industry sectors over time.

The current study contributes to the overall body of knowledge on risk factors associated to bladder cancer. The elimination of smoking can account for a 30 to 60 percent reduction in bladder cancer (IARC 2004). The elimination of chlorination by-products in drinking water can account for a 14 to 16 percent reduction in bladder cancer (King and Marrett, 1996). A further 5 to 6 percent of bladder cancer incidence can be avoided through the elimination of occupational exposures.

The present study may be criticized for attempting to determine the proportion of bladder cancer that is due to occupational exposures. The criticism lies in the complex nature of cancer causation and the many factors involved. It may be inappropriate to assign certain exposures a particular role in causing cancer that will total 100% when no one exposure on its own produces cancer and there are likely many other causes of cancer which are still unknown. However, the objective of this study was not merely to produce a single number to characterize the burden of occupational bladder cancer in Ontario. This number will change as new carcinogens are identified, as risks estimates for bladder cancer are further refined and as the prevalence of exposure to carcinogens in Ontario workers changes. Through trying to estimate the magnitude of occupational bladder cancer in Ontario, those exposed to occupational carcinogens have been identified and most importantly these exposures can be minimized and are preventable.

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APPENDIX A

Carcinogens included in CAREX Canada Database

Carcinogens included in CAREX Canada Database

Occupational Carcinogen	IARC Group
4-Aminobiphenyl	1
Acrylamide	2A
Adriamycin*	2A
Acrylonitrile	2B
Aflatoxins	1
Androgenic steroids*	2A
Arsenic and its compounds	1
Asbestos	1
Azacitidine*	2A
Azathioprine*	1
Bischloroethyl nitrourea (BCNU)	2A
Bis(chloromethyl)ether & chloromethyl methyl ether	1
Benzidine-based dyes	2A
Beryllium and its compounds	1
Benzene	1
Benzidine	1
1,3-Butadiene	2A
1,4-Butanediol dimethanesulfonate (Myleran)*	1
Cadmium and its compounds	1

Captafol	2A
Carbon tetrachloride	2B
Ceramic fibers	2B
Chlorambucil*	1
Chloramphenicol*	2A
Chlorozotocin*	2A
Chromium VI compounds	1
Ciclosporin*	1
Cisplatin*	2A
1-(2-Chlorethyl)-3-(4-methylcyclohexyl)-1-nitrosourea*	1
1-(2-Chlorethyl)-3-cyclohexyl-1-nitrosourea (CCNU)*	2A
Cobalt and its compounds	2B
Cyclophosphamide*	1
Creosotes	2A
Coal-tars	1
Diesel engine exhaust	2A
Diethylstilboestrol	1
Diethyl sulfate	2A
Dimethylcarbamoyl chloride	2A
Dimethyl sulfate	2A
Epichlorohydrin	2A
Erionite	1
Ethylene dibromide	2A
Ethylene oxide	1
Environmental tobacco smoke (at work)	1
Formaldehyde	1
Glasswool	2B
Helicobacter pylori	1
Hepatitis B virus	1
Hepatitis C virus	1
Ionizing radiation and radioactive elements (exclu. Radon)	1

Lead and lead compounds	2A
Melophalan*	1
5-Methoxypsoalen*	2A
8-Methoxyspoalen therapy*	1
Methylene chloride	2B
4,4'-Methylen bis(2-chloroaniline) (MOCA)	2A
Mustard gas (sulphur mustard)*	1
Mineral oils, untreated	1
MOPP and other chemotherapy, including alkylating agents*	1
N-Ethyl-N-nitrosourea	2A
N-Methyl-N'-nitro-N-nitrosoquanidine (MNNG)*	2A
N-Methyl-N-nitrosourea	2A
N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlonaphazine)*	1
N-Nitrosodiethylamine	2A
N-Nitrosodimethylamine	2A
2-Naphthylamine	1
Nickel compounds	1
Nitrogen mustard*	1
Non-arsenical insecticides	2A
Oestrogens, nonsteroidal*	1
Oestrogens, steroidal*	1
Oral contraceptives, combined*	1
Oral contraceptives, sequential*	1
Para-Chloro-ortho-toluidine & its strong acid salts	2A
Pentachlorophenol	2B
Polychlorinated biphenyls (PCBs)	2A
Polycyclic aromatic hydrocarbons (PAHs)	2A
Procarbazine hydrochloride*	2A
Radon and its decay products	1
Shale-oils	1
Silica, crystalline	1
Solar radiation	1
Styrene	2B
Styrene-7,8-oxide	2A

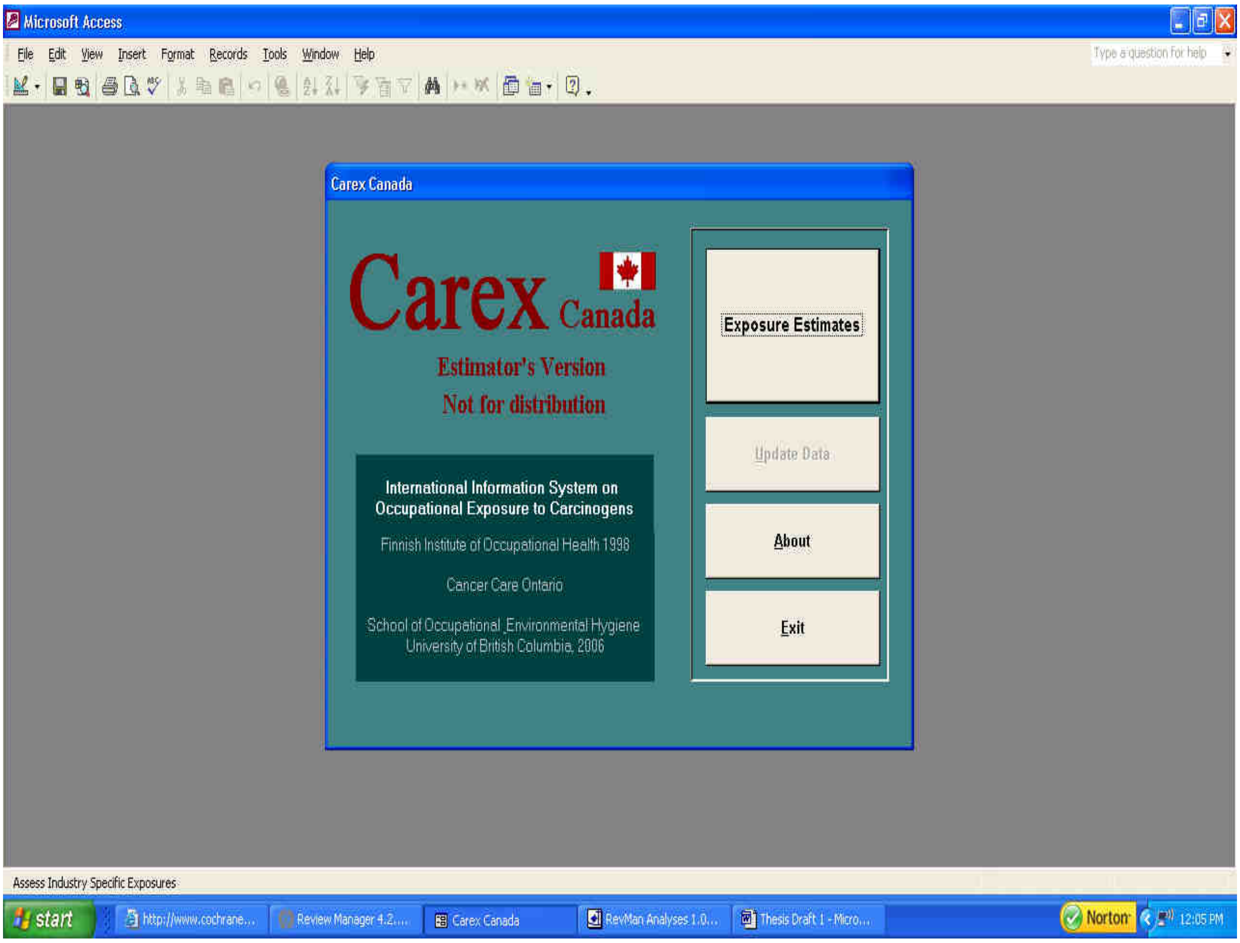
Sulfuric acid mist	1
Talc containing asbestiform fibers	1
Tetrachloroethylene	2A
Thiotepa*	1
Tresulfan	1
Tris(2,3-dibromopropyl)phosphate	2A
1,2,3-trichloropropane	2A
Trichloroethylene	2A
Ultraviolet (UV) radiation, artificial	2A
Vinyl bromide	2A
Vinyl chloride	1
Vinyl fluoride	2A
Wood dust	1

*pharmaceutical agents to which health care and pharmacy industry workers may be exposed, many are now banned from use in Canada.

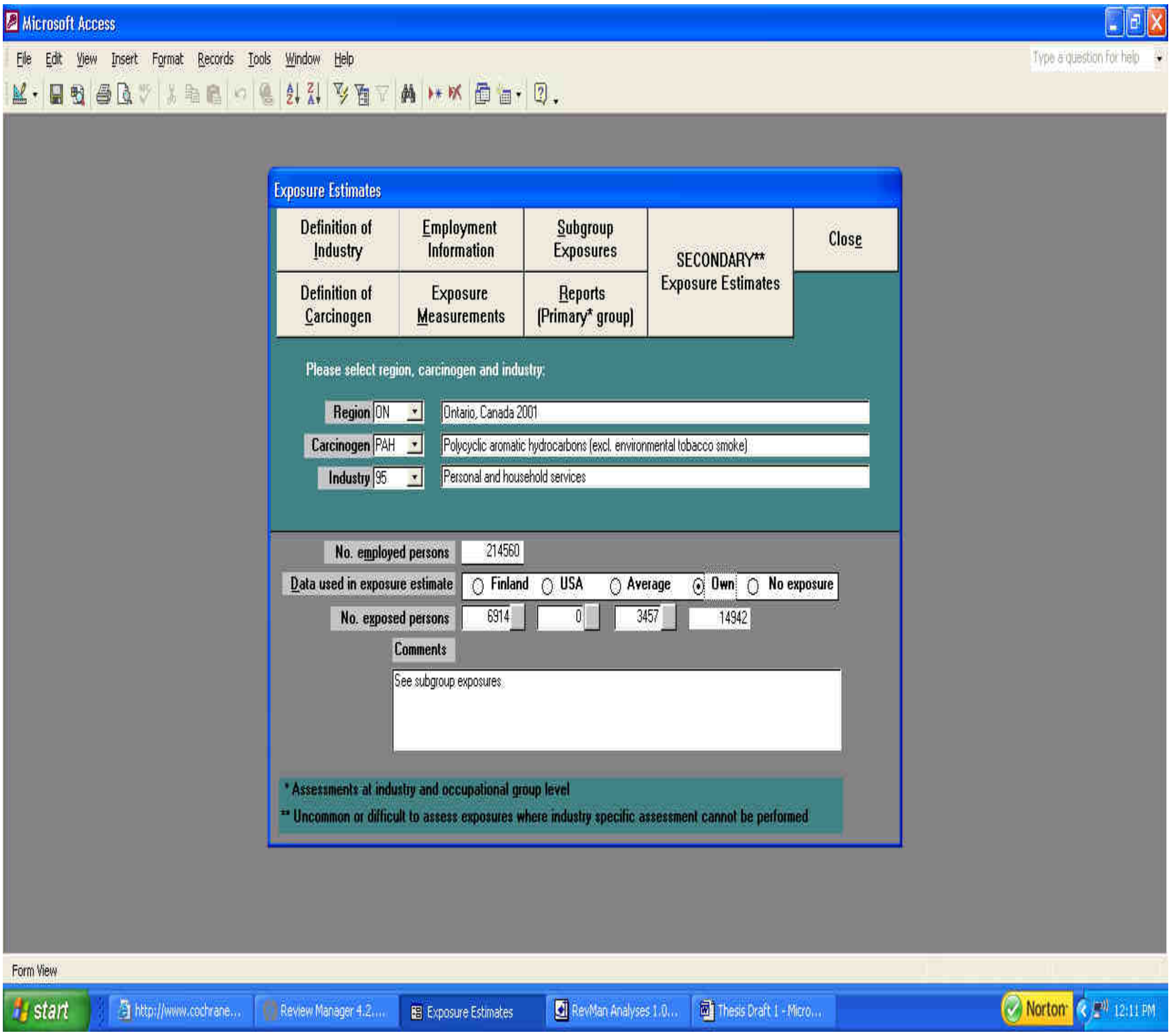
APPENDIX B

CAREX Canada Screenshots

CAREX Canada Opening Screen



CAREX Canada Primary Exposure Estimation Screen



APPENDIX C

Evidence Tables

Cohort Studies
Beta-naphtylamine

Authors	Cassidy LD, Youk AO, Marsh GM
Publication Year	2003
Study type	Cohort study
Geographic Region	Pennsylvania, USA
Outcome	Mortality
Study years (enrolment)	1940 to 1981
Years of follow-up	1960 to 1998
Study population	Workers employed at a chemical plant that produced or used beta-naphthylamine
Occupation/Exposure Data Source	Limited industrial hygiene data and reports from former employees
Reference Population	US Standard Population and Local County Population
Outcome Data Source	National Death Index or death certificates
Total Subjects Included for Analysis	400
Bladder Cancer Risk Estimate	Comparison OBS SMR 95% CI US 4 21.43 5.84-54.87 Local 4 16.83 4.59-43.21
Exposure Quality (EQ) Score/Notes	EQ = 3 Bladder cancer SMRs were highest and statistically significant among subjects at risk before age 45, hired before 1963, employed 5 or more years, followed 20-29 years since first employment, or in the highest BNA exposure risk group

Polycyclic Aromatic Hydrocarbons

Authors	Zeegers MPA, Swaen GMH, Kant I, Goldbohm RA, van den Brandt PA
Publication Year	2001
Study type	Prospective cohort study, case-cohort approach
Geographic Region	Netherlands
Outcome	Incidence
Study years (enrolment)	1986 to 1992
Years of follow-up	1986 to 1992
Study population	General population, cases enumerated from entire cohort
Occupation/Exposure Data Source	Experts in occupational epidemiology and occupational hygiene assessed probability of carcinogenic exposures based on self-administered questionnaires
Reference Population	Subcohort of men randomly sampled from entire cohort after baseline exposure measurement
Outcome Data Source	Record linkage to dutch cancer registries and dutch national database of pathology reports
Total Subjects Included for Analysis	2249
Bladder Cancer Risk Estimate	PAH exp index RR*(95%CI) No exposure 1.00 (reference) Low exposure 0.47 (0.21 to 1.04)

	Medium exposure 0.85 (0.45 to 1.59) High exposure 1.24 (0.72 to 2.13) P Value for trend = 0.98 *adjusted for age PAH exp index RR**(95% CI) No exposure 1.00 (reference) Low exposure 0.51 (0.22 to 1.19) Medium exposure 0.97 (0.40 to 1.90) High exposure 1.18 (0.62 to 2.24) P Value for trend = 0.85 ** adjusted for age, other occupational exposures, cigarette smoking amount and duration
Exposure Quality (EQ) Score/Notes	EQ = 4 Qualitative exposure information assessed by experts in occupational epidemiology and occupational hygiene

Authors	Moulin JJ, Clavel T, Buclez B, Laffitte-Rigaud G
Publication Year	2000
Study type	Retrospective cohort study
Geographic Region	France
Outcome	mortality
Study years (enrolment)	January 1950 to December 1994
Years of follow-up	January 1968 to December 1994
Study population	Every male worker employed in an aluminum reduction plant
Occupation/Exposure Data Source	Personnel files, administrative records
Reference Population	France regional population
Outcome Data Source	National death files, national death certificate files
Total Subjects Included for Analysis	2133
Bladder Cancer Risk Estimate	Obs SMR 95% CI 7 1.77 0.71 to 3.64
Exposure Quality (EQ) Score/Notes	EQ = 2 Only broad definition of PAH exposure “having ever been employed in the potroom, electrode manufacture department, exhaust ventilation operations, pot-lining and maintenance”, other exposures not accounted for

Authors	Romundstad P, Haldorsen T, Andersen A
Publication Year	2000
Study type	Cohort study
Geographic Region	Norway
Outcome	incidence
Study years (enrolment)	1953 to 1995
Years of follow-up	1953 to 1995
Study population	Men employed for more than 5 years at a Norwegian aluminum plant

Occupation/Exposure Data Source	Quantitative estimate of PAH exposure based on personal measurements, stationary measurements and descriptions of changes in the technological processes over time, for periods with very little measurements, a panel of 3 occupational hygienists agreed on subjective estimates. The results were summed in a job-exposure matrix for PAHs.
Reference Population	National population
Outcome Data Source	Cancer Registry of Norway
Total Subjects Included for Analysis	1790
Bladder Cancer Risk Estimate	Obs SIR 95% CI 23 1.3 0.8 to 1.9
Exposure Quality (EQ) Score/Notes	EQ = 5 Quantitative exposure measurements used

Authors	Romundstad P, Haldorsen T, Andersen A
Publication Year	2000
Study type	Retrospective cohort study
Geographic Region	Norway
Outcome	Incidence
Study years (enrolment)	1954 to 1995
Years of follow-up	Time of hire to 1995
Study population	Men employed for six months or more at one of the two plants under study
Occupation/Exposure Data Source	Estimation of exposure to PAHs based on statistical modeling of personal measurements, stationary measurements and process data.
Reference Population	National population
Outcome Data Source	Cancer Registry of Norway
Total Subjects Included for Analysis	5627
Bladder Cancer Risk Estimate	Less than 3 yrs of employment Obs SIR 95% CI 5 0.78 0.25 to 1.82 More than 3 yrs of employment Obs SIR 95% CI 36 1.37 0.96 to 1.90 Lag = 30 years Cumulative PAH exposure ($\mu g/m^3$. year) Obs SIR 95% CI <50 24 1.29 0.83 to 1.92 50-500 3 1.04 0.21 to 3.03 500-2000 4 1.16 0.32 to 2.97 >2000 5 4.08 1.32 to 9.51
Exposure Quality (EQ) Score/Notes	EQ = 5 Quantitative exposure measurements used

Diesel Exhaust

Authors	Guo J, Kauppinen T, Kyyronen P, Heikkila P, Lindbohm M, Pukkala E
Publication Year	2004
Study type	Cohort study
Geographic Region	Finland
Outcome	incidence
Study years (enrolment)	Finns born between 1906 and 1945
Years of follow-up	1971 to 1995
Study population	Economically active Finns born between 1906 and 1945 who participated in the 1970 national population census
Occupation/Exposure Data Source	Data on occupation held for the longest period in the 1970 Censes record, exposure estimates for the cohort were derived from FINJEM based on exposure measurements, hazard surveys and judgements of 20 occupational hygienists
Reference Population	Finnish population
Outcome Data Source	Finnish cancer registry
Total Subjects Included for Analysis	8110
Bladder Cancer Risk Estimate	Diesel exhaust exposure (mg/m^3 x years) Cases / RR / 95% CI None: 6026 / 1.00 <2.0: 493 / 1.00 / 0.91 to 1.11 2.0-9.9: 200 / 0.95 / 0.83 to 1.10 ≥10.0: 78 / 0.97 / 0.77 to 1.21
Exposure Quality (EQ) Score/Notes	EQ = 4 Semi-quantitative exposure assessment using FINJEM

Authors	Zeegers MPA, Swaen GMH, Kant I, Goldbohm RA, van den Brandt PA
Publication Year	2001
Study type	Prospective cohort study, case-cohort approach
Geographic Region	Netherlands
Outcome	Incidence
Study years (enrolment)	1986 to 1992
Years of follow-up	1986 to 1992
Study population	General population, cases enumerated from entire cohort
Occupation/Exposure Data Source	Experts in occupational epidemiology and occupational hygiene assessed probability of carcinogenic exposures based on self-administered questionnaires
Reference Population	Subcohort of men randomly sampled from entire cohort after baseline exposure measurement
Outcome Data Source	Record linkage to dutch cancer registries and dutch national database of pathology reports
Total Subjects Included for Analysis	2249
Bladder Cancer Risk Estimate	Diesel exp index RR*(95%CI)

	No exposure 1.00 (reference) Low exposure 1.00 (0.68 to 1.51) Medium exposure 0.99 (0.65 to 1.52) High exposure 1.07 (0.70 to 1.62) P Value for trend = 0.78 *adjusted for age Diesel exp index RR**(95% CI) No exposure 1.00 (reference) Low exposure 1.00 (0.65 to 1.54) Medium exposure 0.96 (0.60 to 1.53) High exposure 1.17 (0.74 to 1.84) P Value for trend = 0.76 ** adjusted for age, other occupational exposures, cigarette smoking amount and duration
Exposure Quality (EQ) Score/Notes	EQ = 4 Qualitative exposure information assessed by experts in occupational epidemiology and occupational hygiene

Aromatic Amines

Authors	Ouellet-Hellstrom R, Rench J
Publication Year	1996
Study type	Cohort study
Geographic Region	United States
Outcome	incidence
Study years (enrolment)	June 1965 to December 1989
Years of follow-up	1990 to 1993
Study population	704 workers employed at a Connecticut chemical from mid-1965 to 1989. The plant produced a variety of chemicals including arylamines
Occupation/Exposure Data Source	Work histories and demographic information obtained from corporate database and personnel records. Exposure Assessment Committee of former and current workers knowledgeable about work processes developed exposure score for each job title. The exposure scoring system was based on intensity of exposure (0 – no exposure to 5 – greatest exposure) and frequency of contact (0% no time spent to 100% of time spent). The exposure scoring system took into account exposure-control measures at the plant. Work histories also obtained through mail survey.
Reference Population	Connecticut cancer incidence rates through 1990
Outcome Data Source	Company's medical surveillance, cancer cases register at the Connecticut Tumor Registry, review of death certificate of

	deceased workers and mail survey to identify and confirm reported cancers
Total Subjects Included for Analysis	698 workers (583 men, 115 women)
Bladder Cancer Risk Estimate	Obs SIR* 95% CI 7 8.3 3.3 to 17.1 *regression model included confounders such as sex, smoking and age at hire
Exposure Quality (EQ) Score/Notes	EQ = 4 Qualitative exposure scoring system based on intensity of exposure and frequency of contact

Authors	Zeegers MPA, Swaen GMH, Kant I, Goldbohm RA, van den Brandt PA
Publication Year	2001
Study type	Prospective cohort study, case-cohort approach
Geographic Region	Netherlands
Outcome	Incidence
Study years (enrolment)	1986 to 1992
Years of follow-up	1986 to 1992
Study population	General population, cases enumerated from entire cohort
Occupation/Exposure Data Source	Experts in occupational epidemiology and occupational hygiene assessed probability of carcinogenic exposures based on self-administered questionnaires
Reference Population	Subcohort of men randomly sampled from entire cohort after baseline exposure measurement
Outcome Data Source	Record linkage to dutch cancer registries and dutch national database of pathology reports
Total Subjects Included for Analysis	2249
Bladder Cancer Risk Estimate	Aromatic amines RR*(95%CI) No exposure 1.00 (reference) Low exposure 0.77 (0.21 to 2.85) High exposure 2.00 (0.68 to 5.88) P Value for trend = 0.24 *adjusted for age Aromatic amines RR**(95% CI) No exposure 1.00 (reference) Low exposure 0.64 (0.13 to 3.22) High exposure 1.36 (0.42 to 4.35) P Value for trend = 0.72 ** adjusted for age, other occupational exposures, cigarette smoking amount and duration
Exposure Quality (EQ) Score/Notes	EQ = 4 Qualitative exposure information assessed by experts in occupational epidemiology and occupational hygiene

Case Control Studies
Polycyclic Aromatic Hydrocarbons

Authors	Tremblay C, Armstrong B, Theriault G, Brodeur J
Publication Year	1995
Study type	Nested case-control study
Geographic Region	Quebec
Outcome	incidence
Study years (enrolment)	January 1950 to December 1979
Years of follow-up	1970 to 1988
Study population	Cohort of 16 000 males employed for more than one year at a aluminum plant in Quebec
Occupation/Exposure Data Source	JEM constructed by company hygienists
Reference Population	Random sample of cohort members, 3 matched controls per case
Outcome Data Source	Record linkage from regional hospital and Quebec tumour registry
Total Subjects Included for Analysis	138 cases, 414 controls
Bladder Cancer Risk Estimate	Cases / OR / 95% CI Never Smokers: – / 1.00 / – Current Smokers: 91 / 2.63 / 1.29 to 5.37 Ex-smokers: 20 / 1.79 / 0.68 to 4.67 Benzene-soluble matter (BSM) mg/m^3-years / Cases / OR* / 95% CI 0-0.9 / 136 / 1.0 / 1.0-9.9 / 146 / 1.67 / 0.89 to 3.16 10.0-19.9 / 47 / 3.93 / 1.85 to 8.49 20.0-29.9 / 40 / 7.31 / 3.36 to 14.99 30.0+ / 45 / 5.18 / 2.47 to 10.89 Benzo(a)pyrene (BaP) $\mu g/m^3$-years / Cases / OR* / 95% CI 0-9.9 / 215 / 1.0 / 10.0-99.9 / 96 / 1.97 / 1.10 to 3.51 100.0-199.9 / 32 / 6.24 / 3.00 to 12.97 200.0-299.9 / 38 / 6.66 / 3.42 to 12.99 300+ / 33 / 4.36 / 2.10 to 9.17 *controlled for smoking
Exposure Quality (EQ) Score/Notes	EQ = 5 Quantitative exposure estimates used

Authors	Clavel J, Mandereau L, Limasset J, Hemon D, Cordier S
Publication Year	1994
Study type	Multicentre hospital-based case-control study
Geographic Region	France
Outcome	incidence
Study years (enrolment)	1984 to 1987
Years of follow-up	1984 to 1987

Study population	Patients admitted to multiple hospitals in five areas in France
Occupation/Exposure Data Source	Structured questionnaire, occupational exposures were evaluated by industrial health experts who were blind to case/control status, semi-quantitative classification of PAH exposure
Reference Population	Controls were patients admitted to variety of diseases other than cancer, haematuira and work accidents, matched to controls by gender, date of birth, hospital, place of residence and ethnic origin
Outcome Data Source	Cases presenting with histologically-confirmed bladder cancer, aged <80 years
Total Subjects Included for Analysis	765 cases, 765 controls
Bladder Cancer Risk Estimate	Overall Exposure to PAH (ng/m^3) Cases OR* 95% CI Unexposed 424 1.0 Exposed 231 1.3 1.0 to 1.7 Maximum exposure to PAH Unexposed 424 1.0 Low 129 1.2 0.9 to 1.7 Medium 64 1.3 0.9 to 2.1 High 29 1.8 0.9 to 3.6 P for trend <0/.05 Average exposure to PAH Unexposed 424 1.0 Low 127 1.2 0.9 to 1.7 Medium 64 1.4 0.9 to 2.2 High 26 1.8 0.8 to 3.9 P for trend <0.05 Cumulative exposure to PAH (ng/m^3 x years) Unexposed 424 1.0 <100 108 1.7 1.2 to 2.4 100-499 37 0.8 0.5 to 1.3 500- 14 999 48 1.3 0.8 to 2.0 ≥15 000 24 1.8 0.8 to 3.9 p for trend not significant *adjusted for cumulative smoking, coffee consumption, and subjects possibly exposed to aromatic amines
Exposure Quality (EQ) Score/Notes	EQ = 4 Semi-quantitative exposure estimates used Slight dose-response relationship observed

Authors	Pesch B, Haertling J, Ranft U, Klimpel A, Oelschlagel B, Schill W
Publication Year	2000
Study type	Population-based case-control study
Geographic Region	Germany
Outcome	incidence
Study years (enrolment)	1991 to 1995
Years of follow-up	1991 to 1995
Study population	German nationals
Occupation/Exposure Data Source	Face-to-face interview, structured questionnaire
Reference Population	Randomly selected population controls selected from local residency registries, controls matched to cases by region, sex and age
Outcome Data Source	Histologically confirmed urothelial cancer
Total Subjects Included for Analysis	704 male cases, 2650 controls
Bladder Cancer Risk Estimate	PAH Exposure Index Cases OR 95% CI Medium 97 1.0 0.8 to 1.3 High 123 1.3 1.0 to 1.7 Substantial 47 1.6 1.1 to 2.3
Exposure Quality (EQ) Score/Notes	EQ = 3 Qualitative exposure assessment using British JEM

Diesel Exhaust

Authors	Kellen E, Zeegers M, Paulussen A, Vlietinck R, Vlem E, Veulemans H, Bintinx F
Publication Year	2007
Study type	Population-based case-control study
Geographic Region	Belgium
Outcome	incidence
Study years (enrolment)	1999 to 2004
Years of follow-up	1999 to 2004
Study population	Population of Limburg Belgium
Occupation/Exposure Data Source	Structured interview, occupational exposure to PAHs, aromatic amines and diesel were blindly coded by 2 occupational hygienists
Reference Population	Simple random sampling of social security among all citizens 50+ years in the province of Limburg
Outcome Data Source	Histologically confirmed cases selected from the Limburg Cancer Registry
Total Subjects Included for Analysis	200 cases, 385 controls
Bladder Cancer Risk Estimate	Diesel Exposure Cases OR* 95% CI No exposure 144 1.00 Low exposure 20 0.80 0.40 to 1.57 High exposure 36 1.51 0.85 to 2.75 P for trend = 0.25

	*OR adjusted for sex, age, smoking status
Exposure Quality (EQ) Score/Notes	EQ = 4 Qualitative exposure estimates made by occupational hygienists

Authors	Soll-Johanning H, Bach E, Jensen S
Publication Year	2003
Study type	Nested case-control
Geographic Region	Denmark
Outcome	No distinction between incident and deceased cases
Study years (enrolment)	1900 to 1994
Years of follow-up	
Study population	Cohort of 18 174 bus and tramway employees employed by the Copenhagen Traffic Company from 1900 to 1994
Occupation/Exposure Data Source	Information on length of employement obtained from employment files
Reference Population	Random sample controls from cohort
Outcome Data Source	Danish cancer registry
Total Subjects Included for Analysis	84 cases, 255 controls
Bladder Cancer Risk Estimate	> 10 year lag cumulated employment Cases RR 95% CI <3 months 1 1.21 0.12 to 12.34 3 mo-2 yrs 11 1.00 10-<20 yrs 15 1.61 0.57 to 4.55 20+ yrs 33 1.28 0.52 to 3.13 *adjusted for smoking
Exposure Quality (EQ) Score/Notes	EQ = 3 Diesel exposure highly prevalent in this occupation, but exposure assessed only at level of occupation, no employment measurements estimated or obtained, environmental exposure to pollution estimated and accounted for

Authors	Steineck G, Plato N, Gerhardsson M, Norell S, Hogstedt C
Publication Year	1990
Study type	Population based case-control study
Geographic Region	Stockholm
Outcome	Incident cases
Study years (enrolment)	1985 to 1987
Years of follow-up	1985 to 1987
Study population	Men born between 1911 and 1945 living in County of Stockholm
Occupation/Exposure Data Source	Postal questionnaire on occupational history, hygienist blinded to case status classified subjects as exposed or unexposed, as well as level of exposure
Reference Population	Stratified random sample of register covering the population of Stockholm

Outcome Data Source	All incident cases of uorthelial cancer and/or squamous-cell carcinoma in the lower urinary tract
Total Subjects Included for Analysis	256 cases, 287 cases
Bladder Cancer Risk Estimate	Cases RR* 95% CI Diesel Exhausts 25 1.7 0.9 to 3.3 Diesel Exhaust Exposure RR* 95% CI Low 1.3 0.6 to 3.1 Moderate 2.2 0.7 to 6.6 High 2.9 0.3 to 30.0 *adjusted for year of birth and smoking
Exposure Quality (EQ) Score/Notes	EQ = 4 Occupational hygienist provided qualitative analysis levels of exposure for exposure of interest

Authors	Silverman D, Hoover R, Mason T, Swanson M
Publication Year	1986
Study type	Population-based case control study
Geographic Region	United States
Outcome	Incident cases
Study years (enrolment)	1977 to 1978
Years of follow-up	1977 to 1978
Study population	Residents of states that participate in the National Cancer Institute's SEER program aged 21 to 84 years
Occupation/Exposure Data Source	Interviews conducted by trained interviewers using questionnaire eliciting every job held for at least 6 months since the age of 12 years
Reference Population	Random digit dialing to contact controls from the general population of the study areas and stratified random sample drawn from health care financing administrative list of the population over 64 years for each study area
Outcome Data Source	All histologically confirmed cases of urinary bladder cancer as identified through population based cancer registry
Total Subjects Included for Analysis	1909 male cases, 3569 white male controls
Bladder Cancer Risk Estimate	Occupation cases RR* 95% CI Never any Motor exhaust Related occ 1353 1.0 Truck driver or deliveryman Ever 488 1.3 1.1 to 1.4 Usual 99 1.5 1.1 to 2.0 Taxi driver or chauffeur Ever 77 1.6 1.2 to 2.2 Usual 10 6.3 1.6 to 29.3 Bus driver Ever 49 1.3 0.9 to 1.9

	Usual 9 1.5 0.6 to 3.9 *adjusted for age and smoking Duration of employment Ever truck driver or deliveryman Years cases RR* <5 208 1.1 5-9 102 1.3 10-14 58 1.7 15-24 59 2.2 25+ 54 1.1 p<0.001 *adjusted for age and smoking No duration-response gradient observed for either taxi drivers or bus drivers
Exposure Quality (EQ) Score/Notes	EQ = 2 Diesel exhaust exposure prevalent in occupations studied but other exposures may be possible and are not accounted for

Authors	Smith E, Miller E, Woolson R, Brown C
Publication Year	1985
Study type	Population based case control study
Geographic Region	United States
Outcome	Incident cases
Study years (enrolment)	1977 to 1978
Years of follow-up	1977 to 1978
Study population	Residents of states that participate in the National Cancer Institute's SEER program aged 21 to 84 years
Occupation/Exposure Data Source	Face-to-face interviews using structured questionnaire
Reference Population	Age-sex-frequency matched to cases at 2:1 ratio in each geographic area
Outcome Data Source	Newly diagnosed, histologically confirmed carcinoma of the urinary bladder, including papillomas not specified as benign
Total Subjects Included for Analysis	2108 cases, 4046 controls
Bladder Cancer Risk Estimate	Mechanics RR 95%CI Smokers 1.21 0.90 to 1.63 Non-smokers 1.33 0.77 to 2.31 Chemically related Exposed Smokers 0.99 0.81 to 1.20 Non-smokers 1.53 1.13 to 2.07 Duration Smoker Nonsmoker Years RR (95%CI) RR (95%CI) 1-5 1.53 (1.07-2.20) 1.48 (0.73-2.75) 6-10 0.74 (0.43-1.28) 1.29 (0.54-3.11) 11-20 1.13 (0.67-1.92) 0.73 (0.21-2.53)

	21-29 2.77 (1.34-5.71) 0.51 (0.06-4.11) 30+ 1.19 (0.66-2.13) 2.13 (0.78-5.80)
Exposure Quality (EQ) Score/Notes	EQ = 3 Attempted to account for other possible exposures/similar exposures in analysis

Aromatic Amines

Authors	Bonassi S, Merlo F, Pearce N, Puntoni R
Publication Year	1989
Study type	Population-based case-control study
Geographic Region	Italy
Outcome	incidence
Study years (enrolment)	1972 to 1982
Years of follow-up	1972 to 1982
Study population	Population of Bormida Valley Italy
Occupation/Exposure Data Source	Standardized questionnaire administered by trained interviewers. Subjects classified into 11 occupational categories identified a priori. A job-exposure matrix constructed to assess potential lifetime exposure to PAH and aromatic amines.
Reference Population	Randomly selected from demographic registries of 19 communities from which the cases were identified
Outcome Data Source	Histologically confirmed cases identified from hospital admission-discharge records
Total Subjects Included for Analysis	121 cases, 342 controls
Bladder Cancer Risk Estimate	Aromatic Amine (w/ exposure to PAH) Exposure Cases OR* 95% CI No exposure 32 1.00 Low exposure 17 0.81 0.33 to 1.96 Med exposure 32 1.14 0.50 to 2.45 High exposure 39 3.55 1.56 to 8.06 *OR adjusted for smoking status
Exposure Quality (EQ) Score/Notes	EQ = 3 Occupations included where aromatic amines are highly prevalent and other exposures such as PAHs have been accounted for. JEM used to assess potential lifetime exposure to PAH and aromatic amines.

Authors	Boyko R, Cartwright R, Chir B, Glashan R
Publication Year	1985
Study type	Hospital-based and population-based case-control
Geographic Region	England
Outcome	incident and prevalent cases
Study years (enrolment)	Incident cases from 1978 to 1981, prevalent cases (diagnosed within the previous five years) from April to September 1978
Years of follow-up	1978 to 1981
Study population	Six districts in West Yorkshire England

Occupation/Exposure Data Source	Subjects classified as chemical dye workers or non-chemical dye workers according to information collected in face-to-face interviews
Reference Population	Controls were patients of the same sex and age who occupied a hospital bed in the same hospital within 3 months of a case. Small subset of population-based controls also interviewed.
Outcome Data Source	Any bladder cancer identified in the records of the District Health Authority of six districts in West Yorkshire
Total Subjects Included for Analysis	932 cases, 1457 controls
Bladder Cancer Risk Estimate	RR* 95% CI 2.60 1.84 to 3.66 *adjusted for age and smoking
Exposure Quality (EQ) Score/Notes	EQ = 2 Aromatic amine exposure highly prevalent in dye manufacturing workers, but exposure assessed only at level of occupation, no employment measurements estimated or obtained

Authors	Kellen E, Zeegers M, Paulussen A, Vlietinck R, Vlem E, Veulemans H, Bintinx F
Publication Year	2007
Study type	Population-based case-control study
Geographic Region	Belgium
Outcome	incidence
Study years (enrolment)	1999 to 2004
Years of follow-up	1999 to 2004
Study population	Population of Limburg Belgium
Occupation/Exposure Data Source	Structured interview, occupational exposure to PAHs, aromatic amines and diesel were blindly coded by 2 occupational hygienists
Reference Population	Simple random sampling of social security among all citizens 50+ years in the province of Limburg
Outcome Data Source	Histologically confirmed cases selected from the Limburg Cancer Registry
Total Subjects Included for Analysis	200 cases, 385 controls
Bladder Cancer Risk Estimate	Aromatic Amines Exposure Cases OR* 95% CI No exposure 176 1.00 Low exposure 6 2.16 0.54 to 8.69 High exposure 18 5.75 2.09 to 15.83 P for trend = 0.00 *OR adjusted for sex, age, smoking status
Exposure Quality (EQ) Score/Notes	EQ = 4 Qualitative exposure estimates made by occupational hygienists

Authors	Schulte P, Ringen K, Hemstreet G, Altekruse E, Gullen W, Tillett S, Allsbrook W, Crosby J, Witherington R, Stringer W, Brubaker M.
Publication Year	1986
Study type	Nest case-control study
Geographic Region	United States
Outcome	Incidence
Study years (enrolment)	1940 to 1972
Years of follow-up	1940 to 1983
Study population	All hourly workers ever employed at plant between January 1 1940 and December 31 1972.
Occupation/Exposure Data Source	As part of a medical screening program work in high exposure departments of the plant was identified. Information on potential risk factors such as race, marital, educational and income status, use of tobacco, work in other high risk occupations etc was gathered by questionnaire.
Reference Population	Remaining 1372 workers in overall cohort
Outcome Data Source	Bladder cancer assessed through medical screening program, contacting local urologists and death certificates of deceased members of the cohort
Total Subjects Included for Analysis	1385 workers (13 cases, 1372 controls)
Bladder Cancer Risk Estimate	Cases OR* 95% CI 13 4.3 1.8 to 10.3 *controlled for age, smoking and source of drinking water
Exposure Quality (EQ) Score/Notes	EQ = 3 Qualitative exposure information determining areas of high exposure and questionnaire used for information on other potential exposures

Authors	Vineis P, Esteve J
Publication Year	1987
Study type	Hospital-based case-control study (did not specify if cancer controls were included)
Geographic Region	Italy
Outcome	Incidence
Study years (enrolment)	Not specified
Years of follow-up	Not specified
Study population	Hospital patients under 70 years residing in Turin, Italy
Occupation/Exposure Data Source	Standardized questionnaire administered by trained interviewers capturing items such as life history of smoking and complete occupational history.
Reference Population	Hospital controls less than 70 years at time of diagnosis.
Outcome Data Source	Hospital based bladder cancer patients (no indication of how bladder cancer diagnosis

	was confirmed or ascertained)
Total Subjects Included for Analysis	461 cases, 566 controls
Bladder Cancer Risk Estimate	Cases OR* 95% CI 42 2.96 1.7 to 5.3 *controlled for age, and dose, duration of smoking and smoking status
Exposure Quality (EQ) Score/Notes	EQ = 2 Exposed individuals were considered if worked for at least 6 months in the rubber industry or in dyestuff production. Carcinogens of interest are present in these occupational groups but no indication if other possible occupational exposures were accounted for