Exhibit 300

American Journal of
EPIDEMIOLOGY

Volume 140
Number 12
December 15, 1994

Sponsored by the Society for Epidemiologic Research

ORIGINAL CONTRIBUTIONS

Occupational Risk Factors for Bladder Cancer: Results from a Case-Control Study in Montreal, Quebec, Canada

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A population-based case-control study of the associations between various cancers and occupational exposures was carried out in Montreal, Quebec, Canada. Between 1979 and 1986, 484 persons with pathologically confirmed cases of bladder cancer and 1,879 controls with cancers at other sites were interviewed, as was a series of 533 population controls. The job histories of these subjects were evaluated by a team of chemist/hygienists for evidence of exposure to a list of 294 workplace chemicals, and information on relevant non-occupational confounders was obtained. On the basis of results of preliminary analyses and literature review, 19 occupations, 11 industries, and 23 substances were selected for in-depth multivariate analysis. Logistic regression analyses were carried out to estimate the odds ratio between each of these occupational circumstances and bladder cancer. There was weak evidence that the following substances may be risk factors for bladder cancer: natural gas combustion products, aromatic amines, cadmium compounds, photographic products, acrylic fibers, polyethylene, titanium dioxide, and chlorine. Among the substances evaluated which showed no evidence of an association were benzo(*a*)pyrene, leather dust, and formaldehyde. Several occupations and industries were associated with bladder cancer, including motor vehicle drivers and textile dyers. *Am J Epidemiol* 1994;140:1061–80.

automobile driving; automobile exhaust; benzo(*a*)pyrene; bladder neoplasms; fossil fuels; mineral oil; occupational exposure; paint

Internationally, there is about a 10-fold variation in the incidence of bladder cancer, with the highest rates appearing in western Europe and North America (1). The variation among Caucasian populations in different areas of western Europe and North America is only about twofold, with an annual incidence among males in the range

Received for publication December 21, 1993, and in final form August 29, 1994.

Abbreviation: CI, confidence interval.

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of 15–30 per 100,000 (1). The incidence is about 5 times lower among females.

The most important known risk factor for bladder cancer in North America and Europe is cigarette smoking, which increases the risk two- to fivefold and which may be responsible for as many as 50 percent of all cases (2). There is some evidence that coffee drinking increases bladder cancer risk, but if it does, the carcinogenic effect is weak (3). There is no strong evidence that diet or other lifestyle habits are risk factors for bladder cancer. While there have been some reports implicating various other factors as etiologic agents (diet, water chlorination by-products, some medications, urinary tract infections), for none of them is the current evidence strong enough to conclude that they are responsible for significant fractions of bladder cancer in industrialized countries (4).

Bladder cancer has long been recognized as an occupation-related tumor. It has been estimated that as much as 20 percent of bladder cancers could be attributable to occupational carcinogens (5). There are several known and suspected occupational bladder carcinogens, some of which have been recognized for many decades. Most notable among these are 2-naphthylamine and benzidine, which have been associated with relative risks as high as 10–50 among highly exposed workers (6, 7). Excess risks of bladder cancer have been documented in cohorts from several industries: magenta or auramine manufacturing, the rubber industry, aluminum production, and coal gasification. However, some of these industries have been transformed or virtually eliminated, and it is not clear whether substantial risks of occupational bladder cancer remain.

In 1979, a population-based case-control study was undertaken in Montreal, Quebec, Canada, to search for evidence on the possible associations between many types of cancer and hundreds of occupational exposures (8). Detailed job histories were collected from cancer cases and population controls, and a specially trained team of industrial hygienists and chemists translated the job descriptions into histories of occupational exposures. In an initial statistical analysis, estimates were made of the odds ratio between each cancer site and each occupational exposure (9). The present paper reports results from much more refined analyses, focusing only on bladder cancer as a target organ and on two sets of occupational exposures: those that were associated with bladder cancer in the initial analysis and those for which there was prior evidence of an effect.

MATERIALS AND METHODS

The study's overall design and data collection methods have been detailed elsewhere (9–11) and will be briefly sketched here. A total of 19 cancer sites were selected for study among males aged 35–70 years who resided in the Montreal area. Participation of all large hospitals in the area assured virtually complete population-based ascertainment of cases. A case was eligible for inclusion in the study only if the diagnosis was new and had been histologically confirmed. Between 1979 and 1986, out of 4,576 eligible cancer patients, a total of 3,730 patients (82 percent) were successfully interviewed, mostly face-to-face. Over 82 percent of the subjects responded for themselves; proxies provided information for the rest. During the same period, 740 population controls were selected, in some years from electoral lists and in some years by random digit dialing. (In Canada, an active enumeration process results in virtually complete electoral lists. However, they are compiled just prior to elections, and thus become outdated within a few years.) Of these, 533 persons (72 percent) were successfully interviewed.

The questionnaire had two parts: a structured section requesting information on important potential confounders and a semistructured probing section designed to obtain a detailed description of each job the subject had had in his working lifetime.

A team of chemists and hygienists examined each completed questionnaire and translated each job into a list of potential exposures by means of a checklist form which included 294 substances. For each exposure thought to be present in a given job, the chemists noted three dimensions of information, each on a three-point scale: their degree of confidence that the exposure had actually occurred (possible, probable, or definite), the frequency of exposure during a normal workweek (<5 percent, 5–30 percent, or >30 percent), and the level of concentration of the agent in the environment (low, medium, or high).

Bladder cancer cases and controls

There were 484 bladder cancer patients interviewed out of 575 eligible subjects (a response rate of 84 percent). Among the 484 bladder cancers, 91 percent were papillary or transitional cell types, 8 percent were adenocarcinomas, and 1 percent were squamous cell carcinoma. Two distinct sets of controls were used, population controls and cancer controls. The population control group consisted of the 533 subjects mentioned above. A cancer control group was formed, consisting of most other cancer patients interviewed in the study, excluding those with lung or kidney cancer. Among the remaining sites, we subsampled some of the more numerous ones to ensure that no single site would constitute more than 25 percent of all cancer controls. In total, there were 1,879 cancer controls, consisting of the following sites: esophagus (n = 97), stomach (n = 247), small intestine (n = 20), colon (n = 197), rectum (n = 255), liver (n = 47), gallbladder (n = 30), pancreas (n = 115), prostate (n = 390), testis (n = 25), melanoma (n = 120), lymphoid tissue (n = 266), myeloma (n = 23), and others (n = 47).

Selected characteristics of the bladder cancer cases and the two control groups are given in table 1. The distributions of the following variables were similar across case and control groups: age, ethnic group, family income, and vitamin A consumption index. There were differences in smoking, coffee consumption, and status of the respondent (self vs. proxy).

TABLE 1. Selected characteristics of case and control groups in a study of bladder cancer and occupational exposures, Montreal, Quebec, Canada, 1979–1986

Non-occupational factor	Cases (n = 484)	Control group: Cancer (n = 1,879)	Control group: Population (n = 533)
Mean age (years)	59.3	58.5	59.6
Mean annual family income (dollars)*	25,818	25,522	26,430
Ethnic French-Canadian (%)	60	60	61
Ever a regular smoker (%)	91	82	80
Ever a regular coffee drinker (%)	89	84	86
Mean vitamin A index	113	109	112
Proxy respondent (%)	14	22	13

* Indexed to 1981 values.

Previous analysis

A preliminary analysis of this data set has been conducted focusing on 294 exposures, 98 occupation categories, and 77 industry categories (i.e., a total of 469 occupational circumstances) (9). The occupation and industry categories were exhaustive but not mutually exclusive (e.g., truck driver and motor vehicle worker were separate categories, although the former was a subset of the latter). Risk due to each occupational circumstance (substance, job group, or industrial group) was evaluated in four different analytic configurations based on population controls or cancer controls and ever exposed or substantially exposed, where the latter was a function of duration and intensity of exposure. All analyses were carried out using the Mantel-Haenszel method (12). For bladder cancer, there was stratification on the following confounding variables: age, ethnicity, smoking, socioeconomic status, regular coffee consumption, and respondent status (self or proxy). Many occupational circumstances were apparently associated with bladder cancer. Whereas these initial analyses were based on one-exposure-at-a-time models, it was desirable to carry out analyses in which the mutual confounding among exposures might be taken into account.

Selection of exposure variables for the present analysis

It was not feasible to carry out multivariate analyses in which all 469 occupational circumstances that were available for analysis would be included in a statistical model. Two subgroups of circumstances were selected for in-depth evaluation in the present analysis: those that are recognized or suspected bladder cancer risk factors, irrespective of how they performed in our initial analyses, and those that showed evidence of association in our initial analyses. Based partly on the IARC Monograph program (13) and partly on our own review of the literature, and using rather liberal criteria, we compiled a list of exposures, occupations, and industries that are recognized or suspected risk factors for bladder cancer. Some of these could not be assessed in our data set, either because the relevant information had not been collected or because the exposure was too rare in our study population. For instance, although various specific aromatic amines have been shown to be bladder carcinogens, our coding of exposure did not extend to that level of detail; we only assessed exposure to aromatic amines as a class. In addition, the following high-risk industrial processes were not present in our study population in sufficient numbers to justify separate analyses: magenta or auramine manufacturing, leather tanning, coal gasification, rubber production, and aluminum refining. For most of the circumstances that were selected on the basis of the literature and that we were able to evaluate, the preponderance of existing literature is, at most, suggestive of an association. Only a handful of them may be thought of as established risk factors for bladder cancer.

With regard to circumstances selected on the basis of our initial results, the criteria for selection were the following: The occupational circumstance was associated with bladder cancer with an odds ratio of at least 1.3 and a one-sided p value less than 0.10, and there were at least four exposed cases. As indicated above, the odds ratios were estimated with two control groups (cancer and population) and at two exposure levels (any and substantial). The risk factor was flagged for inclusion if any of the four odds ratio estimates satisfied the criteria.

Because of the high correlations among some occupational substances and the risk of collinearity in multivariate analyses, some further pruning was carried out. One reason for high correlations among substances is the fact that our substance checklist involved some hierarchies of categories (e.g., titanium dioxide was on the list, as well as the more general category of titanium compounds). Where two such variables were earmarked by the process described above and if one represented a substantial subset of the other, we removed the more general category. Thus, the following general exposure categories were dropped in favor of more specific ones: aliphatic aldehydes in favor of formaldehyde and titanium compounds in favor of titanium dioxide. Polyester fibers was dropped in favor of acrylic fibers, because nearly everyone exposed to the former was exposed to the latter.

On the basis of these inclusion and exclusion criteria, a total of 19 occupations, 11 industries, and 23 substances were retained for the present analyses. The Appendix shows the 53 circumstances selected, grouped by type of circumstance and by whether they were selected from previous literature or from our own initial analyses.

Present analyses

The objective was to estimate odds ratios between bladder cancer and each of the 53 selected occupational circumstances. All analyses were carried out using unconditional logistic regression models, fitted with SPSS (14, 15). The following non-occupational variables were retained as potential confounders in all regression models: age, family income, ethnicity, cumulative smoking index, index of coffee consumption, and respondent status (self or proxy). Ethnicity and respondent status were entered as categorical variables, the rest as continuous linear variables.

Parallel sets of analyses were carried out with three control groups: the cancer controls (n = 1879), the population controls (n = 533), and the pooled group of cancer and population controls (n = 2412). For most occupational circumstances analyzed, there was rather little difference between results based on cancer controls and those based on population controls. Consequently, for the sake of economy, we present mainly the results based on the pooled controls. However, a test was carried out to assess the "poolability" of the control groups with regard to each circumstance. Including only the two control groups in the analysis, and using control group status as the outcome variable, each occupational circumstance was included in a logistic regression model containing the non-occupational confounders. Any circumstance that made a statistically significant contribution at $p < 0.05$ was deemed to differ according to control group, and for these factors only, we present separate results from the two different control groups.

For occupations, mutual confounding by other occupations is not a problem, since correlations among occupations tend to be low. The same holds true for industries. Thus, the only analyses carried out for occupations and industries were those based on models in which each occupation or industry was included in a separate model with the above set of non-occupational confounders, with exposure categorized into two categories: 10 years or less of employment in the occupation or industry of interest, and more than 10 years.

For substances, there were several stages of analysis. The first stage was similar to that for occupations and industries. It focused on estimating the odds ratio associated with each selected substance on bladder cancer risk, adjusting only for the non-occupational confounders, and ignoring the mutual confounding by other occupational exposures. We refer to these as "partially adjusted" models. From the partially adjusted results, we selected 10 substances that showed some evidence of an association with bladder cancer, and these were included in a core group of substances to be entered into a set of multivariate "fully adjusted" models. Each substance was reanalyzed in a model containing all of the substances in this core group, as well as the non-occupational variables. For these analyses, three mutually exclusive exposure groups were defined, using criteria shown in table 2.

The two exposed groups were compared with the unexposed. On the basis of these results, we did a further subselection of substances, and these were analyzed with

TABLE 2. Criteria for defining an unexposed group and two exposed groups for each exposure variable: study of bladder cancer and occupational exposures, Montreal, Quebec, Canada, 1979–1986

Exposure group*	Confidence†	Latency‡ (years)		Duration (years)	Concentration (1, 2, 3) × frequency (1, 2, 3)§
Substantial exposure	Probable or definite	>5		>5	≥4
Nonsubstantial exposure	Probable or definite	>5		<5	Any
			or		
	Probable or definite	>5		>5	<4
Unexposed	Possible	Any		Any	Any
			or		
	Any	<5		≤5	Any
			or Not exposed		

* The three categories given are exhaustive and mutually exclusive.
† Possible, probable, or definite.
‡ Number of years since first exposure.
§ Scores (1, 2, 3) correspond to low, medium, and high.

respect to frequency, concentration, and duration of exposure and with regard to substance-specific risks in different occupations and industries.

RESULTS

Occupations and industries

Table 3 presents the logistic regression results for each industry and occupation selected for analysis, using the pooled controls. If the analysis using either cancer controls or population controls conveyed substantially different information, this is indicated in a footnote. Based on the magnitude of the odds ratio, its statistical significance, and the duration-response trend, there was some evidence of an effect for the following occupations: production managers, teachers and professors (particularly vocational school teachers), and textile dyers and finishers. For a number of occupations—slaughterers and meat processors, metal machinists, sheet metal workers, masons and tile setters, construction painters, insulation workers, air transport workers, and motor transport workers—there were excesses that were not statistically significant or for which the significant excess was seen only in the short duration workers. Analogously, among industries, there was some evidence of an effect for pulp and paper mills, motor transport, and communications, with more equivocal evidence for printing and publishing, metal fabricating and machining, motor vehicle sales and service, and welfare and religious services.

Substances

Table 4 presents, for each substance evaluated, the main occupations in which the substance was present and the corresponding lifetime prevalence of exposure. Table 5 presents the logistic regression results for each substance selected for analysis, using the pooled controls. The table shows results from both the "partially adjusted" models and the "fully adjusted" model, at two levels of exposure. Most of the substances that were selected on the basis of previous literature did not show any evidence of positive associations in these analyses, except for aromatic amines and possibly cutting fluids and diesel exhaust. In the fully adjusted models, there was, as expected, a diminution of statistical precision, as manifested in wider confidence intervals.

In general, the estimates were not greatly changed as a result of inclusion of all the other occupational exposures. There were slightly more changes toward the null than away from the null. There were no overwhelmingly high and statistically significant odds ratios. The only substance that showed statistically significant odds ratios at the substantial level in the fully adjusted model was natural gas combustion products. Aromatic amines and cadmium compounds were significant at the substantial level only in the partially adjusted model. Calcium carbonate and titanium dioxide were significant only at the nonsubstantial level in the partially adjusted model. Chlorine, acrylic fibers, and polyethylene had odds ratios over 1.4, with indications of dose response, but the findings were not statistically significant.

Seven substances were subjected to further more detailed analyses. These were substances which had large enough numbers exposed to sustain detailed statistical analyses, and which either showed evidence of an effect in table 5 or aroused suspicion in other studies. For each of the substances selected, table 6 shows the odds ratios by each of the following dimensions: confidence, concentration, frequency, and duration. Because of small numbers, the three categories in each dimension were collapsed to two. To simplify the analyses, each of these logistic regression models (a separate regression was run for each dimension) included only one substance plus the non-occupational covariates. Thus, if one believes that the fully adjusted model gives a more valid estimate than the partially adjusted model, one might think that the odds ratios in table 6 may be biased, but the trends across levels of concentration, frequency, etc., are valid.

In addition, analyses were carried out to determine whether there was any particu-

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TABLE 3. Odds ratios for the relations between bladder cancer and selected occupations and industries, by duration of employment, Montreal, Quebec, Canada, 1979–1986*

Occupation or industry	Duration of exposure†					
	<10 years			≥10 years		
	No.	OR‡	95% CI‡	No.	OR	95% CI
Occupations						
Selected on the basis of literature						
Barbers and hairdressers	0	—§		4	1.0	0.3–2.9
Textile dyers and finishers	2	0.8	0.2–3.7	2	10.8	1.0–120
Metal machinists‖	11	1.1	0.5–2.0	16	1.4	0.8–2.5
Sheet metal workers	21	1.7	1.0–2.9	18	1.3	0.7–2.1
Leather workers	12	1.0	0.5–1.9	14	0.7	0.4–1.3
Shoemakers	5	2.0	0.7–5.6	1	0.3	0.0–2.0
Construction painters	5	1.2	0.4–3.2	8	1.5	0.7–3.4
Other painters	5	1.1	0.4–3.0	4	0.9	0.3–2.7
Motor transport workers	40	1.4	0.9–2.0	46	1.3	0.9–1.9
Truck drivers (subset of the above group)	25	1.1	0.7–1.8	26	1.2	0.8–1.9
Added on the basis of results of initial analyses						
Production managers	0	—¶	0.0–1.4	7	3.5	1.3–9.4
Teachers and professors	5	0.7	0.3–1.8	19	2.4	1.3–4.1
Vocational school teachers (subset of the above group)	3	1.2	0.3–4.5	7	4.3	1.6–11.9
Slaughterers and meat processors	8	2.8	1.2–6.7	4	0.7	0.2–2.0
Wood machinists#	4	1.5	0.5–4.7	2	2.1	0.4–11.0
Concrete finishers	0	—¶	0.0–2.0	4	2.6	0.7–9.2
Masons and tile setters	6	2.1	0.8–5.4	6	1.6	0.6–4.0
Insulation workers	4	4.3	1.0–17.8	0	—¶	0.0–2.7
Air transport workers	6	3.3	1.2–9.1	0	—¶	0.0–5.5
Industries						
Selected on the basis of literature						
Textiles	17	1.1	0.7–1.9	7	1.0	0.4–2.3
Printing and publishing	2	0.3	0.1–1.2	11	1.9	0.9–3.9
Metal fabricating and machining**	31	1.4	0.9–2.1	26	1.2	0.7–1.8
Petroleum and coal products	4	0.9	0.3–2.7	2	0.4	0.1–1.6
Chemical production	16	1.1	0.6–2.0	7	1.0	0.4–2.3
Motor transport	34	1.9	1.2–2.8	40	1.7	1.2–2.5
Added on the basis of results of initial analyses						
Flour, feed, and bakery products††	10	1.2	0.6–2.4	8	1.1	0.5–2.4
Pulp and paper mills	4	0.5	0.2–1.5	7	2.6	1.0–6.6
Communications	4	0.5	0.2–1.5	14	2.2	1.2–4.1
Motor vehicle sales and service	25	1.8	1.1–3.0	13	0.9	0.5–1.6
Welfare and religious services	8	2.2	0.9–5.0	3	0.9	0.3–3.0

* The control group consisted of the pool of cancer controls and population controls. If the two control groups differed significantly, the results are presented separately in a footnote. For each occupation or industry, the reference (unexposed) group consisted of all those who did not work in that occupation or industry. Each logistic regression model included the occupation/industry of interest as well as age, ethnicity, socioeconomic status, smoking, coffee consumption, and the status (self/proxy) of the respondent.

† The 5 years preceding the interview are not counted in the duration of exposure.

‡ OR, odds ratio; CI, confidence interval.

§ There were no exposed cases or controls. The odds ratio and confidence interval are undefined.

‖ OR for <10 years of exposure was 1.3 with cancer controls, 0.6 with population controls.

¶ There were no exposed cases. The odds ratio and lower confidence limit are both undefined. The upper confidence limit from the crude 2 × 2 table was calculated by Fisher's exact method.

\# OR for <10 years of exposure was 2.4 with cancer controls, 0.6 with population controls.

** OR for >10 years of exposure was 1.3 with cancer controls, 0.9 with population controls.

†† OR for <10 years of exposure was 1.5 with cancer controls, 0.6 with population controls.

TABLE 4. Main occupations in which the selected substances occurred: study of bladder cancer and occupational exposures, Montreal, Quebec, Canada, 1979–1986

Substance (lifetime prevalence*)	Main occupations†
Selected on the basis of literature	
Aromatic amines (7%)	Painters; printshop workers; shoemakers and repairmen
Leather dust (3%)	Shoemakers; leather cutters; hide and pelt processors
Diesel engine emissions (15%)	Truck drivers; bus drivers; heavy machinery operators
Cutting fluids, mildly refined (7%)	Machinists; pipefitters and plumbers; tool and die makers
Cutting fluids, highly refined (6%)	Machinists; pipefitters and plumbers; tool and die makers
Coal tar and pitch (2%)	Roofers; pipefitters and plumbers; aluminum refinery workers
Benzo(*a*)pyrene (22%)	Motor vehicle mechanics; machinists; foundry workers
Creosote (1%)	Railway trackmen; roofers; power linemen
Added on the basis of results of initial analyses	
Clay dust (2%)	Foundry molders and coremakers; painters; foundry laborers
Cadmium compounds (1%)	Tool and die makers; jewelers; pipefitters and plumbers
Calcium carbonate (7%)	Painters and plasterers; teachers; stationary engineers
Lead chromate (3%)	Construction painters; motor vehicle refinishers; motor vehicle mechanics
Titanium dioxide (4%)	Construction painters; motor vehicle refinishers; motor vehicle mechanics
Chlorine (2%)	Launderers; textile processors; pipefitters and plumbers
Natural gas combustion products (3%)	Food and beverage workers; sheet metal workers; stationary engineers
Fabric dust (10%)	Tailors and dressmakers; textile cutters; textile shippers and material handlers
Acrylic fibers (2%)	Tailors and sewing machine operators; upholsterers; pressers
Polyethylene (0.5%)	Shoemakers and repairmen; plastic molders
Other mineral oils (4%)	Printshop workers; textile workers; forgers
Formaldehyde (15%)	Carpenters; textile workers; laundry workers and dry cleaners
Carbon tetrachloride (4%)	Firefighters; metal machinists; electricians
Laboratory products (1%)	Chemical engineers; chemists; physical science technicians
Photographic products (0.6%)	Photoengravers; photographers; photographic processors

* Percentage of all study subjects who, according to our coding, were ever exposed to this substance. Subjects with possible exposure (i.e., confidence = 1) were not considered exposed. Rounded to the nearest percentage for prevalence ≥1; rounded to the nearest decimal for prevalence <1.

† Occupations with the largest numbers of men exposed to this substance in our sample. These are not necessarily the occupations with the highest concentrations of exposure.

larly high risk among workers exposed to the substance in any particular occupation or industry. If so, this might indicate that the apparent excess risk was due not to the substance per se but rather to something else about that subset of workers. This was done by identifying the most prevalent occupations and industries among all persons exposed to the substance (e.g., for natural gas combustion products, the occupations were cooks/chefs and sheet metal workers) and estimating odds ratios for the combination of the substance and each occupation. The odds ratios for the substance-occupation combinations were compared with the odds ratio for the substance as a whole, irrespective of where exposure occurred. If one or more of the substance-occupation combinations evidenced particularly high risk, this was considered noteworthy, and we will comment below when any such interaction was observed. The absence of a comment implies that there was no such concentration of the risk.

Aromatic amines did not manifest an evident dose-response pattern with any of the dimensions of exposure, but there were few subjects exposed at high confidence or at medium to high concentrations. For diesel engine emissions, the odds ratios hardly varied by concentration, confidence, and frequency; the highest odds ratio by duration was in the middle category. This pattern does not argue for a causal association

TABLE 5. Odds ratios for the relations between bladder cancer and selected occupational exposures, at two levels of exposure and using two statistical models, Montreal, Quebec, Canada, 1979–1986*

Substance	Partially adjusted model†						Fully adjusted model‡			
	Nonsubstantial§			Substantial§			Nonsubstantial		Substantial	
	No.	OR‖	95% CI‖	No.	OR	95% CI	OR	95% CI	OR	95% CI

TABLE 5. Odds ratios for the relations between bladder cancer and selected occupational exposures, at two levels of exposure and using two statistical models, Montreal, Quebec, Canada, 1979–1986*

Substance	Partially adjusted model†						Fully adjusted model‡			
	Nonsubstantial§			Substantial§			Nonsubstantial		Substantial	
	No.	OR‖	95% CI‖	No.	OR	95% CI	OR	95% CI	OR	95% CI
Selected on the basis of literature										
Aromatic amines	30	1.0	0.7–1.5	9	2.1	1.0–4.8	0.7	0.4–1.2	1.7	0.7–4.0
Leather dust	8	0.7	0.3–1.6	5	0.6	0.3–1.7	0.7	0.3–1.5	0.6	0.2–1.5
Diesel engine emissions	46	1.3	0.9–1.8	32	1.0	0.7–1.5	1.3	0.9–1.9	1.0	0.6–1.4
Cutting fluids, mildly refined	24	1.1	0.7–1.7	13	1.2	0.7–2.3	1.1	0.7–1.7	1.3	0.7–2.5
Cutting fluids, highly refined	13	0.8	0.4–1.4	13	1.2	0.6–2.2	0.7	0.4–1.4	1.0	0.5–2.1
Coal tar and pitch	7	0.8	0.4–1.9	6	1.2	0.5–3.0	0.7	0.3–1.7	1.3	0.5–3.3
Benzo(*a*)pyrene	91	1.0	0.8–1.3	15	0.8	0.4–1.3	1.0	0.8–1.3	0.6	0.3–1.1
Creosote	6	1.2	0.5–2.9	1	0.4	0.1–3.3	1.1	0.4–2.9	0.4	0.1–3.3
Added on the basis of results of initial analyses										
Clay dust	8	1.4	0.6–3.2	5	1.1	0.4–3.0	1.1	0.5–2.7	0.9	0.3–2.6
Cadmium compounds	2	0.6	0.1–2.8	4	4.0	1.0–16.3	0.5	0.1–2.4	3.2	0.7–13.6
Calcium carbonate	38	1.5	1.0–2.2	8	1.1	0.5–2.4	1.4	0.9–2.2	1.0	0.4–2.3
Lead chromate	22	1.5	0.9–2.4	1	0.8	0.1–7.2	1.1	0.5–2.2	0.6	0.1–5.8
Titanium dioxide	25	1.5	1.0–2.5	3	1.8	0.5–6.5	1.3	0.8–2.2	1.8	0.4–7.6
Chlorine¶	5	0.6	0.2–1.4	9	1.9	0.8–4.1	0.5	0.2–1.4	1.8	0.8–3.9
Natural gas combustion products	14	1.1	0.6–2.0	8	3.1	1.3–7.7	1.2	0.6–2.2	3.0	1.2–7.5
Fabric dust	22	0.8	0.5–1.3	25	0.9	0.6–1.5	0.8	0.5–1.3	0.7	0.4–1.2
Acrylic fibers	9	1.5	0.7–3.2	7	1.5	0.6–3.6	1.5	0.7–3.3	1.6	0.7–3.8
Polyethylene	3	1.3	0.4–4.7	2	8.1	0.7–93.6	1.3	0.4–4.8	5.9	0.5–71.1
Other mineral oils	16	1.2	0.7–2.0	5	1.5	0.5–4.0	1.1	0.6–1.9	1.3	0.5–3.7
Formaldehyde	67	1.2	0.9–1.6	17	1.2	0.7–2.0	1.2	0.9–1.6	0.9	0.5–1.7
Carbon tetrachloride	10	0.7	0.3–1.3	11	1.4	0.7–2.8	0.5	0.2–1.1	1.4	0.7–2.8
Laboratory products	1	0.3	0.0–2.3	5	1.6	0.6–4.6	0.3	0.0–2.5	1.4	0.5–3.9
Photographic products	0	—#	0.0–12.1	4	3.0	0.9–10.1	—#	0.0–12.1	3.0	0.9–10.1

* The control group consisted of the pool of cancer controls and population controls. If the two control groups differed significantly, the results are presented separately in a footnote. For each substance, the reference (unexposed) group consisted of all those who were not exposed to that substance.

† The partially adjusted model included the exposure of interest as well as age, ethnicity, socioeconomic status, smoking, coffee consumption, and status (self/proxy) of the respondent.

‡ The fully adjusted model included, in addition to the above, all of the following substances: titanium dioxide, acrylic fibers, polyethylene, chlorine, mildly refined cutting fluids, cadmium compounds, and aromatic amines.

§ See text for explanation of nonsubstantial and substantial exposure levels. The unexposed have an OR of 1.0, by definition.

‖ OR, odds ratio; CI, confidence interval.

¶ The OR for substantial exposure (fully adjusted) using population controls was 10.3; the OR using cancer controls was 2.9. The difference was significant at $p \leq 0.05$.

\# There were no exposed cases. The odds ratio and lower confidence limit are both undefined. The upper 95% confidence limit from the crude 2×2 table was calculated by Fisher's exact method.

TABLE 6. Time- and dose-related odds ratios between bladder cancer and selected substances, Montreal, Quebec, Canada, 1979–1986

Substance and parameter	No.	OR*	95% CI*
Aromatic amines			
Confidence			
Probable	31	1.3	0.9–2.0
Definite	8	0.7	0.3–1.6
Concentration			
Low	31	1.1	0.7–1.7
Medium/high	8	1.2	0.5–2.5
Frequency			
Low/medium	31	1.2	0.8–1.9
High	8	0.8	0.4–1.8
Duration (years)			
1–10	12	0.9	0.5–1.7
≥11	27	1.3	0.8–2.0
Diesel engine emissions			
Confidence			
Probable	28	1.0	0.7–1.6
Definite	50	1.2	0.9–1.7
Concentration			
Low	27	1.2	0.8–1.9
Medium/high	51	1.1	0.8–1.5
Frequency			
Low/medium	48	1.1	0.8–1.5
High	30	1.3	0.8–1.9
Duration (years)			
1–10	22	1.2	0.7–1.9
≥11	56	1.3	0.8–1.5
Cutting fluids, mildly refined			
Confidence			
Probable	13	1.0	0.5–1.9
Definite	24	1.2	0.7–1.9
Concentration			
Low	16	1.1	0.6–1.8
Medium/high	21	1.2	0.7–1.9
Frequency			
Low/medium	23	1.1	0.7–1.7
High	14	1.2	0.6–2.1
Duration (years)			
1–10	19	1.2	0.7–2.0
≥11	18	1.0	0.6–1.8
Calcium carbonate			
Confidence			
Probable	26	1.3	0.8–2.0
Definite	20	1.7	1.0–3.0
Concentration			
Low	35	1.6	1.1–2.4
Medium/high	11	1.0	0.5–2.0
Frequency			
Low/medium	35	1.4	1.0–2.1
High	11	1.4	0.7–2.7

(Table continues)

TABLE 6. Continued

Substance and parameter	No.	OR*	95% CI*
Duration (years)			
1–10	9	0.8	0.4–1.7
≥11	37	1.7	1.2–2.6
Titanium dioxide			
Confidence			
Probable	3	0.8	0.2–2.9
Definite	25	1.7	1.1–2.8
Concentration			
Low	24	1.4	0.9–2.4
Medium/high	4	2.6	0.8–8.7
Frequency			
Low/medium	16	1.5	0.9–2.7
High	12	1.6	0.8–3.2
Duration (years)			
1–10	8	2.1	0.9–5.0
≥11	20	1.4	0.8–2.4
Natural gas combustion products			
Confidence			
Probable	5	1.3	0.5–3.6
Definite	17	1.5	0.8–2.6
Concentration			
Low	11	0.9	0.5–1.8
Medium/high	11	2.9	1.4–6.2
Frequency			
Low/medium	7	1.0	0.4–2.2
High	15	1.9	1.0–3.5
Duration (years)			
1–10	9	1.9	0.9–4.3
≥11	13	1.2	0.6–2.3
Other mineral oils			
Confidence			
Probable	6	0.8	0.3–1.9
Definite	15	1.6	0.9–2.9
Concentration			
Low	10	0.9	0.4–1.7
Medium/high	11	1.9	0.9–3.9
Frequency			
Low/medium	11	1.2	0.6–2.4
High	10	1.2	0.6–2.4
Duration (years)			
1–10	11	1.3	0.7–2.5
≥11	10	1.2	0.6–2.3

* OR, odds ratio; CI, confidence interval.

with diesel exhaust. Two occupational groups—motor vehicle drivers and excavation and paving workers—made up about half of all diesel exhaust-exposed workers, and the excess risk was largely confined to these groups. The excess risk among those exposed to calcium carbonate was highest among those definitely exposed and those with the longest exposure, but there were

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no clear trends with concentration or frequency. The risk was concentrated among teachers who used chalk for blackboard writing but whose exposure levels were very low. For titanium dioxide, there was a hint of increasing risks with increasing confidence, concentration, and frequency, but the trend for duration was in the opposite direction. Natural gas combustion products displayed some evidence of increasing risks by confidence level, concentration, and frequency, but there was an inverse relation by duration. For mildly refined cutting fluids, there was a hint of a trend in odds ratios with confidence, concentration, and frequency, but not with duration. For other mineral oils, there were trends with confidence, concentration, and duration. There were no discernible trends for formaldehyde.

DISCUSSION

For the most part, previous epidemiologic evidence regarding occupational risk factors for bladder cancer has been derived from either 1) cohort studies or studies in which job titles mentioned on death certificates were used to derive proportionate or standardized mortality ratios for different occupations or 2) case-control studies in which job titles were collected from cases and controls and used as exposure variables in the analyses. All of these approaches were limited (7). In the present study, we had histologically confirmed incident cancers, information on a host of potential confounders, and detailed job history information permitting analysis of a whole range of substances, occupations, and industries.

There are pros and cons to both "cancer controls" and population controls (9). By assembling both types of controls and pooling the data, we hoped to mitigate the "worst-case biases" of either type used alone. In any case, by testing for heterogeneity between the control groups, we allowed the data to inform the decision as to whether to pool the controls or leave them separate. For the most part, pooling was not contraindicated. When the control groups differed, it was usually the cancer controls that gave the higher odds ratio estimate, contrary to our expectation. It is noteworthy that, as reported elsewhere (16), the association between cigarette smoking and bladder cancer was as strong when we used cancer controls as when we used population controls.

We have reported new information on each of 53 occupational circumstances in relation to bladder cancer. Proper evaluation of the body of evidence regarding each association would require considerable effort and perhaps even a formal meta-analysis for each occupational circumstance. Such an endeavor would have been beyond the scope of this paper. Furthermore, many studies have collected information on the associations between bladder cancer and all occupations but only reported on those which produced evidence of an effect (17). This insidious publication bias compromises any attempt to review the literature. Nevertheless, below we shall attempt to put our findings into the context of other research.

Occupations and industries

Selected on the basis of literature. Many studies have found excess risks for motor vehicle drivers (18–31), and we found similar evidence, particularly among drivers in the motor transport industry, who are more likely to drive full time than drivers in other industries. The risks were slightly lower for truck drivers than for other motor vehicle drivers. The excess risk in the motor vehicle sales and service industry was concentrated among short-term workers, which detracts from the plausibility of an association. Furthermore, several of the short-term workers in that industry were also drivers for part of their careers, and it was among this subset that the excess risk occurred. It therefore seems unlikely that there is an excess risk associated with the motor vehicle sales and service industry per se.

While we did not have dyestuff producers in our study population, it is noteworthy that the two bladder cancers occurring among long-term textile dyers represented a 10-fold excess risk, albeit one of marginal statistical significance. A previous Canadian study also reported an excess risk of bladder cancer among textile dyers (24), as have some other studies on textile dyers (25, 32, 33). Other textile workers were at no excess risk in our study. Many studies have reported on the risks of bladder cancer among textile workers as a whole; some have found excess risk (25, 32, 34, 35) and some have not (26, 27, 33, 36–38).

Painters have been reported to have excess risk in many informative studies (22, 26, 28, 39–41) but not in all (24, 42, 43). Our results, although imprecise, are compatible with the hypothesis of an excess risk for construction painters, but not for other painters.

Leather workers and shoemakers have been found to have excess bladder cancer risk in many (24, 26, 37, 44–49) but not all (23, 31, 50–53) studies. Our findings were negative for these occupations, though numbers were small. Similarly, barbers and hairdressers have been found to be at risk of bladder cancer in many but not all studies (54), but there was no association in Montreal.

Metal machinists and sheet metal workers each showed a hint of excess risk in our study. Taken together into a single category for analysis, these occupations, which have much in common, show an odds ratio at >10 years' duration of 1.3 (95 percent confidence interval (CI) 0.9–2.0). Several other studies have reported that persons in metalworking occupations are at risk (21, 25, 26, 33, 48, 55, 56), but the evidence has tended to be equivocal, with slightly elevated odds ratios of borderline significance. The most powerful other study reported a statistically significant odds ratio estimate of 1.3, similar to ours (26). Few studies have reported no excess risk (24, 34).

A few studies have reported small excess risks in the petroleum and coal products industry (23, 26, 31, 43, 55). Based on small numbers, we found no excess, in agreement with several other studies (24, 37, 57–59).

There have been a few reports of excess risk in the printing industry (28, 47–49, 60), but the associations have been weak or not statistically significant. There have been several negative reports (26, 31, 33, 61, 62). Our results weakly support the hypothesis of an excess risk.

There have been many reports of excess risk among chemical industry workers (21, 31, 34, 45, 48, 55, 63), and several studies produced no evidence of excess risk (38, 56, 59, 64). The designation "chemical industry" can cover a very broad array of processes and products. Different study populations of chemical industry workers probably had different exposure profiles. There was no excess risk among our chemical industry workers.

Selected on the basis of results of initial analyses. We found an excess risk among air transport workers, particularly among those with less than 10 years of service. Whereas all six of the exposed cases were in this occupation during the 1940s, only a minority of the exposed controls were. One distinguishing characteristic of exposure during that era compared with more recent exposure in these occupations was the use of avgas as fuel compared with the later use of jet fuel. Three of the six exposed cases were members of the ground crew and three were air crew, although the distinction was probably blurred in that era, because air crews of small aircraft often did their own refueling and maintenance.

The apparent excess risk among insulation workers was concentrated in a group with short-term exposure; there were no exposed cases with long-term exposure. It is noteworthy that our analysis of asbestos did not show any excess risk (9). There have been some previous reports of excess bladder cancer risk associated with asbestos (65) or with insulation work (26), but most of the literature on asbestos does not argue for an effect of asbestos on bladder cancer (17, 66). There is weak evidence from our study that masons/tile setters and concrete finishers are at excess risk. Since these jobs involve similar exposures, we combined

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them and derived an odds ratio of 1.9 (95 percent CI 0.9–4.1) for more than 10 years of exposure. A few studies have hinted at excess risks in these construction occupations (26, 28, 67), but others have reported no excess risk (38, 48).

In previous studies, there have been some reports of excess risk among slaughterers and meat processors (26, 45, 47, 48) and some reports of no excess risk (23, 59). In our data, there was a hint of excess risk among slaughterers and meat processors that was confined to short-term workers.

Teachers have not previously been reported to be a high-risk group (23, 56, 68). We found excess risks for teachers, particularly vocational school teachers. Examining the individual job histories, there were no common exposures, except for chalk (calcium carbonate). The pattern of results for calcium carbonate argues against its being a risk factor. Consequently, we believe that the apparent excess among teachers is either a statistical fluke or a reflection of a non-occupational risk factor among teachers.

Our findings also weakly support the association between bladder cancer and working in the pulp and paper industry. However, there is very little support for this in previous studies (26, 31, 33, 59).

Although we found a significant excess of bladder cancer among workers in the communications industry, this industry designation is so broad that it is doubtful that we should credit these observations. It covered such diverse aspects as radio and television repair, newspaper journalism, and postal delivery. The apparent excess risk among production managers is also likely to be spurious, since these men were working in different industries and had quite disparate exposure profiles. The nonsignificant excess risk seen in our study for workers in welfare and religious services was concentrated among short-term workers, which detracts from the evidence of a true effect of occupational exposure, as do the facts that there are no exposures to speak of in these services nor any previous supporting evidence.

Substances

Selected on the basis of literature. The strength of this study as compared with previous studies is its ability to focus on exposure to substances. In interpreting the results, it is not clear whether to give greater credibility to the partially adjusted odds ratios or the fully adjusted ones. While the latter would appear, at first glance, to provide better estimates, it is in fact possible that the fully adjusted models give too low an estimate of the odds ratio for a true risk factor. This can happen because the covariates are measured with error and some of the effect of a true risk factor may be "soaked up" by covariates with which it is correlated. The best estimate may lie somewhere between the partially adjusted and fully adjusted odds ratios, and our interpretation reflects this.

The strongest evidence from the literature concerns the aromatic amines, 2-naphthylamine and benzidine, in dyestuff workers and in rubber workers active before 1950 (6, 7). Our coding could not discriminate between different types of aromatic amines, and consequently we only coded the entire family, which probably includes noncarcinogens such as aniline as well as carcinogens. The workers exposed to aromatic amines in our study came from such diverse industrial settings as auto mechanics, construction workers, painters, printers, and chemical processors. The exposure levels of these workers, active from the 1940s through the 1970s, were probably much lower than those of the workers studied by Case et al. (6, 7). Our findings for aromatic amines, while inconclusive in themselves, are compatible with the hypothesis that workers exposed to aromatic amines experienced excess risk. Several other recent studies have also reported excess bladder cancer risk in workers exposed to aromatic amines. Generally, the population-based case-control studies have found relative risk estimates in the range of 1–3 (47, 59, 69, 70), whereas studies which focused exclusively on very highly exposed cohorts found much higher relative risks (71–76). We also examined risk related to photographic products, and although it was a very rare exposure category, there was some evidence of an effect. A plausible explanation for this increase is the presence of aromatic amines in photographic products.

As indicated above, several studies have reported increased bladder cancer risk among leather workers. Although it has been hypothesized that leather dust may itself be a risk factor for bladder cancer, this has not yet been demonstrated. Our evidence, based on small numbers exposed to leather dust, does not support this.

There has been some speculation that excess risks of bladder cancer among motor vehicle drivers may be due to exposure to diesel exhaust, which contains polycyclic aromatic hydrocarbons. While we also found an excess risk among drivers, our evidence on diesel exhaust does not strongly support a causal role for that agent, though the odds ratios were slightly greater than 1.0 and are compatible with a slight excess risk. Among occupational subsets of workers exposed to diesel exhaust, only drivers and excavators and pavers showed some evidence of excess bladder cancer risk. Other subsets, such as mechanics, rail transport workers, miners, and miscellaneous construction workers, showed no excess risk of bladder cancer. Some other studies that have attempted to focus on diesel exhaust have also tended to produce equivocal evidence, although the overall pattern is of a slight excess risk (18, 56, 77–81).

The term "cutting [or machining] fluids" covers a tremendous variety of different complex mixtures. There are fundamentally different types of fluids, depending on such factors as the degree of refining and the use of emulsifiers and additives, and within each type, the chemical composition depends on the source of crude oil, the industrial process in which it is used, and other local factors. There has been some shift over time, with cutting fluids being more highly refined and containing more additives and emulsifiers than they used to. We distinguished the earlier fluids (mildly refined, with fewer emulsifiers and additives) from the later types by using 1955 as an operational cutpoint to create the two exposure variables. Although neither of the cutting fluid variables was even close to being statistically significant, there was a suggestion of elevated risk for the older, mildly refined cutting fluids. A few previous studies hinted at excess bladder cancer related to cutting fluids (31, 56, 59, 69, 82), and our results are in line with these. In a cohort study of US autoworkers, Tolbert et al. (83) apparently found no excess of bladder cancer, although the numbers were not reported. The set of other mineral oils, as coded in our study, covered such diverse substances as textile oils, heat treating oils, rolling oils, and rubber oils. Despite the different uses, several of these would, in chemical composition, probably resemble mildly treated cutting fluids. It is therefore noteworthy that the odds ratios for other mineral oils were slightly elevated, as were those for mildly refined cutting fluids.

Polycyclic aromatic hydrocarbons have been linked to bladder cancer risk in two Canadian cohorts of aluminum refinery workers (84, 85), as well as in a population-based case-control study in Italy (86). In the aluminum refinery in Quebec, there was a dose-response relation with exposure to coal tar/pitch volatile compounds, as represented by measured benzo(*a*)pyrene (84). Other studies have produced equivocal evidence regarding hydrocarbon exposure and bladder cancer (77). We evaluated exposure to benzo(*a*)pyrene and to coal tar and pitch and found no evidence of excess risk for either. The discrepancy with the aluminum refinery reports may be due to differences in levels of exposure. Alternatively, it may be that the excess of bladder cancer in the aluminum refineries was not due to benzo(*a*)pyrene but to some other exposure with which it is correlated in that environment, such as aromatic amines. There was no excess risk for creosote, for which a Swedish study suggested a slight excess (17).

Selected on the basis of results of initial analyses. A few metallic compounds were included in the present analysis. There

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was a hint that cadmium compounds may be related to bladder cancer; although numbers were very small, the dose-response pattern supported the hypothesis. Once again, metal machinists represented the major exposed subgroup with excess risk, and this could simply reflect some other hazard in metal machining. There was a hint of an excess for lead chromate, but dose response was difficult to assess because hardly any workers had high exposure levels, even on our relative scale. Painting constituted the major occupation in which this exposure occurred. Titanium dioxide is another exposure found mainly among painters. The evidence in favor of an association was a bit stronger than that for lead chromate, but it remains rather weak evidence in the absence of corroboration.

Calcium carbonate or chalk had a suggestively elevated odds ratio, but only at the nonsubstantial exposure level. This reflected the increased risk found among teachers exposed to chalk. Construction workers and others, exposed at higher levels than teachers, exhibited no excess risk. Thus, it is likely that either this result is due to statistical fluctuation or it is not the chalk but something else about the teaching profession that causes the risk.

In our population, natural gas combustion products were present in such diverse occupations as metal workers and food service workers. The risk estimate at the substantial level was statistically significant, and the trends by confidence, frequency, and concentration were positive. There is no direct evidence in the literature on this exposure, but cooks, who represent one of the major occupationally exposed groups, have had associations with bladder cancer in a few studies (56, 62). Paradoxically, natural gas is one of the cleanest-burning of all combustion sources. In our study, there was no evidence of risk related to combustion products of wood, coal, or petroleum.

There was no evidence in our multivariate analyses that fabric dust, a generic exposure in the textile industry, induced excess risk. We also examined acrylic fibers, and although the odds ratios were suggestive, they were based on small numbers, were not significant, and could easily have been due to chance. There is no corroborative evidence from other studies.

Carbon tetrachloride was assessed and a nonsignificant excess was found in the substantially exposed group. On closer examination, it turned out that the excess was confined to metal machinists exposed to carbon tetrachloride (odds ratio = 9.9, 95 percent CI 1.8–55). Other workers exposed to carbon tetrachloride showed no excess risk. This observation may reflect some other hazard in the metal machining environment, possibly cutting fluids or a solvent, but our multivariate model indicated that there were no important confounders for carbon tetrachloride. There are no other reports specifically dealing with carbon tetrachloride and bladder cancer.

There have been no convincing reports of elevated bladder cancer risk related to formaldehyde exposure (50, 87–89), nor did our evidence support an association between formaldehyde and bladder cancer, though a small excess risk could not be ruled out. Chlorine is used in textile cleaning and in pulp and paper mills, and it has various other uses. Although few people were exposed, it showed suggestive evidence of an association. There is no previous epidemiologic evidence on chlorine, nor is the literature on water chlorination by-products and bladder cancer relevant, since workers exposed to chlorine would not ordinarily be exposed to chlorination by-products. There was a hint of excess risk due to polyethylene exposure, though the estimates were very unstable.

Occupational risk factors for bladder cancer in Montreal

For only one substance, aromatic amines, is there sufficient evidence from our results and other research to confidently infer that there was excess risk of bladder cancer in Montreal. Similarly, for only two occupations (motor vehicle drivers and textile dyers) and one industry (motor transport) was there reason to infer that these probably were risk factors. For some other occupations and industries, including teachers and professors, slaughterers and meat processors, metal machinists, sheet metal workers, masons and tile setters, construction painters, air transport workers, and pulp and paper mills, there was some suggestion of increased risk, but either the evidence was weak in our results or the literature was equivocal or negative. For most of the substances evaluated, there was no corresponding literature with which to compare our results. The following substances showed suggestive, though not persuasive, associations with bladder cancer: cadmium compounds, titanium dioxide, chlorine, diesel engine emissions, natural gas combustion products, acrylic fibers, polyethylene, and photographic products. These are the substances for which further research is recommended.

Given a set of risk factors, the fraction of bladder cancer attributable to occupational exposures can be computed. Accepting only those four circumstances listed above as likely risk factors, combining them into a single exposure variable, and using methods developed by Bruzzi et al. (90), we estimate that 6.5 percent (95 percent CI 2.0–9.9) of bladder cancers in this population were attributable to occupational exposures. This estimate is somewhat lower than some previous estimates in other study areas (5), perhaps because the attributable fraction really is lower in Montreal than in some other study areas, or perhaps because the criteria used by others to designate occupations as risky were more liberal than ours. For our estimate, circumstances which were not evaluated here because of small numbers (e.g., magenta manufacture) or which were evaluated and did not show excess risk in our study (e.g., barbers and hairdressers) were deemed to not be risk factors in Montreal.

False positive findings would have been expected by chance in such a "multiple testing" context, and our analytic strategy was geared to the purpose of screening out false positive results. However, there were probably false negative findings as well. As indicated by the confidence intervals for most associations, the numbers exposed were low, and we cannot exclude the possibility of small excess risks for most of the apparently negative associations in our data set. Furthermore, although considerable effort was devoted to the retrospective assessment of exposure, there was undoubtedly some misclassification of exposure which would have led to attenuation in the odds ratio estimates. It is also conceivable that our age cutoff of 70 years may have served to hide some true hazards if occupation-related carcinogens have an even longer induction period than non-occupation-related ones. Finally, it is possible that the levels of exposure experienced by most subjects in this study were below the levels required to produce a detectable increase in risk.

These caveats about negative results apply as much to the several hundred circumstances evaluated in our initial analysis as to those evaluated in depth here. Thus, it cannot be inferred that the potential risk factors for bladder cancer we have identified are the only ones in this population. Notwithstanding the limited power to detect risks and the likelihood that there are more occupational bladder carcinogens than have been identified here, it is striking that so few were identified. In our preliminary analyses of all cancer sites, there were several sites that produced more significant associations than did bladder cancer (9). With the possible exception of lung cancer, bladder cancer has been the most intensively investigated type of cancer in relation to occupational circumstances, with many case-control studies being conducted in the past two decades, including a few which have tried to evaluate substances as well as occupations and industries. As would be expected in such multiple testing studies, there have been many occupational circumstances found to increase risk in one study or another, but with a few exceptions, there has been very little consistency of elevated odds ratios from study to study. It may well be that the widespread notion that the bladder is a prime target organ for occupational carcinogenesis is no longer war-

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ranted. Still, even if the true attributable fraction were in the range of 5–10 percent, it would represent an important public health issue.

Although our study represents a significant methodological advance over most previous studies in this area, it has not clearly identified any new carcinogens. This may indicate that there are not many major occupational bladder carcinogens remaining to be discovered or that, despite its qualities, the study was not sufficiently sensitive. This could have been due to imperfect exposure assessment and consequent misclassification, to low levels of exposure, or to the limited sample size. We recommend that further studies of occupational causes of bladder cancer be carried out only if they entail high quality exposure assessment, a highly industrialized study base, and larger sample sizes than we had—namely, at least 1,000 cases and controls, and preferably closer to 5,000.

Conclusion

Our case-control study on occupational circumstances and bladder cancer was based on pathologically confirmed diagnoses, included detailed exposure assessment of hundreds of substances, and took account of potentially confounding factors. On the basis of the resulting odds ratio estimates and dose-response patterns and other research, we conclude that there is moderate support for the hypotheses of bladder cancer risks being due to a handful of circumstances, including exposure to aromatic amines and work as a motor vehicle driver or textile dyer. We have provided some evidence of associations between bladder cancer and a number of substances for which there is little other epidemiologic evidence available, either positive or negative. These are noteworthy hypotheses for further investigation.

ACKNOWLEDGMENTS

This study was funded by grants from the Institut de recherche en santé et en sécurité du travail du Québec, the Fonds de recherche en santé du Québec, the National Health Research and Development Program, and the National Cancer Institute of Canada.

The fieldwork was supervised by Lesley Richardson. Among others who played important supporting roles were Denis Bégin, Ramzan Lakhani, Denise Bourbonnais, and Sally Campbell. Dr. Debra Silverman provided helpful comments on a previous draft of the manuscript.

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APPENDIX

A. Occupations

1. Selected on the basis of literature
   Barbers and hairdressers; textile dyers and finishers; metal machinists; sheet metal workers; leather workers; shoemakers; painters (divided for our analyses into construction painters and other painters); motor transport workers; and truck drivers.
2. Added on the basis of results of initial analyses
   Production managers; teachers and professors; vocational school teachers; slaughterers and meat processors; wood machinists; concrete finishers; masons and tile setters; insulation workers; and air transport workers.

B. Industries

1. Selected on the basis of literature
   Textile industry; printing and publishing; metal fabricating and machining; petroleum and coal products; chemical production; and motor transport.
2. Added on the basis of results of initial analyses
   Flour feed and bakery products; pulp and paper mills; communications; motor vehicle sales and service; and welfare and religious services.

C. Substances

1. Selected on the basis of literature
   Aromatic amines as a class; leather dust; diesel engine emissions; cutting fluids;* coal tar and pitch; benzo(*a*)pyrene; and creosote. (*Because of significant changes in chemical formulation, we explicitly distinguished mildly refined from highly refined cutting fluids, using 1955 as an operational cutpoint. For jobs which straddled this cutpoint, we attributed exposure to one or other type of cutting fluids according to whether the duration was longer before 1955 or after.)
2. Added on the basis of results of initial analyses
   Clay dust; cadmium compounds; calcium carbonate; lead chromate; titanium dioxide; chlorine; natural gas combustion products; fabric dust; acrylic fibers; polyethylene; other mineral oils; formaldehyde; carbon tetrachloride; laboratory products; and photographic products.