Exhibit 251

Associations Between Several Sites of Cancer and Occupational Exposure to Benzene, Toluene, Xylene, and Styrene: Results of a Case-Control Study in Montreal

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Background *Except for the leukemogenic effects of benzene, there is inadequate or sparse evidence on the carcinogenicity of the most common monocyclic aromatic hydrocarbons. The purpose of this study was to generate hypotheses on associations between exposure to benzene, toluene, xylene, and styrene and various common types of cancer.*

Methods *In the context of a population-based case-control study carried out in Montreal, 3,730 cancer patients (15 types of cancers, not including leukemia) and 533 population controls were interviewed, and their job histories were translated by a team of experts into occupational exposures, including benzene, toluene, xylene, and styrene. In the present analysis, exposure to these substances was compared between each case series and a control group pooling selected cancer patients and population controls, using logistic regression analysis.*

Results *Exposure levels were low for most exposed subjects, and there was a high correlation between exposure to benzene, toluene and xylene. For most sites of cancer there was no evidence of excess risk due to these substances. However, limited evidence of increased risk was found for the following associations: esophagus-toluene, colon-xylene, rectum-toluene, rectum-xylene and rectum-styrene.*

Conclusions *These latter observations warrant further investigation.* Am. J. Ind. Med. 34: 144–156, 1998. © *1998 Wiley-Liss, Inc.*

KEY WORDS: ***benzene; toluene; xylene; styrene; neoplasms; colon; rectum; prostate; esophagus; lymphoma; case-control study; workplace***

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Benzene, toluene, xylene, and styrene are among the most prominent members of the monocyclic aromatic hydrocarbon family of substances in terms of occurrence and exposure in the general as well as occupational environments. Produced from petroleum, by distillation or indirectly after various operations and reactions, these four substances are cornerstones of the petrochemical industry, serving as feed stock for the synthesis of a variety of other chemical intermediates, solvents, dyes, and explosives, as well as resins used in the manufacture of plastics, elastomers, and textiles. Used in the past extensively as a solvent, notably in paint and rubber products, benzene is presently found as a constituent of motor fuels, together with toluene and xylene, both of which have retained important uses as solvents in a variety of products such as paints and adhesives. In these applications xylene is present as a mixture of its three isomers. The major use of styrene is in the production of various high-volume polymers, such as polystyrene and polyesters [IARC (International Agency for Research on Cancer), 1989, 1994; Agency for Toxic Substances and Disease Registry, 1997].

Because of the volatility of these substances and their presence in many sectors of human activity, opportunities for occupational exposure are widespread and have been the object of sustained attention because of their varied toxic properties. Of the four substances, benzene is the only one recognized as a human carcinogen [IARC, 1987], based on increased risk of neoplasms of the hematopoietic system, notably acute myeloid leukemia, in occupational cohort studies. Benzene is also recognized as a multipotential carcinogen in animal studies [Agency for Toxic Substances and Disease Registry, 1997]. Evidence for the carcinogenicity of toluene and xylene is generally considered to be inadequate, their effect in animals having not been demonstrated and epidemiologic evidence being inadequate in part due to the difficulty of disentangling the exposure of one substance versus the other [IARC, 1989]. While there is limited evidence of the carcinogenicity of styrene in experimental animals, the evidence from epidemiologic studies has been evaluated as inadequate, although there are some inconsistent indications of excess risk of lymphohematopoietic cancers. On the strength of evidence of genetic and related effects, styrene has been classified as a possible human carcinogen [IARC, 1994].

The present report concerns possible associations between occupational exposure to benzene, toluene, xylene, and styrene and 15 different types of cancer in the context of a large population-based, case-control study of cancer in Montreal. Compared with cohort studies, such a design allows us to evaluate risk across the range of industries and occupations in which exposure might occur. Furthermore, it entails a high quality cancer diagnosis, a comparable local comparison group, control for confounding, and lifetime job histories.

SUBJECTS AND METHODS

The overall design and data collection methods of our large population-based case-control study have been described in detail elsewhere [Gérin et al., 1985; Siemiatycki et al., 1987, 1991c]. A brief outline will be given here focusing on the specifics of the present analysis.

Case Groups and Control Groups

Nineteen sites of cancer were selected for study among men 35–70 years of age resident in the metropolitan area of Montreal. Participation of all large hospitals in the area ensured virtually complete population-based ascertainment of cases. Between 1979 and 1986, 4,576 eligible cases were ascertained of whom 3,730 (82%) agreed to participate; 82% of responses were obtained from the subject and the rest from a next-of-kin.

The three-digit level of the International Classification of Disease Revision 9 [World Health Organization (WHO), 1977] was used to code the diagnosis abstracted from medical records. We included as case series for the analysis each of the following three histologic subcategories of lung cancer: oat cell carcinoma, squamous cell carcinoma, and adenocarcinoma. The 78 cases that were diagnosed with primary tumors at two different sites have been included in both relevant case series.

In addition to the cancer cases, we selected a series of population controls. These subjects were men selected from electoral lists of the Montreal area, age-stratified to the age distribution of cancer patients. Of 740 persons selected, 533 persons (71%) were successfully interviewed. Three types of control groups were used in the analyses: cancer controls, population controls, and a subset of the pool of cancer and population controls. For each case series, the cancer control group consisted of patients with cancers of all other sites in the study with the following exclusions. Lung cancer was excluded from all control series as well as anatomically contiguous sites for any given site. For three sites that were not ascertained in certain years of the study—lung, rectum, and prostate—the controls consisted of other subjects who were ascertained in the same years as the corresponding cases. Table I presents the number of cases and cancer controls considered for each of 15 types of cancer that had at least 50 cases interviewed and on which the present study was focused. Cancer sites with less than 50 cases were kept in the cancer control pool.

For each case series, a pooled control group consisting of 1,066 subjects was formed by the addition to the 533 population control group of an additional 533 cancer controls selected randomly from the eligible cancer control group. A separate set of 533 cancer controls was selected for each case series.

Fieldwork and Questionnaires

A questionnaire was administered by interviewers visiting subjects in the hospital or at home. Telephone interviews or a self-administered questionnaire were restricted to hard-to-interview subjects or next-of-kin situations. The questionnaires consisted of two parts: a structured part requesting information on important nonoccupational confounders (e.g., age, socioeconomic status, smoking), and a semistructured probing section designed to obtain a detailed description of each job the subject has had in his working lifetime. The interviewers were trained to elicit for each job as much information as possible on the company's activities; the raw materials and final product; the machines used and

TABLE I. Types of Cancer Analyzed as Case Series, Sites Excluded From the "Cancer Controls" Series, and Number of Cases and "Cancer Controls," Montreal, 1979–1986

Cancer case series (ICD code)[a]	Cancer sites excluded from control series[b]	No. of cases	No. of controls[c]
Esophagus (150)	Lung, stomach	99	2301
Stomach (151)	Lung, esophagus, small intestine	251	2280
Colon (153)	Lung, other colorectal, peritoneum	497	2050
Rectum (154)	Lung, other colorectal, peritoneum	257	1295
Pancreas (157)	Lung, liver, gallbladder, peritoneum	116	2448
Lung (162)	Pleura, peritoneum	857	1349
Oat cell	Other lung, pleura, peritoneum	159	1349
Squamous cell	Other lung, pleura, peritonea	359	1349
Adenocarcinoma	Other lung, pleura, peritoneum	167	1349
Prostate (185)	Lung	449	1550
Bladder (188)	Lung, kidney	484	1879
Kidney (189)	Lung, bladder	177	2004
Melanoma of the skin (172)	Lung	103	2525
Non-Hodgkin's lymphoma (200, 202)	Lung, Hodgkin's lymphoma, myeloma, sarcoma	215	2341
Hodgkin's lymphoma (201)	Lung, non-Hodgkin's lymphoma, myeloma, sarcoma	54	2341

[a]In addition to the cancer types listed in the left hand column of this table, the cancer controls included the following rare types of cancer: small intestine, gallbladder, testis, penis, liver, myeloma, sarcomas, pleura, and peritoneum.
[b]For each case series, all cancer patients interviewed served as referents with the exceptions listed in this column. Furthermore, for rectum, lung, and prostate, only those subjects interviewed during the same ascertainment periods as the three respective site series were used as referents.
[c]Numbers of controls of which 533 cancer controls were selected randomly.

the worker's responsibility for machine maintenance; the type of room or building in which he worked; activities of work mates around him; presence of gases, fumes, or dusts; and any other information that could furnish clues as to possible chemical or physical exposures incurred by the subject.

Exposure Assessment

A team of chemists and hygienists was responsible for examining each completed questionnaire and translating each job into a list of potential exposures [Gérin et al., 1985; Siemiatycki et al., 1991b]. They used a checklist form that was developed to include some 300 of the most common occupational agents in Montreal, including benzene, toluene, xylene, and styrene. For each product thought to be present in each job, the chemists noted three dimensions of exposure: their confidence that the exposure actually occurred (possible, probable, definite), the frequency of exposure during a normal workweek (less than 5% of the time, 5–30%, more than 30%), and the concentration of the agent in the environment (low, medium, high). The designation of low, medium, or high was determined in relation to certain occupations that were used as reference points. In making coding decisions, chemists drew upon a variety of sources of information, including old and new bibliographical material and the consultation of experts. Over the time of this study a considerable body of information was accumulated on retrospective exposures according to jobs and industries, which served as the basis of interpretation for each individual job evaluated. Additionally, for the purpose of this specific report, the coding of benzene, toluene, and xylene for all subjects has been the object of a special review involving additional background research on sources and levels of exposure. The dates of beginning and ending for each job provided information on the duration of exposure. Job and industry titles were coded according to the Canadian classifications. The chemists were not aware of the subject's case or control status. Examples of occupations coded for benzene, toluene, xylene, and styrene are shown in Table II.

Statistical Analyses

The objective of our analyses was to estimate the odds ratio (OR) between exposure to each of benzene, toluene, xylene, or styrene and each of the 15 sites of cancer selected. Separate analyses were carried out using the three control groups: cancer controls, population controls, and pooled controls, and separate analyses were carried out on each of the four substances of interest. For some sites that had two or more of these substances with elevated ORs, we carried out analyses using all of these significantly associated substances in the same model. To distinguish those models in which only one of the four substances has been included from those in which more than one has been included, we will use the phrases "single exposure models" and "multiple exposure models." All analyses were carried out using unconditional logistic regression, fitted with SPSS [Breslow and Day, 1980; SPSS, Inc., 1994]. Selected nonoccupational covariates were included in all models. Age, family income, and a cumulative smoking index were entered as continuous variables. Ethnicity, smoking status, and respondent status (self or proxy) were entered as categorical variables. Furthermore, for lung cancer and its subsites, the following occupational exposures were also included: arsenic, asbestos, chromium VI, nickel, crystalline silica, beryllium, cadmium, and polycyclic aromatic hydrocarbons. For bladder cancer, exposure to aromatic amines was also included.

An exposure index was developed to categorize each subject's lifetime occupational exposure status. Concentration

TABLE II. Selected Occupations Corresponding to Low, Medium, and High Concentrations of Exposure for Benzene, Toluene, Xylene, and Styrene, Montreal, 1979–1986

	Low	Medium	High
Benzene	Service station attendants	Chemists	Shoe makers and repairer[a]
	Mechanics	Painters[a]	Rubber coatings & calendering workers[a]
	Machinists	Leather product workers[a]	Paint mixers[a]
Toluene	Service station attendants	Rubber processors[a]	Rubber cement mixers[a]
	Mechanics	Cabinet & wood furniture makers[a]	Shoe makers
	Machinists	Printers[a]	Paint mixers[a]
Xylene	Service station attendants	Chemists	Rubber cement mixers[a]
	Machinists	Cabinet & wood furniture makers[a]	Paint mixers
	Mechanics		Rubber coating & calendering workers[a]
	Rubber processors[a]		
Styrene	Foremen of mechanics and repairers	Motor vehicle painters	Plastic mouldmakers
	Garage owners	Motor vehicle repairers	
		Firemen	

[a]It should be noted that exposure to benzene, toluene, and xylene in these occupations has changed substantially over time. Benzene levels were reduced between 1950 and 1970, and toluene and xylene levels were increased.

and frequency levels coded on an ordinal 1, 2, and 3 scale were transformed to 1, 4, and 9 scores, which correspond more closely to relative levels for these variables. The sum product of duration, frequency, and concentration was then computed over the various jobs of each subject, creating a synthetic form of cumulative exposure. For each substance, this cumulative exposure index was categorized as low, medium, or high, as defined by cut points at the 70th and 90th percentiles of the distribution among all study subjects. When numbers permitted, we estimated ORs in three cumulative exposure categories (low, medium, and high); however, when numbers were quite small, typically less than 20 exposed cases, we regrouped medium and high into a single category, or when numbers were very small, typically less than 8 exposed cases, we were only able to estimate the OR for ever exposed. These guidelines were applied in a flexible fashion to maintain symmetry among benzene, toluene, and xylene, in the numbers of categories, and to avoid categories with fewer than three exposed cases.

For those associations that showed an apparent excess risk, we calculated occupation-specific ORs to evaluate whether the elevated risk associated with a particular substance was concentrated in any particular occupation. Occupations were aggregated to have sufficient numbers of subjects in each [Siemiatycki et al., 1991a], and only those with at least three exposed cases in the highest exposure category were assessed in this regard. For each occupation selected, ORs were calculated for persons having had that occupation and exposure to the substance in question, as compared with persons having had no exposure and none of the selected occupations.

RESULTS

Table III describes the lifetime exposure patterns among all 4,263 study subjects to each of the four substances as coded by the chemist/hygienist group. Although 12 to 19% were considered exposed to either benzene, toluene, or xylene, a much smaller fraction (2%) was attributed styrene exposure. For benzene, toluene, and xylene, the majority of subjects were coded with certain exposure, medium frequency, and low concentration. For all substances, only a small minority of the exposed (3 to 7%) were coded in the high concentration category. Styrene was the least reliable of the exposure assignments with only 45% of exposed being in the "certain" category of reliability. Except for styrene, most subjects had their first exposure before 1950. Overall, men who were coded as exposed had lengthy exposure periods and had their initial exposure long enough ago to allow for a reasonable period of latency.

Table IV shows the main occupation groups in which exposure to each substance occurred in our population. Most of the substances also occurred in many other occupation groups than those shown in the table. In addition, the indication that a substance was attributed to some workers bearing a given job title does not suggest that all workers with that job title were attributed that exposure.

There was a high degree of correlation between exposure to benzene, to toluene, and to xylene. For instance, 58, 74, and 88% of subjects exposed to benzene, toluene, and xylene, respectively, were exposed to all three substances. This finding reflects that all three substances were compo-

TABLE III. Exposure to Benzene, Toluene, Xylene, and Styrene Among all 4,263 Subjects Interviewed, Montreal, 1979–1986

Exposure pattern	Benzene (%)	Toluene (%)	Xylene (%)	Styrene (%)
Unexposed	81.2	85.2	87.6	98.0
Exposed	18.8	14.8	12.4	2.0
Confidence levels				
Possible	1.1	0.8	1.2	0.1
Probable	5.0	5.6	4.5	1.0
Certain	12.7	8.4	6.7	0.9
Frequency				
<5% of workweek	3.6	1.8	1.5	0.4
5–30% of workweek	10.2	8.6	6.8	1.4
>30% of workweek	5.0	4.4	4.1	0.2
Concentration				
Low	12.5	7.6	10.0	0.3
Moderate	5.8	6.2	1.9	1.6
High	0.5	1.0	0.4	0.1
Duration				
1–10 years	8.0	5.8	5.1	0.4
11–20 years	3.7	3.0	2.5	0.4
>20 years	7.1	6.0	4.8	1.2
Era of first exposure				
Before 1950	11.0	8.1	6.8	0.6
1950–1960	4.9	4.1	3.5	0.8
After 1960	2.9	2.6	2.1	0.6

TABLE IV. Main Occupations for Which Exposure to Benzene, Toluene, Xylene, and Styrene Was Attributed in the Entire Study Group of 4,263 Subjects, Montreal, 1979–1986

Substance	No.[a]	Main occupations for which exposure to the substance was coded[b]
Benzene	737	Mechanics and repairmen (12%); shoe makers and repairers (5%); service station attendants (5%)
Toluene	586	Painters, except construction (8%); mechanics and repairmen (8%); shoe makers and repairers (7%); carpenters and wood furniture makers and repairers (5%)
Xylene	482	Mechanics and repairmen (10%); painters, except construction (8%); shoemakers and repairers (7%)
Styrene	93	Firefighters (35%); mechanics and repairmen (20%); painters, except construction (11%)

[a]This is the number of persons exposed at any level. No. is the denominator for each percentage corresponding to the substance in question.
[b]Percentage of exposed persons in the occupation in question in parentheses.

nents of products such as gasoline, mineral spirits (older formulations), and mixed aromatic solvents in professions such as mechanics, service station attendants, painters, and leather workers.

For the vast majority of associations analyzed, there was little difference between ORs based on each of the three control group strategies; therefore, we present in Table V only the results based on pooled controls. Of the 15 × 4 associations examined, most showed no indication of an excess risk. The most suggestive ones were esophagus-toluene, colon-benzene, colon-toluene, colon-xylene, rectum-benzene, rectum-toluene, rectum-xylene, rectum-styrene, lung (squamous)-xylene, and prostate-styrene.

A first attempt was made at disentangling the effects of the highly correlated benzene, toluene, and xylene by analyzing those subjects exposed to only one of the three substances. However, the only site-substance combinations that had enough subjects to warrant such an analysis were colon-benzene and rectum-benzene. No association was found for either site with benzene only exposure at low or medium/high levels (Table VI).

For colon and rectum, the sites that were associated with two or more of the substances of interest in the single exposure models, multiple exposure models were developed. In the colon cancer analysis (Table VII), the OR increased for the colon-xylene association, whereas it decreased for both colon-benzene and colon-toluene. For rectal cancer (Table VIII), all ORs at the medium/high category decreased somewhat compared with the respective ORs in the single exposure models; none exceeded 1.3 (none significant). Styrene exposure was still strongly associated with rectal cancer, although based on small numbers.

The associations that were statistically suggestive in the single exposure models were subjected to analyses attempting to estimate risks due to exposure to the substance in specific occupations. For each association, the risk was estimated among those exposed in the occupation groups with the most numbers. For the most part, these associations were not concentrated in any occupational group. There were a few exceptions. The esophagus-toluene association was concentrated among two occupation groups, carpenters and mechanics (OR of 4.8 for both); the prostate-styrene association was concentrated among firemen (OR of 5.4, marginally significant).

DISCUSSION

The four substances examined in this study are large volume industrial chemicals with significant past and present occurrence in the occupational and general environments. Their toxic properties have been the object of intense scrutiny. Of the four, benzene is the only one currently recognized as a human carcinogen on the basis of epidemiologic studies linking occupational exposure to the development of leukemia. The only other cancer type with some evidence of association with benzene exposure is lymphoma [Wong, 1987; Blair et al., 1993; Yin et al., 1996]. The epidemiologic evidence linking toluene and xylene exposure

TABLE V. Odds Ratios Between Exposure to Four Aromatic Hydrocarbons and 15 Types of Cancer by Exposure Level, Using Pooled Controls, Montreal, 1979–1986

Cancer site/substance	Exposure level[a]	No. of controls	No. of cases	Odds ratio[b]	95% Confidence interval[c]
Esophagus					
Benzene	Unexposed	871	85	1.0	na
	Low	144	9	0.6	0.3–1.3
	Medium/high	51	5	0.9	0.3–2.4
Toluene	Unexposed	919	83	1.0	na
	Low	95	7	0.8	0.4–1.8
	Medium/high	52	9	1.9	0.9–4.2
Xylene	Unexposed	943	88	1.0	na
	Low	83	6	0.8	0.3–2.0
	Medium/high	40	5	1.4	0.5–3.8
Styrene	Unexposed	1033	96	1.0	na
	Ever	33	3	1.0	0.3–3.5
Stomach					
Benzene	Unexposed	879	198	1.0	na
	Low	137	36	1.1	0.8–1.7
	Medium	29	11	1.5	0.8–3.2
	High	21	6	1.3	0.5–3.2
Toluene	Unexposed	916	208	1.0	na
	Low	105	31	1.3	0.8–1.9
	Medium	31	7	1.0	0.4–2.2
	High	14	5	1.7	0.6–4.8
Xylene	Unexposed	948	218	1.0	na
	Low	82	24	1.2	0.8–2.0
	Medium	31	7	1.0	0.4–2.3
	High	5	2	1.8	0.3–9.5
Styrene	Unexposed	1042	249	1.0	na
	Ever	24	2	0.3	0.1–1.5
Colon					
Benzene	Unexposed	881	414	1.0	na
	Low	127	48	0.8	0.6–1.2
	Medium	35	19	1.2	0.7–2.1
	High	23	16	1.5	0.8–2.8
Toluene	Unexposed	926	420	1.0	na
	Low	93	50	1.2	0.8–1.7
	Medium	36	18	1.1	0.6–2.0
	High	11	9	1.8	0.7–4.4
Xylene	Unexposed	955	429	1.0	na
	Low	77	44	1.3	0.9–1.9
	Medium	31	16	1.2	0.6–2.1
	High	3	8	5.8	1.5–22.0
Styrene	Unexposed	1045	486	1.0	na
	Ever	21	11	1.2	0.6–2.5
Rectum					
Benzene	Unexposed	867	194	1.0	na
	Low	142	43	1.3	0.9–2.0
	Medium	36	16	2.0	1.1–3.6
	High	21	4	0.8	0.3–2.5
Toluene	Unexposed	913	206	1.0	na
	Low	107	34	1.4	0.9–2.1
	Medium	35	9	1.1	0.5–2.4
	High	11	8	3.2	1.3–8.0

(continued)

TABLE V. Odds Ratios Between Exposure to Four Aromatic Hydrocarbons and 15 Types of Cancer by Exposure Level, Using Pooled Controls, Montreal, 1979–1986 (continued)

Cancer site/substance	Exposure level[a]	No. of controls	No. of cases	Odds ratio[b]	95% Confidence interval[c]
Rectum					
Xylene	Unexposed	937	213	1.0	na
	Low	88	30	1.5	1.0–2.3
	Medium	33	9	1.2	0.6–2.6
	High	8	5	2.7	0.9–8.3
Styrene	Unexposed	1045	248	1.0	na
	Low	17	4	1.0	0.3–2.9
	Medium/high	4	5	5.1	1.4–19.4
Pancreas					
Benzene	Unexposed	858	98	1.0	na
	Low	152	15	.9	0.5–1.6
	Medium/high	56	3	.4	0.1–1.4
Toluene	Unexposed	915	97	1.0	
	Low	106	16	1.4	0.8–2.6
	Medium/high	45	3	0.6	0.2–2.2
Xylene	Unexposed	946	103	1.0	na
	Low	85	9	1.1	0.5–2.2
	Medium/high	35	4	1.1	0.4–3.3
Styrene	Unexposed	1043	115	1.0	na
	Ever	23	1	0.3	0.0–2.6
Lung					
Benzene	Unexposed	854	683	1.0	na
	Low	150	127	1.1	0.8–1.5
	Medium	43	34	0.8	0.5–1.3
	High	19	13	0.7	0.3–1.7
Toluene	Unexposed	895	728	1.0	na
	Low	121	92	0.9	0.7–1.3
	Medium	37	25	0.7	0.4–1.2
	High	13	12	1.1	0.5–2.7
Xylene	Unexposed	927	748	1.0	na
	Low	104	81	0.9	0.7–1.3
	Medium	23	12	0.7	0.3–1.5
	High	12	16	1.6	0.7–3.8
Styrene	Unexposed	1039	847	1.0	na
	Low	19	5	0.3	0.1–0.9
	Medium/high	8	5	0.9	0.2–3.3
Lung-oat cell					
Benzene	Unexposed	856	130	1.0	na
	Low	147	24	1.1	0.6–1.9
	Medium/high	63	5	0.3	0.1–0.9
Toluene	Unexposed	896	134	1.0	na
	Low	121	20	1.0	0.6–1.8
	Medium/high	49	5	0.6	0.2–1.6
Xylene	Unexposed	927	142	1.0	na
	Low	103	14	0.8	0.4–1.5
	Medium/high	36	3	0.5	0.1–1.8
Styrene	Unexposed	1040	158	1.0	na
	Ever	26	1	0.2	0.0–1.8
Lung-squamous cell					
Benzene	Unexposed	855	272	1.0	na
	Low	149	61	1.3	0.9–1.9
	Medium/high	62	26	1.2	0.7–2.1

(continued)

TABLE V. Odds Ratios Between Exposure to Four Aromatic Hydrocarbons and 15 Types of Cancer by Exposure Level, Using Pooled Controls, Montreal, 1979–1986 (continued)

Cancer site/substance	Exposure level[a]	No. of controls	No. of cases	Odds ratio[b]	95% Confidence interval[b]
Lung-squamous cell					
Toluene	Unexposed	897	297	1.0	na
	Low	121	43	1.0	0.7–1.5
	Medium/high	48	19	1.1	0.6–2.0
Xylene	Unexposed	926	307	1.0	na
	Low	105	35	1.0	0.6–1.5
	Medium/high	35	17	1.5	0.8–3.0
Styrene	Unexposed	1039	353	1.0	na
	Ever	27	6	0.7	0.3–1.9
Lung-adenocarcinoma					
Benzene	Unexposed	856	133	1.0	na
	Low	149	23	1.1	0.6–1.8
	Medium/high	61	11	0.9	0.4–1.9
Toluene	Unexposed	899	142	1.0	na
	Low	117	19	1.0	0.5–1.7
	Medium/high	50	6	0.6	0.3–1.6
Xylene	Unexposed	930	142	1.0	na
	Low	99	20	1.3	0.7–2.3
	Medium/high	37	5	0.9	0.3–2.6
Styrene	Unexposed	1040	165	1.0	na
	Ever	26	2	0.6	0.1–2.5
Prostate					
Benzene	Unexposed	866	354	1.0	na
	Low	145	64	1.1	0.8–1.5
	Medium	33	22	1.7	0.9–3.0
	High	22	9	0.9	0.4–2.1
Toluene	Unexposed	904	378	1.0	na
	Low	116	51	1.0	0.7–1.5
	Medium	30	17	1.3	0.7–2.5
	High	16	3	0.4	0.1–1.4
Xylene	Unexposed	932	386	1.0	na
	Low	93	46	1.2	0.8–1.8
	Medium	31	11	0.8	0.4–1.7
	High	10	6	1.4	0.5–4.0
Styrene	Unexposed	1046	437	1.0	na
	Low	17	5	1.0	0.4–2.9
	Medium/high	3	7	5.5	1.4–21.8
Bladder					
Benzene	Unexposed	860	395	1.0	na
	Low	143	65	1.0	0.7–1.3
	Medium	37	22	1.2	0.7–2.0
	High	26	2	0.2	0.0–0.6
Toluene	Unexposed	897	419	1.0	na
	Low	116	52	0.9	0.6–1.3
	Medium	40	6	0.3	0.1–0.7
	High	13	7	1.0	0.4–2.5
Xylene	Unexposed	929	430	1.0	na
	Low	98	35	0.8	0.5–1.1
	Medium	32	16	1.0	0.5–1.8
	High	7	3	0.8	0.2–3.2

(continued)

TABLE V. Odds Ratios Between Exposure to Four Aromatic Hydrocarbons and 15 Types of Cancer by Exposure Level, Using Pooled Controls, Montreal, 1979–1986 (continued)

Cancer site/substance	Exposure level[a]	No. of controls	No. of cases	Odds ratio[b]	95% Confidence interval[c]
Bladder					
Styrene	Unexposed	1040	472	1.0	na
	Low	17	9	1.0	0.4–2.4
	Medium/high	9	3	0.7	0.2–2.6
Kidney					
Benzene	Unexposed	865	138	1.0	na
	Low	141	27	1.2	0.7–1.9
	Medium/high	60	12	1.3	0.7–2.4
Toluene	Unexposed	902	152	1.0	na
	Low	115	17	0.9	0.5–1.5
	Medium/high	49	8	1.0	0.5–2.1
Xylene	Unexposed	929	154	1.0	na
	Low	99	17	1.0	0.6–1.7
	Medium/high	38	6	1.0	0.4–2.4
Styrene	Unexposed	1045	176	1.0	na
	Ever	21	1	0.3	0.0–2.0
Melanoma					
Benzene	Unexposed	879	92	1.0	na
	Ever	187	11	0.6	0.3–1.2
Toluene	Unexposed	922	98	1.0	na
	Ever	144	5	0.4	0.1–0.9
Xylene	Unexposed	948	100	1.0	na
	Ever	118	3	0.3	0.1–0.8
Styrene	Unexposed	1048	101	1.0	na
	Ever	18	2	1.0	0.2–4.4
Non-Hodgkin's Lymphoma					
Benzene	Unexposed	865	187	1.0	na
	Low	144	19	0.6	0.4–1.0
	Medium/high	57	9	0.8	0.4–1.6
Toluene	Unexposed	919	192	1.0	na
	Low	98	15	0.8	0.4–1.4
	Medium/high	49	8	0.9	0.4–1.9
Xylene	Unexposed	949	195	1.0	na
	Low	82	14	0.8	0.5–1.5
	Medium/high	35	6	1.0	0.4–2.5
Styrene	Unexposed	1047	207	1.0	na
	Ever	19	8	2.0	0.8–4.8
Hodgkin's Lymphoma					
Benzene	Unexposed	865	42	1.0	na
	Ever	201	12	1.2	0.6–2.5
Toluene	Unexposed	919	45	1.0	na
	Ever	147	9	1.3	0.6–3.0
Xylene	Unexposed	949	46	1.0	na
	Ever	117	8	1.4	0.6–3.3
Styrene	Unexposed	1047	52	1.0	na
	Ever	19	2	2.4	0.5–11.6

[a]Low, medium, and high were distinguished on the basis of duration, concentration, and frequency of exposure (see text for details).
[b]Derived from logistic regression models. For all sites, the following covariates were included: age, family income, ethnic group, cigarette smoking, and respondent status. For lung cancer and its subsites, the following covariates were included: arsenic, asbestos, chromium VI, nickel, crystalline silica, beryllium, cadmium, and polycyclic aromatic hydrocarbons. For bladder cancer, exposure to aromatic amines was used as a covariate.
[c]na, not applicable.

TABLE VI. Odds Ratios Between Exposure to Benzene and Cancers of the Colon and the Rectum for Those Subjects Exposed Only to Benzene, and Not to Toluene or Xylene, Using Pooled Controls, Montreal, 1979–1986

Cancer site	Exposure level[a]	No. of controls	No. of cases	Odds ratio[b]	95% Confidence interval[c]
Colon	Unexposed	843	393	1.0	na
	Low	64	17	0.6	0.3–1.0
	Medium/high	13	5	0.8	0.3–2.4
Rectum	Unexposed	828	185	1.0	na
	Low	63	17	1.2	0.7–2.1
	Medium/high	12	3	1.1	0.3–3.9

[a]Low, medium, and high were distinguished on the basis of duration, concentration, and frequency of exposure (see text for details).
[b]Derived from logistic regression models. The following covariates were included: age, family income, ethnic group, cigarette smoking, and respondent status.
[c]na, not applicable.

TABLE VII. Odds Ratios Between Exposure to Benzene, Toluene, Xylene, or Styrene and Cancers of the Colon in Single Exposure Models and Multiple Exposure Models, Using Pooled Controls, Montreal, 1979–1986

				Single exposure model		Multiple exposure model	
Substance	Exposure level[a]	No. of controls	No. of cases	Odds ratio[b]	95% Confidence interval[c]	Odds ratio[b]	95% Confidence interval
Benzene	Unexposed	881	414	1.0	na	1.0	na
	Low	127	48	0.8	0.6–1.2	0.6	0.4–0.9
	Medium/high	58	35	1.3	0.8–2.0	0.8	0.4–1.5
Toluene	Unexposed	926	420	1.0	na	1.0	na
	Low	93	50	1.2	0.8–1.7	1.0	0.5–1.8
	Medium/high	47	27	1.3	0.8–2.1	0.9	0.4–1.8
Xylene	Unexposed	955	429	1.0	na	1.0	na
	Low	77	44	1.3	0.9–1.9	2.0	1.0–4.3
	Medium/high	34	24	1.6	0.9–2.7	2.1	0.9–4.7

[a]Low, medium, and high were distinguished on the basis of duration, concentration, and frequency of exposure (see text for details).
[b]Derived from logistic regression models. The following covariates were included: age, family income, ethnic group, cigarette smoking, and respondent status.
[c]na, not applicable.

to cancer has been considered as inadequate, due in good part to the difficulty of separating exposure to one substance from exposure to the other [IARC, 1989]. In the case of toluene, however, suggestive evidence has been reported for respiratory tract or lung cancers [Svensson et al., 1990; Walker et al., 1993], stomach cancer, and colorectal cancer [Svensson et al., 1990]. Lymphatic and hematopoietic cancers have been associated in several studies with occupational styrene exposure, but there are inconsistencies in the results that render this association doubtful [IARC, 1994]. Thus, with the exception of leukemia, a cancer type not covered in our study, and to a lesser extent lymphoma, only sparse evidence of effects exists from previous epidemiologic studies for the cancer types and exposures examined in this study.

Two considerations on exposure are crucial to the interpretation of our results and derive from our population-based design. First, there was a high degree of correlation between exposure to benzene, toluene, and xylene, the three exposures originating mainly from common mixtures such as gasoline or a number of solvents. Although we attempted to disentangle the effects of the various substances, this effort was limited by the high degree of colinearity. Second, there were relatively few highly exposed individuals (in terms of both level and frequency).

Separate analyses were carried out using cancer controls, population controls, and a pooled control group equally weighing cancer and populations controls. There are advantages and disadvantages for each of the two available control groups, cancer controls, and population controls [Siemiatycki et al., 1991c], and we thus place greatest weight on the results using the pooled controls, although recognizing that this represents a pooling of two imperfect sources. For most of the 56 associations studied, the results

TABLE VIII. Odds Ratios Between Exposure to Benzene, Toluene, Xylene, or Styrene and Cancers of the Rectum in Single Exposure Models and Multiple Exposure Models, Using Pooled Controls, Montreal, 1979–1986

				Single exposure model		Multiple exposure model	
Substance	Exposure level[a]	No. of controls	No. of cases	Odds ratio[b]	95% Confidence interval[c]	Odds ratio[b]	95% Confidence interval[c]
Benzene	Unexposed	867	194	1.0	na	1.0	na
	Low	142	43	1.3	0.9–2.0	1.2	0.7–1.9
	Medium/high	57	20	1.6	0.9–2.7	1.2	0.6–2.5
Toluene	Unexposed	913	206	1.0	na	1.0	na
	Low	107	34	1.4	0.9–2.1	1.1	0.5–2.4
	Medium/high	46	17	1.6	0.9–2.9	1.3	0.6–3.1
Xylene	Unexposed	937	213	1.0	na	1.0	na
	Low	88	30	1.5	1.0–2.3	1.2	0.5–2.8
	Medium/high	41	14	1.5	0.8–2.8	1.0	0.4–2.8
Styrene	Unexposed	1045	248	1.0	na	1.0	na
	Low	17	4	1.0	0.3–2.9	0.8	0.3–2.6
	Medium/high	4	5	5.1	1.4–19.4	4.4	1.1–17.3

[a]Low, medium, and high were distinguished on the basis of duration, concentration, and frequency of exposure (see text for details).
[b]Derived from logistic regression models. The following covariates were included: age, family income, ethnic group, cigarette smoking, and respondent status.
[c]na, not applicable.

based on the three groups were very similar. There were no associations that were significant in the analyses using population or cancer controls, which were not noted in the analysis using pooled controls.

An approximate doubling of the risk of esophageal cancer was observed in subjects exposed to medium/high levels of toluene. A nonsignificant excess of esophageal cancer mortality has been observed in a large cohort study of Chinese men exposed to benzene in a variety of industries and occupations, most of which might entail concurrent exposure to toluene [Yin et al., 1996]. In our study, the excess was concentrated in the occupations of carpenter and mechanic in which the ORs, in the medium/high category, approached 5.0. These two occupations are characterized by exposure to many substances, including a variety of dusts and organic vapors. Exposure to toluene in these professions stems from several possible sources: contact cement, wood varnishes, and paint removers (carpenters); gasoline, metal paints, and rubber-based adhesives (mechanics). That the esophagus-toluene association is not found outside those two occupations detracts from the likelihood that toluene is the causal factor, if indeed the association is real.

Elevated ORs were observed for colon cancer in the high category of exposure to benzene, toluene, and xylene. Based on the relative magnitudes of ORs in the single exposure and multiple exposure models, and on the analysis of benzene-only exposed subjects, it seems that xylene is the predominant candidate as a risk factor for colon cancer. The occupation-specific analysis did not reveal a specific subgroup in xylene-exposed subjects in which the excess seemed concentrated. There is no confirmatory evidence from other studies on this association. However, that one of the three highly correlated aromatic hydrocarbons seems much more strongly associated with colon cancer than the two others argues in favor of a more specific effect of xylene, or of yet another correlated exposure, rather than of the mixtures or the situations in which the three are usually encountered together.

Significant associations were found between exposure to each of the four aromatic hydrocarbons under study and rectal cancer. In the case of benzene, however, the absence of a consistent dose-response pattern, combined with the absence of excess in the benzene only exposed subjects gives limited credibility to this association. Approximate trebling of risk was observed in the high exposure group for both toluene (significant) and xylene (marginally significant), whereas the OR for styrene exposure in the medium/high group reached 5.1 (significant). When all four substances were included in the model, all ORs decreased compared with the corresponding single exposure models, and styrene remained the only exposure significantly associated with rectal cancer. Given the high correlations in exposure patterns and the likely high correlation in errors of exposure attribution, our multiple exposure models should be interpreted cautiously; they do not exclude the possibility that one or more of benzene, toluene, or xylene is a risk factor for rectal cancer, with the latter two being more likely than the former. It is possible that the excesses observed in toluene- and xylene-exposed workers were due to the confounding effect of exposure to styrene; however, there is no supporting evidence from other studies of a styrene-rectal cancer association. This association could also be the result of confounding by another exposure with which styrene is strongly correlated. We have previously reported an association between colon cancer and exposure to glass fibers (OR: 6.2 (2.3–17.1) in the substantial exposure category) [Siemiatycki et al., 1991a]. Concurrent exposure to glass fibers and styrene is frequently found in workers forming glass fiber-reinforced polyester plastics used in the manufacture of a large variety of molded objects and in the repair of automobiles. No external evidence could be found, however, linking glass fiber exposure and colon cancer. There has been a report of excess risk of colorectal cancer in Swedish toluene-exposed rotogravure workers [Svensson et al., 1990].

When examining lung cancer results, the only noteworthy association was between exposure to xylene, at the high exposure category, and squamous cell lung cancer. This association was significant only when using the population control group. The absence of an effect when using the cancer controls detracts from the likelihood of a true association as does an absence of supporting evidence from other studies.

Prostate cancer was associated with exposure to styrene, but not to the other aromatic hydrocarbons. Analysis by profession revealed that this excess was due to an excess risk among firemen exposed to styrene. Even though most firemen are exposed to styrene, as a decomposition product of several plastics during combustion, including construction insulation material, the frequency and concentration of exposure is not high. Firemen constitute the occupational group with the highest percentage of workers coded for exposure to styrene, and because of their relatively long job duration, several of these were in the medium/high cumulative exposure category. There is some evidence of an excess risk of prostate cancer among firefighters in two studies [Aronson et al., 1994; Demers et al., 1994] but not in a third [Beaumont et al., 1991]. Styrene is one of a large number of exposures incurred by firemen, which include several toxic dusts, fumes, gases, and vapors such as polycyclic aromatic hydrocarbons, benzene, asbestos, and formaldehyde [Jankovic et al., 1991]. Consequently, it is possible that the prostate-styrene association due to employment as a fireman in Montreal is due to another exposure or lifestyle factor among firefighters.

Significant excesses of malignant lymphoma (mostly non-Hodgkin's) have been found in several cohorts of benzene-exposed workers [Wong, 1987; Blair et al., 1993; Yin et al., 1996) and among styrene-exposed workers [IARC, 1994]. Our results on benzene, toluene or xylene do not indicate that those substances increased the risk of non-Hodgkin's or Hodgkin's lymphoma, although the wide confidence intervals do not exclude the possibility. Our results are compatible with an excess risk of these same tumours in relation to styrene exposure, but again the sparseness of the data precludes stronger inferences. Although there has been a report of excess stomach cancer risk among Swedish rotogravure printers exposed to toluene [Svensson et al., 1990], our results on stomach cancer do not support such an association, although there was a hint of increased OR in the high exposure category. For all other cancer sites investigated there was no significant excess of cancer.

Most men whom we considered as exposed to the substances under study had over 10 years' exposure in situations involving exposure for at least 5% of the workweek. However for most, the concentration of exposure was probably quite low. Although our results are informative about the risks experienced by the bulk of workers exposed to these substances, it is possible that this level of exposure produces excess risk but to a degree undetectable by epidemiologic methods.

Considerable resources were devoted to the retrospective exposure assessment. Nevertheless, there was undoubtedly some random exposure misclassification in this process, which would bias the observed odds ratios toward the null value of 1.0.

An advantage of the present data set over most cohort studies is the availability of information on potential confounding factors. The strategy adopted here was to include as covariates a set of nonoccupational risk factors, notably cigarette smoking, and those occupational variables that are known or strongly suspected of being risk factors for each type of cancer. Of course if an important confounding variable was not included, then bias could ensue, in any direction.

In conclusion, for 15 common cancer types, not including leukemia, our study does not provide persuasive evidence of an increased risk that could be related directly to occupational exposure to benzene, toluene, xylene, or styrene. However, there were some results suggesting possible excess risks. In our view, the most promising leads to follow-up from our results are the following associations: esophagus-toluene; colon-xylene; rectum-toluene; rectum-xylene, and rectum-styrene. The high degree of correlation between exposure to benzene, toluene, and xylene makes it difficult to draw inference on one of these substances vs. the others.

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