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Chronic Disease and Early Exposure to Air-Borne Mixtures: 1. The Environmental Quality Database

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This is the first in a continuing study examining the impact of early exposure to air-borne mixtures of chemicals from industrial sources on the etiology of cancer. The Environmental Quality Database (EQDB) contains lifetime residential histories for ∼20 000 cases in 18 rare or poorly understood sites and ∼5000 controls. The EQDB contains all known industrial point sources in ∼50 U.S.-SIC code operating in Canada, all geolocated, from 1993 to about 1950. Cases and controls were collected in 1993−1995. Both source-centric and case-centric searching is possible. It is possible to search all instances of a source-type or only one. Three features of the design are the management of mobility and latency as epidemiological confounders and a considerable simplification of Retrospective Exposure Assessment by using the RASH relative potency methodology.

Introduction

Human health environmental cause−effect relationships involving long-term chronic exposure to industrial point sources are notoriously difficult to establish due to mobility, latency, and chemical mixtures. These factors all complicate the exposure assessment process. An estimate has been made attributing 5−15% of cancers to a cause of chronic chemical exposure to the physical environment (*1*).

Air-borne industrial pollutant levels have long been recognized as a risk factor in acute respiratory health, especially with asthma and bronchitis (*2*), heart disease, or colon cancer (*3*, *4*). The Sellafield study generated scientific interest in the statistical and epidemiological methods available for small-area health studies and led to the Small Area Health Unit at London School of Hygiene and Tropical Medicine (*5*).

Within Canada the federal government initiated a study of the impact of *early* exposure to environmental contaminants on the health of Canadians in a variety of residential settings with special consideration of mobility, latency, and retrospective exposure assessment (*6*).

The work includes four interacting components of which two are relevant to this work. (1) A comprehensive inventory of environmental sources that includes the following: all known locations of commercial manufacturing activity in 50+ U.S.-SIC codes in Canada from about 1955 in some cases and 1970 in all others to 1993 (Table 1); all thermal generating stations including those diesel-fueled in the Arctic; and all municipal waste disposal sites as of 1986 to estimate average daily exposure at a residential address over as much as 35+ years prior to 1993. (2) A case-control study in cooperation with eight of the ten Provincial Cancer Registries to identify cases of 18 rare cancers included in the study and the controls. The overall objective of the case-control component is to enhance an existing cancer surveillance system to facilitate more detailed examination of cancer concerns.

The linked inventories are called the Environmental Quality Database (EQDB) (*7*). They situate a residence in relation to a source type for any time between ∼1960 and 1993 when collection of cases began. The distance between a source and a subject is validated to ±150 m in an urban location. The cancer sites include a sample of new cases of primary M/F bladder, bone, brain, colon, kidney, leukemia, liver, lung, non-Hodgkins lymphoma (NHL), pancreas, rectal, stomach, female breast and ovary, male prostate, and testis.

A selection of known organic, inorganic, and physical risk factors for these sites are included in Table 2 (*8*−*11*). The final distribution of male and female cases in each site is in Table 3.

Residential data were collected for a total of 20 540 subjects including 5108 controls. This represents in excess of 126 000 individual residences. The case-control ratio is (250 400−5108)/5108 = 3.902. The number of new cancers in Canada in 1993 was 117 191 for both genders and all sites and is closely similar in 1994 and 1995 (*12*−*14*). New cases were collected from 1993 to 1995.

Cases and controls received a detailed questionnaire designed to collect lifetime information about where the subject had lived within Canada (*7*). The main question was about residential history from which the risk factor of interest, residential environmental exposure, is derived. Other questions relate to possible confounding factors such as sex, age, ethnic group, diet, occupation, and socioeconomic status. The EQDB provides full coverage of the impact of industrial activity on cancer incidence in all the Provinces except Quebec and New Brunswick. Nunavut, Northwest Territories, and Yukon were excluded because of their small populations.

Examples of ecological studies at the small-area level such as this are rare as often the health environment and population data are not available (*5*). In this work all residences are coded with the 6-character alphanumeric Canadian postal code, viz. K0H2Y0. The first three characters in the code correspond to the Forward Sortation Area (FSA), an area of fixed boundaries containing up to about 25 000 persons (*15*). Demographic data including gender, marital status, and income are available for each FSA. The completeness of the residence file in respect of FSA is about 82.5%. The postal code location methodology is accurate enough to identify a person moving down the block and across the street.

At least four methods of identifying controls were considered: spousal, Statistics Canada Labor Survey, hospital noncancer patients, and random-digit dialing interviews with or without a financial incentive. These were all considered in some detail, and all except random-digit dialing telephone interviews were rejected. A financial incentive was found to make little difference. Interviews were performed by incredibly dedicated staff within the Provincial Registry. Controls were administered the same questionnaire.

The number of subjects in each 5-year birth-cohort from before 1915 to 1980 was analyzed with stochastic analysis. The shape of the distribution of cases and controls by age has skewness = 1.35 and kurtosis ≈ 5.78−5.83. We conclude the age distribution of cases and controls are sufficiently similar, differing only in average amount.

The number of residences occupied by cases and controls was examined. On average, cases occupied a median of 5.27 (95th C.I. 3.50−7.59) residences, while controls occupied a

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TABLE 1. Summary of Point Source-Types in the EQDB

SIC	no.	lumber and wood
2429	295	special wood products
2435	131	hardwood veneer
2436	47	softwood veneer
2491	465	wood preserving [b]
2492	39	particle board
		paper and allied products
2611	~45	pulp mills[a]
2621	~45	paper mills[a]
2631	49	paperboard[b]
2661	96	building paper and board[b]
		printing
2741	many	misc publishing
		chemicals and allied products
2812	42	alkalis and chlorine
2816	47	inorganic pigments[b]
2819	429	industrial inorganic chemical [b]
2821	422	plastic materials[b]
2822	54	synthetic rubber
2823	21	cellulosic MMF
2824	37	synthetic fibers
2834	384	pharmaceuticals
2843	33	surfactants[b]
2851	426	paints and allied products[b]
2861	37	gum and wood chemicals
2865	56	cyclic chemicals and dyes
2869	156	industrial organic chemicals[b]
2873	98	nitrogenous fertilizers[b]
2874	46	phosphatic fertilizers[b]
2875	102	fertilizer mixing
2879	108	agro-chemicals
2891	205	adhesives and sealants[b]
2893	121	printing inks
2895	11	carbon black[b]
		petroleum and coal products
2911	45	petroleum refining[b]
2952	102	asphalt felts
2992	127	lubricating oils and greases[b]
2999	17	petroleum coke[b]
1311	~6500	upstream oil/gas (not geolocated yet)

SIC	no.	rubber and plastics
3011	94	tires and tubes[b]
3031	18	reclaimed rubber
3041	56	rubber and plastic hose
		leather
3111	154	tanning and finishing
		stone clay and glass
3251	142	brick and structural tile
3253	61	ceramic floor tile
3255	58	clay refractories
3291	all	abrasives[b]
3292	88	asbestos
3296	105	mineral wool /fiberglass
		primary metals
3312	8	blast furnace and coke ovens[a]
3313	17	electrometallurgical products[a]
3315	all	steel reinforcing products
3317	all	steel pipe and tube[a]
3321	200	gray iron foundries[b]
3322	43	malleable iron foundrie[b]
3325	all	steel investment foundries
3327	all	steel foundries nec
3331	7	copper smelters and refiners[a]
3332	5	lead smelters[a]
3333	2	zinc smelters and refiners[a]
3334	49	aluminum smelters and refiners[a]
3339	50	nickel smelters and refiners[a]
3341	136	secondary NFM
3356		steel rolling[a]
3361	207	aluminum casting
3362	134	brass, bronze, and copper casting
3369	121	NFM casting
3398	89	metal heat treating
		fabricated metals
3471	526	plating and polishing
3479	416	metal coating
		municipal services
4911	356	thermal power[a]
4941	~2200	water supply[c]
9998	8200	waste dumps[a]

[a] Major exposure model. [b] Potential major exposure model. [c] Major source outside EQDB.

median of 1.60 (95th C.I. 0.76−2.90) residences. This equates to cases potentially receiving more variety of exposure than controls. It is a basic premise of the study that all residences are potentially exposed to some form of industrial point-source emissions.

There are two copies of the EQDB, an original and a development copy. The original has proprietary confounders, including diet, gender, site code, etc. To the best of the author's knowledge the original version has never been used, due to the absence of financial and technical support to prepare exposure assessments and queries.

This work uses the development copy. It contains birth year, a complete residence file with cases and control identified, and a complete environment file. Gender is determined with census data or with FSA data. The FSA record with lifestyle parameters including population, gender, fraction married, and percent with income over a certain amount is used to provide small-area parameters for regression. Percent income > $35 000 is used in an FSA as an index of socioeconomic status (SES).

Correction for Smoking

The smoking habits of Canadians were identified from 1964 to 1996 as part of an effort to decrease smoking and improve personal health (*16*−*18*). These data allow a correction for smoking to be made by adjusting for the nonsmokers fraction of the population. This adjustment corrects the population, and the risk ratios, to a value that corresponds with considering only nonsmokers are exposed. In this work we use the data from refs *16* and *17* to obtain an estimate of the male and female prevalence of nonsmokers. This covers the period ~1960 to ~1990. The prevalence of male and female nonsmokers *P*% in any year *Y* is

$$P_{\text{male}}\% = \exp(-23.228 + 0.01378 \times Y) \quad p < 0.0008$$

$$P_{\text{female}}\% = \exp(-4.7224 + 0.004518 \times Y) \quad p < 0.11$$

The average prevalence of nonsmokers in 1967−1969 is 49.5% for males and 64.7% for females.

Releases

Releases are estimated from ~10 000 references (reports and literature) to identify and characterize the sources of approximately 220 separate chemicals in the emissions (*19*). A public source of recent release data for the EQDB is the National Pollutant Release Inventory, published annually by Environment Canada (*20*). Data are supplemented with emission data from FIREv6.23 (*21*) and AP-42 (1972) for historic reference.

TABLE 2. Organic and Inorganic Chemical Risk Factors and Cancer Sites

cancer site	organic risk factors (known)	inorganic and physical risk factors
bladder n/s	aromatic amines, painting, chlorination by products	rubber industry
bone	alkylating drugs in childhood	radiation
brain	vinyl chloride, maternal exposure to chemicals, paternal exposure to solvents	prenatal X-rays
connective tissue	phenoxyacetic acid pesticide and herbicides, (dioxins)	radiation
colon	none known	
kidney n/s	petroleum dry cleaning	
leukemia	benzene, alkylating agents	radiation
liver	vinyl chloride	arsenic
non-Hodgkins lymphoma	organic solvents, phenoxy acids, chlorophenols, pesticides, (dioxins)	dioxins
pancreas n/s	petroleum products, paint thinner	
rectal	none known	
stomach	none known	
trachea, bronchus, lung (TBL)	PAHs, cigarette smoke, BCME, vinyl chloride	radiation, arsenic, asbestos, chromium cmpds, air pollution
breast	none known	
cervix	none known	HPV
endometrial	none known	
ovary	none known	
prostate	none known	SES
testes	none known	

TABLE 3. Final Distribution of Cancer Sites Collected 1993−1995

site	code ICD-9	female EQDB	prob. F	F equiv site	male EQDB	prob. M	M equiv sites	F sites collected	M sites collected
bladder	188	498	0.0509	2.374	518	0.0532	6.6094	1182	3425
bone	170	94	0.0096	1.424	98	0.0100	1.7259	134	169
brain	191−92	487	0.0498	1.813	507	0.0520	2.1622	883	1096
breast	174	2442	0.2495	6.329				15455	
colon	153	847	0.0856	6.068	882	0.0905	5.5402	5142	4884
kidney	189	658	0.0672	1.873	684	0.0702	2.8668	1232	1978
leukemia	204−208	522	0.0534	2.603	544	0.0558	3.1786	1360	1728
liver	155	137	0.140	5.198	143	0.0147	6.3654	713	909
lung (TBL)	162	1638	0.1630	3.870	1704	0.1749	6.8540	6338	11682
NHL	200−202	729	0.0745	2.766	759	0.0779	3.2616	2017	2475
ovary	183	238	0.0135	16.611				2190	
pancreas	157	304	0.0310	4.625	316	0.0325	4.3611	1405	1379
prostate	185				1809	0.1857	9.6712		17503
rectal	154	708	0.0723	2.965	737	0.0756	4.0112	2099	2956
stomach	151	319	0.0325	3.297	332	0.0340	5.4407	1050	1804
testis	186				688	0.0706	1.2253		843
total		9789	0.9711		9744	0.9976			
controls		2502			2605				

Sources in the EQDB are characterized for convenience, as major or minor. Major sources have annual production figures available, while minor sources have less frequent production figures and therefore less complete emission trend estimates. All production data are industry based and accepted without qualification from industry trade journals, except for obvious errors. All source types are point sources except waste disposal (municipal dumps) and wood preserving. There are about 3500 communities with population > 150 located in the EQDB. The source of community water and treatment, including none, can be selected. Figure 1 illustrates the distribution of subjects from a query of the EQDB to identify persons living within 25 km of any oil refinery operating in Canada 1967−1970 and aged less than 31 years.

Retrospective Exposure

Retrospective exposure assessment in this work is the process of identifying and evaluating historic exposure at a residence from industrial point sources. The source-type(s) within a selected distance of the subject can be identified from a subject-centric query for some known time in the past.

The RASH approximation describes a mixture of chemical species emitted from any source, industrial to social (a refinery, a coal fired generating station, or a cigarette), with a toxicologically weighted index, the relative potency, in terms of a reference compound, benzo[a]pyrene (BaP) (*22*−*27*). Since BaP was extensively tested in about 200 different biological tests and is ubiquitous in the environment, it is an ideal reference material. The reduced mixture is in units of BaP equivalents (BaP eq) and can be dispersed as a single substance. The relative potency of BaP is defined equal to 1. The relative potency of an individual chemical in a biological test is the ratio of the dose for the reference chemical divided by the dose for the test chemical at the same end point (eq 1)

$$\mathrm{rp}_{\mathrm{test}} = \frac{\mathrm{dose}_{\mathrm{BaP}}}{\mathrm{dose}_{\mathrm{test}}} \tag{1}$$

Rearranging eq 1 for the *i*th chemical in a mixture of *n* chemicals in amounts

$$\mathrm{dose}_{\mathrm{BaP}} = \mathrm{fuel} \times \sum_{i=1}^{i=n} \mathrm{RP}_i \times EF_i \tag{2}$$

estimated with an emission factor, EF_i, and relative potency

FIGURE 1. Distribution of oil refineries in Canada, 1967−1970.

RP_i, when fuel is consumed, to obtain eq 2. In practice the reduction of any plume to a BaP equivalent usually involves between ~40% and ~90% of the chemicals in the plume. Approximately 350 chemicals have been analyzed to determine their median relative potency.

Questioning the EQDB: The Query File

A search of the EQDB conforms to one of two options: source-centric or case-centric.

A *source-centric* search will return the distribution of subjects (the query file) around a selected point source. The query file can be for a single source-type in a specific community or for all instances of the source-type throughout Canada in the same time period. When the search includes all instances of a source-type, the result is a sophisticated identification and analysis of risk potentially associated with industry. A risk factor with a small frequency of occurrence may be lost in the statistical noise of a single source. When the risk factor is common to the industry, examining all instances will potentially reveal the effect (*28*, *29*). When the search is of only one instance of a source-type, the result is data for an in-depth assessment of the impact of this one installation.

Maximum distance of 100 km is allowed though distances of ~25 km are more manageable. The time period for exposure is in yearly amounts from 1960. Partial year exposure cannot be searched.

A feature of the EQDB source-centric query file is that it will identify anyone whose residential attributes (time, source type, distance) fit the search terms, regardless of where in the country they are identified. In this manner population mobility is managed. An individual born in Ontario, where they received their early exposure, who eventually retires to British Columbia (BC) is collected in BC and could be identified as a subject during a study of the source of their early exposure in Ontario.

Subject-centric search will identify industries within a specific distance of a single subject, through the course of their exposure history.

A subject-centric query will return information that would identify all the places a single subject resided from birth onward. For each residence the query will identify the selected source-type(s) within the selected distance from a residence. This procedure will be used to unravel cumulative lifetime exposure assessment. It has been tested successfully on a very small scale. See Figure 2 for a schematic of the process of the EQDB.

Validation

An inverted sex ratio, $M/(M+F)$, is associated with chronic exposure to dioxins and furans as a class (*30*, *31*). The ubiquity of dioxins in industrial emissions, from large-scale sources, especially those associated with thermal or chemical processes, means that an inverted sex ratio is relatively common. In the ~90 communities in this study reference to the current census (*32*) showed most have an inverted sex ratio. An inverted sex ratio indicates more females than males are born, consequently potentially more female cancers, including reproductive cancers, are possible.

Questioning the EQDB to identify subjects with attributes satisfying specific conditions of place, time, and age, source-type produces a file of all positive "hits", the query file. The query file contains information obtained in the original sampling procedure that was part of the design of the EQDB. A query file from the EQDB is the beginning of a process that identifies and analyzes the risk of a cancer site associated with exposure to releases from a source-type. A query file is derived from source-centric questioning of the EQDB. The data in the query file are unadjusted for gender, smoking, or site. The process of identifying and analyzing the incidence rate associated with an exposure is, therefore, one of making these adjustments. Adjustment for an equivalent cancer site is a process of reversing the sampling procedure. The process is analogous to ascertaining the equivalent number of controls with the case:control ratio. The size of the query file is associated with the number of study cases in the study area.

The expected number of cancers is based on population and uses age-standardized incidence rates (ASIR) from the

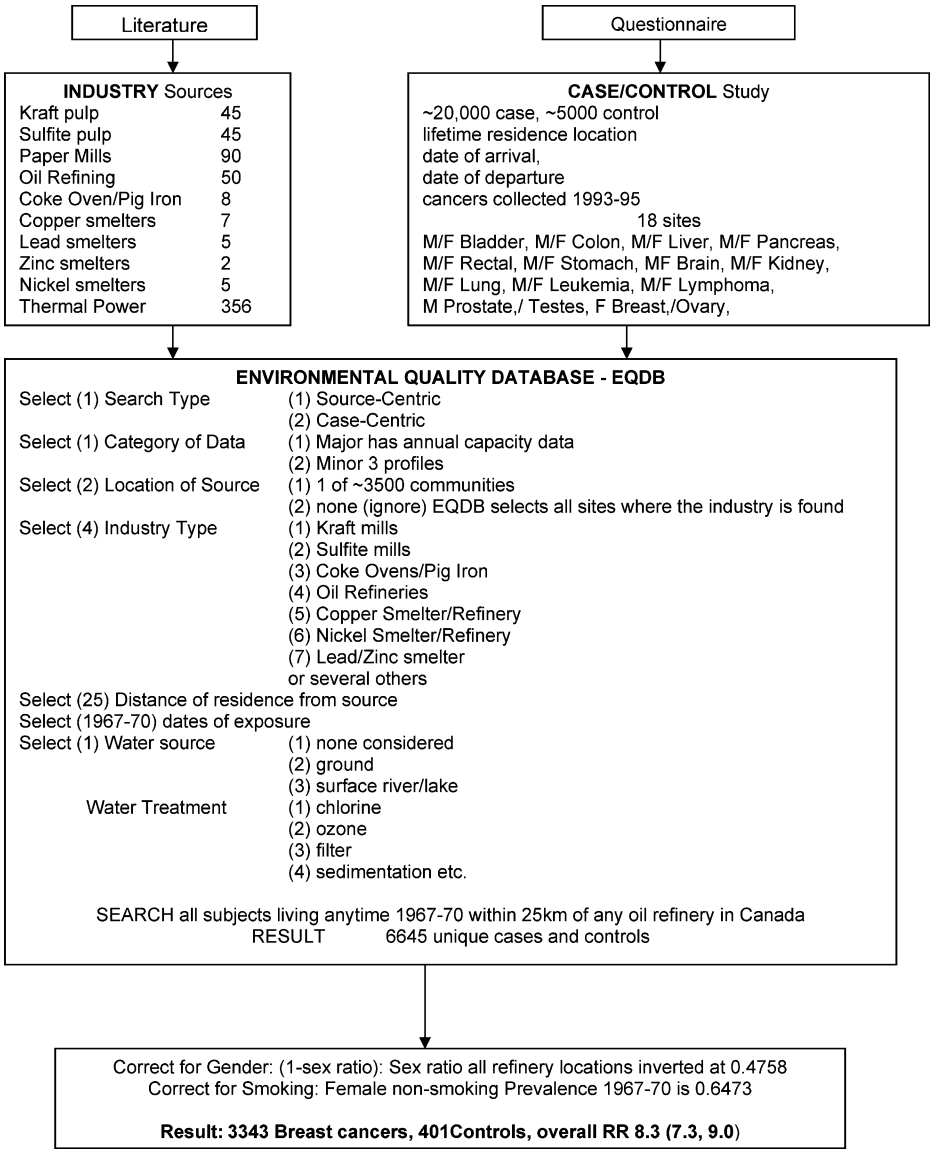

FIGURE 2. Schematic of the process of the EQDB.

contemporary Canadian Cancer Incidence Atlas (Appendix B), corrected for smoking, for all sites in the study (*33*).

In Table 3 the final distribution of cancer sites in the study appears. This includes site name, ICD-9, female and male cases collected in the study, female and male cases collected in 1993, probability of a site in the study, and female and male equivalent site ratios. There are 9789 female and 9744 male study cancers, a total of 19 533, each in 15 sites. The probability of a site in the EQDB is its fraction of the total.

The observed number of cases of a specific site can be related to the total sites sampled within the study area. The total of each cancer collected in 1993 is in Table 3. For example the study collected 498 female bladder cancers, and a total of 1182 were collected in Canada in 1993. Then the equivalent female bladder sites, corrected for smoking, in the sampled area (the study area), is estimated as follows. The example is a query file of size 400 and a sex ratio of 0.4784. Correcting for gender ($400 \times (1-0.4784)$) identifies 208 female components of the query file, and correcting for smoking (208×0.6743) identifies 135 nonsmoking female components of the query file. The probability of a bladder cancer in the EQDB is 5.09% (Table 3). This identifies ~7 female n/s bladder components of the query file. The equivalent number of bladder cancers from the search is $7 \times 2.374 \cong 16$ cases sampled in the study space. We speak of a sampling pool of 16 female, *n*/*s*, bladder cancers in the study space. Further validation can be done using the Atlas of Cancer Incidence in Western Canada (*34*).

Discussion

The EQDB is a unique resource: a GIS with a comprehensive case-control study and a comprehensive inventory of industrial point and area sources provides opportunities to ask, and answer, the most profound questions for cancer prevention.

The period covered by the study covers a time when both population and industry expanded rapidly. This was a time when knowledge of cancer etiology was minimal, a time when a diagnosis of cancer was tantamount to a death sentence, a time when the mathematical concept of a plume was first defined. Environment, as an academic field of study, or a department of government, began during the time covered by this study. This work represents one of only a few studies, explicitly designed to identify the impact of carcinogens from industrial sources on residents at home.

The design feature of the EQDB that permits all instances of an industry to be searched provides an important tool to

examine factors that are common to all or most of the industry. In the same manner that studies of effluents downstream of pulp mills uncovered the presence of dioxins (*35*−*37*) this work is able to examine the impact of air borne chemical exposures on the community.

When only one instance of a source-type is included in the search an appropriate line of study is one examining lifestyle issues, including SES. Under these conditions correction for lifestyle issues of gender and smoking, SES addresses the immediate area of a case/control and makes small area health study applicable to an even smaller area of only several kilometers squared. The use of postal codes in an urban setting provides a contiguous network of exactly interlocking "tiles" with known population and demographics.

Table 1 has been included to provide some sense of the number of sources in the EQDB and their U.S.-SIC code. Approximately 7800 sources have been located with the 4 digit SIC through the use of industrial databases. There are about 2200 municipal water systems identifying the source and treatment of drinking water in the early 1970s, collected from Environment Canada surveys of water quality (*38*−*41*). There are almost 8200 municipal waste dumps in operations before about 1990 (*42*). In all there are close to 18 270 geolocated sources. Major sources are source-types that have annual production figures included in the EQDB. Minor sources can be converted into major sources by obtaining the data concerning production and capacity. A hardcopy description of the sources and the potential chemical releases is available from the author.

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