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Chronic diseases and early exposure to airborne mixtures: Part III. Potential origin of pre-menopausal breast cancers

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This is the third in a series dealing with chronic diseases and early exposure to airborne mixtures from industrial releases. The purpose of this study is to increase the understanding of previously unconsidered factors in the physical environment potentially acting as risk factors for female breast cancer. Data are from the Environmental Quality Database containing lifetime residential records for about 20,000 cases, with 1 of 15 cancers and about 5000 controls. Subjects resided within 25 km of all kraft mills, sulfite mills, coke ovens, oil refineries, copper, nickel and lead/zinc smelters operating in Canada in 1967–1970, and were aged <31 years. Subjects are exposed at home to simultaneous counter-current plumes of dioxin congeners and dimethyl sulfate (DMS) during the exposure period. DMS concentration increases with time of flight from the source and $[SO_2]$ at 2 km. For all source types the number of cancers in an age cohort declines as the age of the cohort increases. The number of cases less than the median distance is less than the number of cases greater than the median distance. This supports the presence of a new source of risk with an origin in the plume. The crude rate of breast cancer, averaged over the 25 km of the study area for each age cohort <31 years of age, as well as source type, is least when the conditions of initial exposure are $[SO_2] \geq [DMS]$ and increases as [DMS] increases. The probability of an adverse effect from early, intermittent and simultaneous exposure to Dioxin and DMS, manifesting as a breast cancer after a latency period of as little as 26 years, is a function of age of first exposure, distance from the source and source type. The most susceptible age cohorts are the youngest.
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Introduction

This study examines early residential exposure to the simultaneous presence of two products of industrial activity, dioxins and dimethyl sulfate. The median carcinogenic potency of dimethyl sulfate has been estimated as 0.83 and that of 2,3,7,8-TCDD, the most toxic dioxin convener, as 6780, with respect to dimethylnitrosamine (Glass et al., 1991b). This study uses data from the Environmental Quality Data Base (EQDB) (Johnson et al., 1994; Argo, 2007a).

The EQDB is explicitly designed to address the epidemiological confounder, mobility. Mobility can be described as the tendency of a subject, case or control, to change residence on a fairly regular basis. The EQDB unites adult cases collected in 1993–1995 with conditions of first exposure, thereby eliminating any effects from mobility. Here, first exposure is in 1967–1970.

This study examines the influence on breast cancer incidence of residing within 25 km of all kraft and sulfite mills, coke ovens, oil refineries, copper, nickel and lead/zinc smelters operating in Canada, in 1967–1970, for female participants aged *in utero* to the age of <31 years. Records of subjects from Quebec and New Brunswick are potentially incomplete and subjects and source types in these provinces are excluded. All similar source types operating in 1967–1970 are represented with a single surrogate (Argo, 2007b). An air pathway is assumed and intermittent exposure attributed to wind is acknowledged. These conditions permit a minimum of 23 (i.e., 1993–1970) years' latency.

A preliminary examination of these seven source types indicated that the number of all cancers downwind increased, after an initial decline, as the distance from the source increased, and the increased number of cases appeared to continue beyond $\sim$12 km for all source types (Argo, 2000). A more recent exposure assessment for these seven source types (Argo, 2007b) documents releases from the process employed by the industry sector and by fueling the process with oil, natural gas, coal or wood/bark in external boilers.

A relative potency methodology is adopted to include as many of the chemicals released into the plume as possible. Retrospective exposure assessment, including releases to air, water, food and soil, is a procedure to identify and evaluate chemical exposures in the past, and is greatly simplified when the toxic mixture of the plume can be simplified to a single, easily determined quantity (Argo, 1998). Plumes are reduced to an expression of dose relative to a reference compound,

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usually benzo[a]pyrene (BaP), in the Rapid Screening of Hazard (RASH) methodology. BaP is an ideal reference compound because of its ubiquity and widespread use as a reference standard in over 200 toxicological tests (Jones et al., 1985, 1988; Owen and Jones, 1990; Glass et al., 1991a, b; Jones and Easterly, 1996). From ~40% to ~90% of the releases documented in FIREv6.23 (US-EPA, 1998) for the source combustion codes selected for this study (Argo, 2007b) have their relative potency evaluated (Jones et al., 1988).

The exposure assessment documents the production of multiple dioxin congeners from the use of coal, wood, wood/bark and heavy oil to fuel Industry and the production of SO_2 from the sulfur content of the fuels. Particulates and NOx have been ignored because of inadequate early documentation.

Polyaromatic hydrocarbons (PAHs) have been ignored in the exposure assessment as risk factors after studies show only modest support for a dose–response between PAH–DNA adducts and breast cancer development (Gammon et al., 2004). PAHs are more associated with post-menopausal risk (Bonner et al., 2005). A study of residence, near industry or traffic, was able to identify significantly elevated risk of breast cancer among post-menopausal subjects potentially exposed to chemical facilities. This was not observed among pre-menopausal subjects (Lewis-Michl et al., 1996).

Dioxin

Chloride is a common contaminant in fuels and its presence in the flame with organic matter is a necessary and sufficient condition to form dioxin congeners downwind of a source (Pandompatam et al., 1997; Fleischer et al., 1999; Mihaltz et al., 2000; Yasuhara et al., 2001). Dioxin congeners, as a by-product of combustion, are reported from the use of wood/bark, coal or heavy oil as fuel in external boilers (US-EPA, 1998).

The IARC classification of dioxin has been upgraded from ''possible human carcinogen'', group 2B, to ''human carcinogen,'' group 1 (Mandal, 2005). A unit risk of $2.9 \times 10^{-6}(\mathrm{pg/m^3})^{-1}$ for dioxin and cancer has been proposed (Paustenbach et al., 1991). The best estimate of lowest observed adverse effect level for dioxins has been recently reported as ~160 ng/g (body burden), and a reference dose (RfD) between 1 and 10 pg/kg BW/day (Greene et al., 2003). Chronic exposure to dioxins carries a long-term excess risk of soft tissue sarcoma associated with exposure to any polychlorinated dibenzodioxin or -furan with an odds ratio (OR) = 5.6 (CI = 1.1–28). This is a substantial risk suggestive of cause (Kogevinal et al., 1995).

Several factors determine the persistence of dioxin congeners in the body, including dose, quantity of body fat, binding to liver proteins and rate of metabolic transformation and excretion. Both humans and animals accumulate dioxin congeners (greenfacts.org/dioxins/1-2/dioxins-99.html). The half-life of dioxin excretion appears to vary from ~8 to 15+ years. Dioxins can alter key biochemical and cellular functions by binding to the cellular AhR receptor. The broad range of Ah-receptor-binding affinities seen in human placenta samples suggests that the response to dioxin congeners varies significantly from person to person (greenfacts.org/dioxins/1-2/dioxins-99.html).

Owing to their larger surface-to-volume ratio, a child's metabolic rate is higher and their oxygen consumption is greater than that of an adult. Therefore, their exposure, by inhalation or dermal transfer, to any air pollutant, is greater. Fetuses and newborns are most sensitive to dioxin exposure.

In most industrialized countries, concentrations of dioxins in environmental samples, food, human tissues and breast milk have declined during the 1990s, mainly owing to the enforced environmental regulations. However, this study is focused on a period approximately 20 years earlier, beginning in the late 60s, at a time when dioxin releases were uncontrolled.

Dioxins have been documented in breast milk worldwide (Koppe et al., 1991; Duarte-Davidson et al., 1992; Koopman-Esseboom et al., 1994). The list includes chemicals from the Indian subcontinent transported to the high Arctic by global winds (Davies and Mes, 1987; Dewailly et al., 1989), and dioxins and furans from incinerator emissions (Smith, 1987).

Rodent experiments have shown that alterations in the fetal hormonal environment, caused by factors such as TCDD, can modify the epigenome, and these changes are inherited and maintained throughout life (Hilakivi-Clarke and de Assis, 2006). Rats exposed to a single dose of TCDD on gestation day 15 retained undifferentiated terminal structures on post-natal day 68 (Fenton et al., 2002). Exposure effects of dioxin include delayed proliferation and differentiation of the mammary gland as well as an elongation of the window of sensitivity to potential carcinogens (Birnbaum and Fenton, 2003). Mammary gland differentiation and cell proliferation in pubertal rats after acute exposure to TCDD show inhibited cell proliferation and gland development (Brown and Lamartinere, 1995).

Persons chronically exposed to urban air pollution show more chromosome damage in human somatic cells, and low DNA repair efficiency increases susceptibility to this damage (Knudsen et al., 1999). Breast cancer patients have more damaged DNA and display decreased DNA repair efficiency (Blasiak et al., 2004).

DMS

During the course of acid rain studies into the transformation of SO_2 to $SO4^{2-}$, dimethyl sulfate (DMS), an intermediate,

metastable state, with an ~3.5-day atmospheric half-life, was identified in the downwind plume from coal- or oil-fired thermal generating stations (Eatough et al., 1986a; Lee et al., 1980, Hansen and Eatough, 1991). DMS forms in a complex series of reactions with SO_2, depending on the fuel. It is assumed that the DMS observed with heavy oil and coal also forms when these fuels are used in other source types. Concentrations of 40–50 p.p.b. were reported in the vicinity of an industrial process using DMS as a reactant (Hansen and Eatough, 1991, p 200).

DMS is an alkylating agent that not only reacts with nucleic acids *in vivo*, but has also produced cancers in rats after a single exposure and is an IARC class 2A probable carcinogen associated with the development of brain tumors in rats (IARC, 1982). An excess of brain, liver and lung cancers, together with local sarcomas that metastasize, was observed (IARC, 1974). Four cases of bronchial carcinoma, in men occupationally exposed to DMS, have been reported (IARC, 1982). DMS has vesicant properties and is considered an ideal poison gas or chemical weapon (Auer, 1918, 1922; Littler and McConnell, 1955; Schettgen et al., 2004). Early examples of DMS poisoning include eyes, mucous membranes, throat, lungs and liver (Molau, 1920; Littler and McConnell, 1955; Rippey and Stallwood, 2005).

The alkylating action of DMS and its carcinogenicity have been described (van Duuren et al., 1974; Hoffman, 1980; Mathison et al., 2004). The potential toxic pathways of DMS in an occupational setting are inhalation, dermal and gastrointestinal (Rippey and Stallwood, 2005). DMS is regulated worldwide, either as a carcinogen or as a potential carcinogen, with exposure limits as low as 50 $\mu g/m^3$ and as high as 5000 $\mu g/m^3$.

Several less potent products have been identified in the downwind plumes where DMS is found, including bis-hydroxymethyl sulfone in aerosols, ethylene sulfite in the gas phase, methane sulfonic acid from the photochemistry of dimethyl sulfide; dimethyl sulfoxide, dimethyl sulfone and hydroxy-methane sulfonic acid (Eatough et al., 1986b).

Growth of DMS, in relation to the total sulfur present as SO_2, was measured *in situ* over a transit time of 5–6 h (Hansen and Eatough, 1991). With average winds of 12 km/h, this would amount to distances of ~75 km, during which time the observed DMS showed constant growth. My graphic estimate, Eq. (1) (Hansen and Eatough, 1991, Figure 1), is used to estimate the growth of DMS downwind of other similar S-rich sources. The observed growth is in terms of ground level concentration (glc) of SO_2 at 2000 m from the source and time of flight.

$$\text{DMS}(\mu g/m^3) = \exp\left(-6.83 + 0.844\left(\frac{\text{Dist.(km}\times 1000)}{\text{windspeed(m/s}\times 3600)}\right)\right) \times SO_2(2\text{Km} - \mu g/m^3) \quad (1)$$

All of the chemicals released from a source, including the SO_2 that ultimately transforms into DMS, have an origin in the stack(s), and will be dispersed in a way that can be described with a Gaussian plume model and variants. Any release described with a Gaussian plume model declines exponentially in glc with distance from the stack, after first passing a maximum, usually in the first 5 km. DMS formed in the plume after it leaves the stack, or any other species depending on time of flight of the plume, will show a pattern of exponential growth with distance.

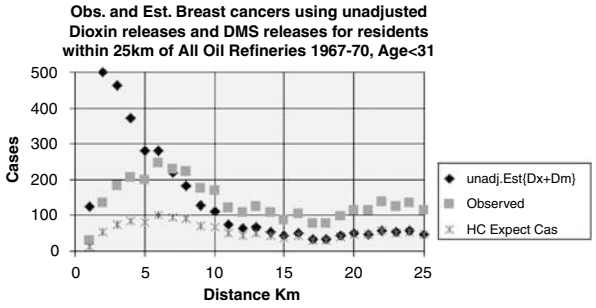

Figure 1. Observed and estimated breast cancers using unadjusted dioxin releases and DMS releases for residents, aged <31 years, within 25 km of all oil refineries in 1967–1970.

An early manual of dispersion (Turner, 1961) was used to build a simple Gaussian plume model, with an output that compares favorably to currently available models (Masters, 1991). Chronic exposures lasting decades can be satisfied with very simple dispersion models, when long-term wind records (30+ years) are of the same order of time as the duration of the minimum exposure (26+ years). Dispersion of a Gaussian plume is from a 75-m stack, with winds from any direction at 3.33 m/s, and emission rates as calculated. Thirty-year winds are from Environment Canada (Environment Canada, 1981). A wind speed of this magnitude is in the 85th percentile for all stations operated by Environment Canada.

The cancer cell phenotype has been presented as a set of necessary genetic changes, from one to three, for any particular set of developmentally identical cells (Thilly, 1988). In theory, a person in whose tissue an early genetic change takes place will have a higher number of cells containing the necessary number of genetic changes. If the genetic changes occur early, then an early tumor is expected; if late, then a late tumor is expected; and if they do not occur, then no tumor is expected. It follows that a study of cancers with an etiology that includes early exposure, when an individual is unusually susceptible during periods of rapid cell proliferation (*in utero*, the developing child and puberty), is of particular value.

An estimate attributing 5–15% of cancers to a cause of chronic chemical exposure to the physical environment was made (Doll and Peto, 1981). It has been suggested that about 80–90% of human cancers are caused by environmental carcinogens, which are closely related to the daily life of humans (Hirono, 1983).

Hypotheses

There are two hypotheses in this study that can be tested.

1. People are predisposed to genetic change that may eventually lead to tumors. A person in whose tissue an early genetic change takes place will have a higher number of cells containing the necessary number of genetic changes. If the genetic changes occur early, then an early tumor is expected; if late, then a late tumor is expected; and if they do not occur, then no tumor is expected.
2. Female participants are predisposed to breast cancers when simultaneously exposed at an early age to plumes of dioxins and DMS, and the earlier the age of first exposure the greater is the risk.

Method

The EQDB is a purpose-built geographic information system that contains over 126,000 lifetime residential addresses for $\sim$20,000 cases, with 1 of 15 rare or poorly understood cancers and $\sim$5000 controls (Argo, 2007a). The EQDB contains the location of all instances in Canada of $\sim$50 source types, coded with US-SICs, the location of $\sim$10,000 municipal waste dumps and water treatment records for $\sim$3500 communities. All sources and subjects are geo-located using the Canadian postal code, with a precision in urban locations of $\pm$100 m, supported by 1:50,000 topographic maps as needed. Sources are classed according to the detail contained in the records: major sources have annual records and their history extends from $\sim$1955 to 1990. Minor sources have less complete records and appear in three profiles, 1972, 1987 and 1990.

The exposed population, shown in Table 1, is from summing the population of all communities with a relevant source type in the 1991 Census of Canada (Statistics Canada, 1991). The median and 5th percentile of the underlying distribution of the male sex ratio, M/(M + F), was obtained with stochastic analysis.

There are seven age cohorts: *in utero,* birth$\leq$5, 5$\leq$10, 10$\leq$15, 15$\leq$20, 20$\leq$25 and 25$\leq$30 years. Any subject born in the study period is included in the *in utero* cohort with age = 0. All other ages are calculated from 1970. The prevalence of non-smoking in women during the study period is 0.6473 (Hackland, 1976; Kaiserman and Rogers, 1992). Breast cancer cases represent 24.95% of the female cases and the female equivalent sites are 6.329 breast cancers per female cancer (Argo, 2007a). Then every query case represents

$$1\times(1-0.4758)\times0.6473\times0.2495\times6.329 = 0.5358\,\mathrm{F,\ n/s,\ breast\ cancers.}$$

The number of control equivalents, partitioned for gender and smoking, adjusted for the case:control ratio, 3.902, is,

$$1\times(1-0.4758)\times0.6473\times3.902 = 1.3240\,\mathrm{F,\ n/s\ controls}$$

Table 1 shows the distribution of female breast cancers and controls as a function of the age of first exposure. There are intervals with no controls. This is dealt with by adding 1 control, on the assumption that it is irrational to concede that there are no unaffected persons of the same age, gender and smoking history, that is, a control, in a cell or interval. The number of blank controls in the cohort that was altered is indicated in parentheses that is, (+3). The total number of controls used in the calculation is to the left of the parentheses, that is, 8(+3).

Table 2 shows the distribution of female breast cancer equivalents and control equivalents as a function of their distance from the source. The underlying distribution of distance is obtained with stochastic analysis (Crystal Ball ver. 4.0, Excel ver.5.0) using 100,000 iterations, repeated. The parameters of a Gamma distribution are shape, scale and location. These are formulated from the mean, μ, and standard deviation, σ. Shape is μ^2/σ^2 and scale is σ^2/μ. Location is the origin, equal to 0 offset. The mean and standard deviation of distance for cases and controls are extracted from the EQDB records for each source type.

The location of the mode, in km the 2.5th, 50th and 97.5th percentiles for cases and controls are in Table 2. The number of cases and controls, in the database records living $\leq$mode, $\leq$2.5th, $>$2.5th$\leq$50th, $>$50th$\leq$97.5th percentiles are in Table 2. There are no subjects living $>$97.5th percentile of distance for any source type. To calculate the relative risk (RR), the cases and controls are taken from the ''space,'' defined by the parameters of the cases.

The expected number of cases, using the age-adjusted rate for breast cancers in Canada, 94.1/100K (Canada Minister of National Health and Welfare, 1995), is estimated on the assumption that the female population is distributed in the same manner as the cases. Any other assumption, other than uniform, infers potential clusters. The distribution of cases is determined from the database records for every 1 km.

Table 3 examines the association of excess female breast cancer within 25 km of each source type *vs* process, boiler, SO_2, DMS, dioxin and flare releases (Strosher, 1996) (oil refineries only) with multiple linear regression.

There are three significant sinks for sulfur: SO_2, the aerosol and gaseous DMS. The concentration of DMS in the gas phase is several orders of magnitude greater than DMS in the aerosol (Hansen and Eatough, 1991, p 204ff.) and DMS in the aerosol is therefore ignored.

A review of the data on nucleation in the atmosphere indicates that when SO_2 is present, SO_2-to-aerosol conversion dominates the Aitken nuclei count, and about 80% of the sulfur released can appear in the aerosol. The dynamics of aerosol formation critically depend on the presence of SO_2, NO and hydrocarbon (Whitely, 1978). In the presence of hydrocarbon and NO_x, releases from kraft, sulfite and coke ovens favor the production of aerosol, and only about 20%

Table 1. Distribution of breast cancer by age cohort (residential exposure in 1967–1970, within 25 km of source type; case:control ratio = 3.902:1).

Cohort	Kraft	Sulfite	Coke	Petroleum	Copper	Nickel	Lead/Zinc
Total population	519,991	732,955	438,125	2,850,781	147,450	107,860	14,369
Sex ratio 50th	0.5026	0.4912	0.4866	0.4992	0.4933	0.4993	0.4816
Sex ratio 5th	0.4784	0.4684	0.4594	0.4758	0.4728	0.4587	0.4816
In utero cases	104	137	115	1162	45	56	9
In utero controls	5 (+2)	17 (+2)	12 (+2)	109	6 (+2)	8 (+4)	(+5)
RR	20.7	8.1	9.5	10.5	4.5	7.0	1.8
Low 95th CI	8.4	4.8	5.3	8.6	2.3	3.3	0.6
High 95th CI	50	13	17	12	8.9	14	5.4
Birth < age ≤ 5 years	131	118	92	798	25	51	8
Controls	7	15	12 (+1)	60	6 (+2)	9 (3+)	5 (+4)
RR	18.7	7.9	7.6	13.3	4.2	5.7	1.6
Low 95th CI	8.7	4.6	4.2	10.2	1.7	2.8	0.8
High 95th CI	39	13	14	17	10.2	4.5	4.9
5 < age ≤ 10 years	89	95	73	655	20	48	7
Controls	10 (+1)	17 (+1)	8 (+1)	91	6 (+2)	6 (+3)	(+5)
RR	8.9	5.6	9.1	7.2	3.3	8.0	1.4
Low 95th CI	4.6	3.3	4.4	5.8	1.3	3.4	0.4
High 95th CI	17	9.4	19	8.9	8.3	10	
10 < age < 15 years	53	66	53	428	13	24	7
Controls	19 (+1)	26 (+2)	13 (+1)	82	6 (+3)	8 (+2)	5 (+4)
RR	2.8	2.5	4.1	5.2	2.2	3.0	1.4
Low 95th CI	1.7	1.6	2.2	4.1	0.8	1.3	0.4
High 95th CI	4.7	4.0	7.4	6.6	5.7	6.7	
15 < age < 20 years	34	38	31	193	15	17	7
Controls	18	11 (+2)	6 (+1)	35	9 (+1)	6 (+2)	6 (+3)
RR	1.9	3.5	5.2	5.8	1.7	2.8	1.2
Low 95th CI	1.07	1.7	2.2	4.1	0.7	1.1	0.4
High 95th CI	3.3	6.7	12	8.4	3.8	7.2	
20 < age < 25 years	12	21	15	83	2	5	3
Controls	6 (+3)	12 (+3)	5 (+1)	18	(+5)	5 (+4)	5 (+5)
RR	2.0	1.75	3.0	4.5	0.4	1.0	0.6
Low 95th CI	0.75	0.86	1.1	2.7			
High 95th CI	5.3	3.5	8	7.3			
25 < age ≤ 30 years	4	5	4	25	1	1	0
Controls	7 (+2)	8 (+1)	5 (+4)	8	(+5)	(+5)	5 (+5)
RR	0.63	0.63	0.8	3.0	0.2	0.2	0
Low 95th CI				1.4			
High 95th CI				10.5			
Overall							
Total case	426	479	383	3343	121	201	37
Total control	86 (+9)	91 (+9)	63 (+13)	405	43 (+20)	46	35 (+31)
RR	4.9	5.2	6.1	8.02	2.8	4.4	1.1
Low 95th CI	3.2	4.2	4.6	7.24	2.0	3.2	0.7
High 95th CI	6.2	6.6	7.9	8.89	4.0	6.0	1.7

of the SO_2 available transforms into DMS. Under ambient conditions around oil refineries, copper, nickel and lead/zinc smelters up to 80% of the SO_2 available may be transformed into DMS. Glc of DMS potentially depends on the time of flight and the [SO_2] at 2 km (Eq. (1)) and is, initially, less than the glc of SO_2.

The sample space for each source type includes seven age cohorts distributed over twenty-five 1-km cells, a total of 175

Table 2. Distribution of breast cancer and female controls by distance and source type (residential exposure <25 km in 1967–1970; case:control ratio = 3.902:1).

Distance	Kraft	Sulfite	Coke	Petroleum	Copper	Nickel	Lead
Cases (total, age <31 years)							
Conditions	$[SO_2]<[DMS]$			$[DMS]\geq[SO_2]$			$[SO_2]<[DMS]$
US-SIC	2611	2611	3312	2911	3331	3339	3332
Stochastic analysis — source to percentile distance (km) — cases							
Mode	5.7	5.0	4.0	7.2	13.4	14.4	1.5
2.5th	1.6	1.8	0.9	1.8	6.3	6.5	0.3
50th	8.5	8.7	7.5	9.9	14.9	16.4	5.9
97.5th	25.2	25.3	27.1	29.6	28.8	33.6	27.7
Stochastic analysis — source to percentile distance (km) — controls							
Mode	6.6	2.4	6.8	8.5	15.2	15.5	—
2.5th	1.8	0.5	1.8	1.9	8.4	8.6	0.00
50th	8.5	5.9	9.9	10.7	16.4	16.8	2.7
97.5th	23.9	24.0	29.7	31.9	28.6	28.8	36.5
No. of cases within bounds of case distribution							
≤Mode	248	166	147	2120	74	85	6
≤2.5th	26	61	13	283	28	25	0
>2.5≤50th	344	230	208	2593	63	66	15
>50≤97.5th	413	351	216	2667	176	158	15
No. of controls within bounds of case distribution							
≤Mode	37	106	29	418	9	11	0
≤2.5th	5	28	3	74	3	1	4
>2.5≤50th	57	68	36	441	9	11	1
>50≤97.5th	54	56	29	588	36	18	4
Relative risk							
≤Mode	6.7	1.6	5.1	5.0	8.2	7.7	—
≤2.5th	5.2	2.2	4.3	3.8	9.3	25	—
>2.5≤50th	6.0	3.4	5.8	5.8	7.0	6.0	15
>50≤97.5th	7.6	6.3	7.4	4.4	4.9	8.8	3.8
Lower 5th confidence interval							
≤Mode	4.7	1.2	3.4	4.5	4.1	4.1	—
≤2.5th	2.0	1.4	1.2	3.0	2.8	3.4	—
>2.5≤50th	4.6	2.6	4.1	5.2	3.5	3.2	2.0
>50≤97.5th	5.7	4.7	5.1	4.1	3.4	5.4	1.2

events for each carcinogen present. Dioxin from the source and DMS from the plume, both recognized carcinogens, represent releases potentially present from both modes of dispersal (exponential decline and growth) and all source types.

$$\Pr\{\mathrm{Dx}\} = \left(\sum_{i=1}^{i=25}\sum_{j=iu}^{j\leq 30}[\mathrm{Dx}_{i,j}]\right)$$
$$\Pr\{\mathrm{Dm}\} = \left(\sum_{i=1}^{i=25}\sum_{j=iu}^{j\leq 30}[\mathrm{Dx}_{i,j}]\right) \quad (2)$$

Let $\Pr\{\mathrm{Dx}\}$ represent the probability of an adverse outcome following intermittent residential exposure to dioxin, and $\Pr\{\mathrm{Dm}\}$ represent the probability of an adverse outcome following intermittent residential exposure to DMS. The square brackets represent chemical concentration in ng BaP equivalents (ng BaP eq/m^3). The concentration of dioxin, in pg/m^3, multiplied by 2500 (the relative potency, rp) (Jones et al., 1988), divided by 1000 is the concentration of dioxin in ng BaP eq/m^3. The concentration of DMS from Eq. (1), in μg/m^3, multiplied by 2.2 (the relative potency, rp) (Jones et al., 1988), multiplied by 1000 is the concentration of DMS in ng BaP eq/m^3. Then from the multiplication rule,

$$\Pr(\mathrm{Dx\ and\ Dm}) = (\Pr(\mathrm{Dx/Dm})\times\Pr(\mathrm{Dm}))$$

Table 3. Excess breast cancer equivalents *vs* residential exposure to process, boiler, flares, SO_2, DMS and dioxin.

	Kraft	Sulfite	Coke	Petroleum	Copper	Nickel	Lead/zinc
Expected	255	367	223	1406	70	55	3
Observed	423	482	385	3442	122	202	38
Excess	168	115	162	2036	52	147	25
Excess/observed	0.397	0.238	0.421	0.592	0.426	0.727	0.658
Excess breast cancer vs process+boiler+DMS+dioxin							
R^2	0.812	0.566	0.830	0.956	0.802	0.607	0.852
SD	3.54	5.07	3.44	12.48	1.46	4.20	1.29
F	16.43	4.96	30.84	51.05	12.17	5.25	8.09
Significance F	2.5E−06	0.004	1.73E−08	1.01E−08	7.7E−05	0.0042	0.008
Intercept	+17.71	+14.3	+3.61	−253.2	−5.22	−7.8	+1.71
P-value	1.8E−06	0.001	0.17	6.02E−05	0.0068	0.068	0.04
Process	+2.08	+4684	−0.87	−6507	+94.18	+103.5	−50.50
P-value	0.55	0.13	0.15	0.0006	0.012	0.65	0.003
SO_2	+489.59	+133.6	+1143.1	−51.06	+0.071	+0.228	+0.019
P-value	0.16	0.48	0.17	0.32	0.28	0.79	0.092
Boiler	−0.38	−0.016	+2.47	+73.17	−1.38	−4.32	+0.131
P-value	0.55	0.091	0.16	0.007	0.012	0.65	0.002
DMS	−245.2	−70.65	−72.8	+1.88	+0.16	+0.124	−0.0051
P-value	4.0E−05	0.008	0.40	6.76E−06	8.42E−05	0.0009	0.24
Dioxin	−0.11	−0.089	−0.053	−0.065	−0.63	−2.84	−0.008
P-value	0.17	0.49	0.18	0.06	0.31	0.79	0.57
Flare				55,427			
P-value				0.25			
Range	1–25	1–25	1–25	5–25	1–21	1–24	1–25

Since dioxin and DMS are independent,

$$\Pr(\mathrm{Dx\,and\,Dm}) = (\Pr(\mathrm{Dx}) \times \Pr(\mathrm{Dm}))$$

The only change that can happen is diminution of the dioxin by dispersion or increase of the DMS with growth. All the age cohorts in a distance cell are assumed to be exposed to the same concentration of dioxin or DMS. The product is calculated for each age cohort and summed. The frequency of occurrence of the summed product, over the twenty-five 1-km distance cells, is applied to the female population in each distance cell of the sample space. This, normalized to the observed cases, is the estimated number of cases, written Est.{Dx + Dm}, to indicate that it is derived from [Dx] or [Dm] and can be compared with the observed cases in the same space.

Results

There is an inverted male sex ratio in all communities in which the source types are located, taken from the 1991 census of Canada. All the male sex ratios (SR = M/(M + F)) in Table 1 favor female births (SR ≤ 0.50) and are an indicator of potential chronic dioxin exposure from every source type (Solomon and Schettler, 2000; Jongbloet et al., 2002; Ryan et al., 2002). With the possible exception of lead/zinc smelters, the sex ratio of the 5th percentile everywhere is below the corresponding value for the entire population calculated from the 1991 census. This infers that external forces other than conventional SES factors are present, and as such the heavy industries in these communities can legitimately be examined for cause (Argo, 2008).

Table 1 shows that the number of cancers in an age cohort declines as the age of the cohort increases, for all source types. For all age cohorts from *in utero* to 15 < age ≤ 20, and for all source types but lead/zinc, the apparent RR is elevated and significant. The overall RR for all source types and age cohorts, except lead/zinc, is apparently elevated and significant. Lead/zinc smelters have the fewest number of the affected population and this may play a role in the associated results.

Table 2 presents the results of a stochastic analysis of the distribution of cases and controls with respect to the source for each source type. The four distance-related terms are the mode; ≤2.5th percentile of distance; from the 2.5th to ≤50th percentile of distance; and from the median to ≤97.5th percentile of distance. For all source types, the number of cases less than the median distance is less than the number of cases greater than the median distance. This cannot be understood with a Gaussian plume alone, which would have a continuous, exponentially declining concentration of the carcinogen, and supports the presence of a new source of risk with an origin in the plume.

Tests of association between excess breast cancers and the calculated dose of emissions from process, SO_2, boilers, DMS and dioxin and flares are in Table 3. Flares are present only with oil refineries. The value of R^2 from the multiple regression ranges from 0.566 for sulfite pulp upward. DMS is a statistically significant term for all source types except coke ovens and lead/zinc smelters.

Table 4 shows that the crude rate of breast cancer, averaged over the 25 km of the study area, for each age cohort and source type, is least when the conditions of initial exposure are $[SO_2] \geq [DMS]$ and increases as $[SO_2]$ increases. Increased SO_2 release leads to more SO_2 at 2 km and this potentially leads to more DMS by Eq. (1), depending on the sulfur sink available. The logarithm of the aggregate crude rate, including all age cohorts, is a function of SO_2 at 2 km during first exposure with $R^2 = 0.635$, $P = 0.057$. As the total is a function of $[SO_2]$ (therefore, DMS), then the parts, the individual averaged crude rates for each age cohort must also be a function of SO_2 (and DMS). Table 4 shows that the youngest cohorts with the highest crude rates are the most susceptible.

Figure 1 shows the observed and estimated breast cancers calculated using releases of dioxin and DMS for subjects within 25 km of all oil refineries. Est$\{Dx + Dm\}$ is the estimate of cases as described earlier, normalized to the observed cases. The estimate can be made with unadjusted (unadj.) or adjusted (adj.) dioxin releases (see below). In Figure 1, HC is the number of cases calculated with the Health Canada rate for the same population. Normalization uses a fraction of the total female population, and this fraction ranges upward from ~ 0.03, with an average value excluding lead/zinc of 0.05 (Table 5). The actual population of young women in the age cohort < 15 for each source type is not readily available from the census, preventing an absolute estimate.

A feature of Figure 1 is the large value predicted in the first 5–7 km. This is found with all source types in approximately the same position, and is an artifact of the model. It derives from the condition $[Dx] > [Dm]$. Dioxin is known as a carcinogenic promoter and has a large value when $[Dx] > [Dm]$ but does not induce a correspondingly large number of observed cases. Figure 2 is provided to show, in a comparative format, the observed cases, estimated cases (Est.$\{Dx + Dm\}$) and profiles Pr$\{Dx\}$ and Pr$\{Dm\}$, all with respect to distance. Figure 2 shows that the trend of observed cases is in contrast to the trend of Pr$\{Dx\}$ but does approximately follow the trend of Pr$\{Dm\}$. Therefore, the model is adjusted to constrain dioxin concentrations to $[Dx] \leq [Dm]$. Figures 3–8 show that estimated cases, adjusted to constrain $[Dx] < [Dm]$ ($=$adj. Est.$\{Dx + Dm\}$), are strongly correlated with observed cases over the full 25-km study space for all source types but lead/zinc smelters. The estimated cases in Figure 9, lead/zinc smelters, use unadjusted [dioxin].

Table 5 shows the one-sided χ^2 test, and the Pearson product moment correlation coefficient applied to Est.$\{Dx + Dm\}$ *vs* observed cancers. Oil refineries show a χ^2 test that is greater than the critical value, 42.98, for $\alpha = 0.005$ and $v = (25-1) = 24$ (Kanji, 1999).

A case with the first exposure during puberty, aged 11–15 years, in 1967–1970 is a woman aged 37–41 years when

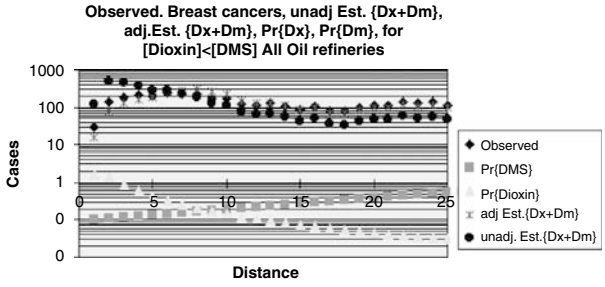

Figure 2. Observed and estimated breast cancers from dioxin and DMS releases for residents, aged < 31 years, within 25 km of all oil refineries in 1967–1970.

Table 4. Crude breast cancer rates averaged over 25 km (exposure age < 31 years in 1967–1970; collection 1993–1995; age cohort, equivalence point and source type).

Age cohort	Kraft	Sulfite	Coke	Petroleum	Copper	Nickel	Lead
Equivalence point		$\sim$24 km			$\sim$16–17 km		$\sim$13 km
In utero	37.8	36.7	48.5	73.6	57.4	110.1	*370*
Birth $<$ age $\leq$ 5 years	49.2	29.5	38.2	62.3	42.1	112.9	*435*
5 $<$ age $\leq$ 10 years	33.8	24.2	30.9	44.0	40.9	84.7	*505*
10 $<$ age $\leq$ 15 years	19.7	16.6	21.2	28.4	27.4	64.7	*285*
15 $<$ age $\leq$ 20 years	12.8	9.7	15.8	13.9	32.2	59.3	*325*
20 $<$ age $\leq$ 25 years	8.1	5.4	11.0	6.0	20.7	25.7	*260*
25 $<$ age $\leq$ 30 years	5.7	1.6	5.1	2.2	9.6	—	
Total	167.1	123.7	170.7	230.4	230.3	457.4	
SO_2 at 2 km ($\mu g/m^3$)	31.4	86.28	18.4	13,312	20,989	18,866	

Table 5. One-sided χ^2 test and Pearson product moment correlation (estimated *vs* observed cases).

Source type	Observed case	Expected case	Fraction of female population	Pearson PMMC	χ^2 test
Kraft	423	255	0.037	0.8867	27.81
Sulfite	482	367	0.029	0.8927	13.47
Coke	385	223	0.043	0.8668	30.93
Oil refineries	3442	1406	0.057	0.8856	72.45[a]
Copper	122	70	0.041	0.9507	4.51
Nickel	202	55	0.092	0.9876	5.75
Lead/zinc	38	3	0.226	0.6303	13.60
Average value			0.0498		

Level of significance, $\alpha = 0.005$ for $v = 25-1 = 24$, Critical value = 42.98.
[a]Omits three estimates at the maximum.

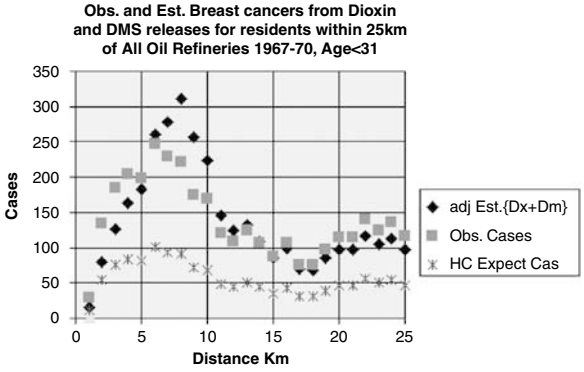

Figure 3. Observed and estimated breast cancer from dioxin and DMS releases for residents, aged <31 years, within 25 km of all oil refineries.

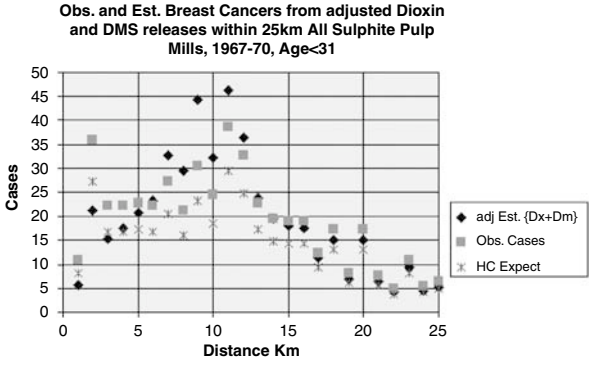

Figure 5. Observed and estimated breast cancers from adjusted dioxin and DMS releases for residents, aged <31 years, within 25 km of all Sulphite pulp mills in 1967–1970.

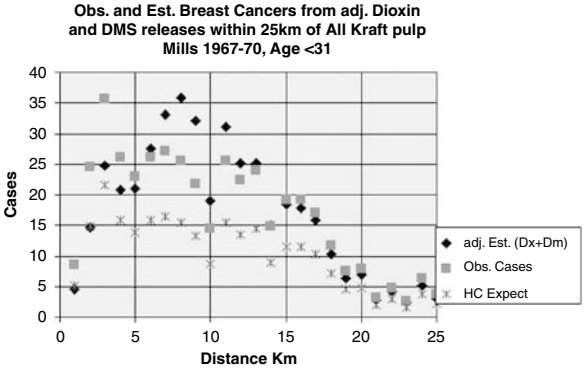

Figure 4. Observed and estimated breast cancers from adjusted dioxin and DMS releases for residents, aged <31 years, within 25 km of all kraft pulp mills in 1967–1970.

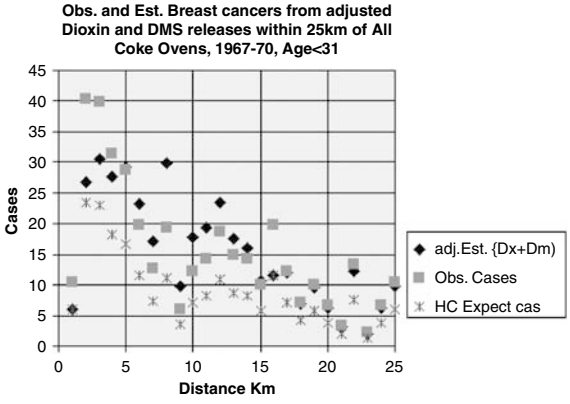

Figure 6. Observed and estimated breast cancers from adjusted dioxin and DMS releases for residents, aged <31 years, within 25 km of all coke ovens in 1967–1970.

collected in 1993, and her age would classify her breast cancer as pre-menopausal. An *in utero* infant case, born in 1968, is 26 years when collected in 1993. These represent the age range of adults in 1993, who comprise the *in utero* to age ≤15 cohorts, and illustrate that this study has principally addressed pre-menopausal breast cancers. The cancers calculated with the Health Canada rate do not make a distinction between pre- and post-menopausal. For all source types, there is everywhere an excess of breast cancers, with respect to the Canada rate.

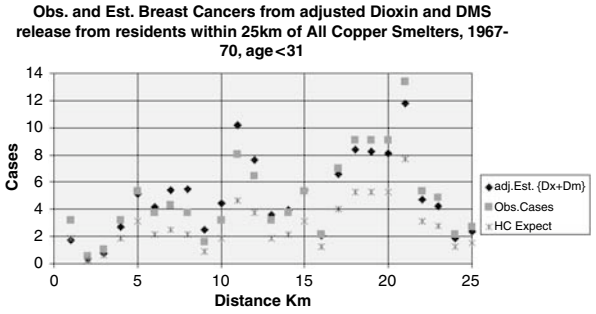

Figure 7. Observed and estimated breast cancers from adjusted dioxin and DMS releases for residents, aged <31 years, within 25 km of all copper smelters in 1967–1970.

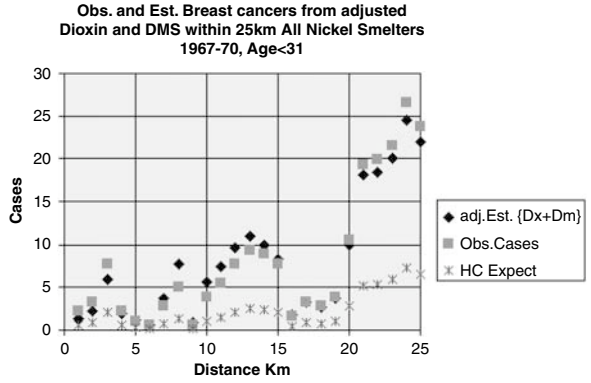

Figure 8. Observed and estimated breast cancers from adjusted dioxin and DMS releases for residents, ages <31 years, within 25 km of all nickel smelters in 1967–1970.

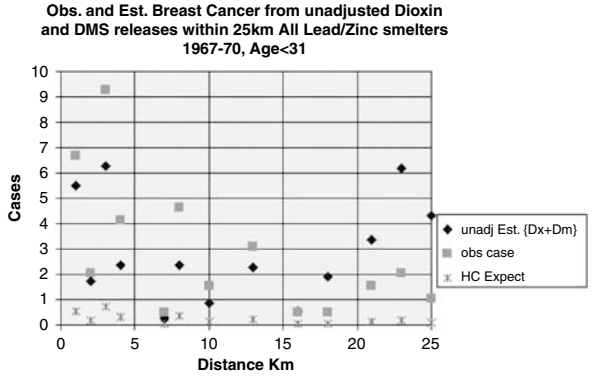

Figure 9. Observed and estimated breast cancers from unadjusted dioxin and DMS releases for residents, aged <31 years, within 25 km of all lead/zinc smelters in 1967–1970.

Discussion

The purpose of this study is to increase the understanding of previously unconsidered factors in the physical environment potentially acting as risk factors for female breast cancer. The EQDB permits a description of the physical location of a resident in terms of distance from multiple source types. Under the conditions of this study, all subjects can be described as exposed, at home, to a common set of carcinogens: dioxin congeners and dimethyl sulfate, each with an origin in the seven source types considered. Other sources are ignored. In 1993, 15,455 new cases of breast cancer were identified; in 1994, 15,860 new cases were identified; and in 1995, 16,161 new cases were identified for a total of 47,476 cases during the collection period (National Cancer Institute of Canada, 1998, 1999, 2000). In this study, 7868 new cases of breast cancer were estimated, or 16.5% of the total.

The counter-current concentration gradients of the two chemicals, as well as their description in terms of BaP equivalents, are seminal to the description of the breast cancer distribution in the sample space. The changing relative proportions of dioxin and DMS constantly modify the exposure in each 1-km segment. At its worst, this study shows that female breast cancers are potentially strongly correlated (Table 5) with simultaneous exposure to two carcinogens, one a promoter, declining exponentially with distance from the source, and the other an initiator, a primary carcinogen, increasing exponentially with distance from the source. At its best, this study names those carcinogens as dioxin congeners and DMS.

The population of cases between the median distance and the upper bound exceeds the population of cases between the lower 2.5th bound and the median distance. This cannot be explained by a single exponentially declining Gaussian plume and confirms that a new source of risk, potentially a plume of DMS, is present for all source types considered.

For all source types, there is a condition in which μg BaP equivalents of $SO_2 \cong \mu$g BaP equivalents of DMS. The median relative potency of SO_2 is rp50 = 0.21 and of DMS is rp50 = 2.2 (Jones et al., 1988). Then at the toxic equivalent point, $[\mu g\ SO_2/m^3 \times 0.21]/[\mu g\ DMS/m^3 \times 2.2] \sim 1$. Table 4 shows that kraft, sulfite and coke ovens reach this point near 24 km; oil refineries, copper and nickel smelters reach this point near 16–18 km and lead/zinc smelters reach it near 13 km. Occupational regulation of DMS ranges worldwide down to 50 $\mu g/m^3$. In our study, this value is exceeded for oil refineries at 21 km, for copper smelters at 15 km and for nickel smelters at 16 km. For all other source types, the value of 50 $\mu g/m^3$ is exceeded at ≥ 25 km.

The failure to account for lead/zinc smelters stems principally from using only one example, that at Trail BC. The other large lead/zinc smelter, at Belledune NB, was inaccessible because New Brunswick opted out of the original EQDB study. Trail is in the mountains where conventional dispersion is obstructed by geographic impediments, and has a relatively small population.

The first hypothesis is supported by the observation that the greatest number of cases appears in the youngest cohorts

(*in utero* and $b<5$) and the number of cases in a cohort declines as the cohort ages. The first hypothesis is also supported by the data on crude rates calculated for age cohorts and source type. The youngest subjects have the greatest crude rate. The aggregate crude rate is positively and significantly correlated with [SO_2]. From Eq. (1), the concentration of DMS is positively correlated with [SO_2] at 2 km, and therefore the aggregate crude rate is also positively correlated with [DMS].

The second hypothesis is supported by data in Figures 3–8 in which cases estimated from the concentration of dioxin and DMS in a cell (adj. Est.$\{Dx + Dm\}$ = adj. Pr$\{Dx + Dm\} \times$ F. Pop. for [dioxin]$<${DMS]) are strongly correlated with the observed cases (Table 5). The probability of an adverse effect from simultaneous, early and intermittent exposure to dioxin and DMS, manifesting as a pre-menopausal breast cancer after a latency period of as little as 26 years, can be expressed as a function of age of first exposure, dioxin congener concentration and DMS concentration.

A study of children dying from leukemia or cancer, aged 0–15 years, in England, Wales and Scotland, from 1953 to 1980, included a goal to identify relationships between birth and death addresses and potential environmental hazards. Excess leukemias and solid cancers were found near oil refineries, major users of petroleum products and users of kilns and furnaces, including steelworks, power stations, aluminium, zinc and iron and steel foundries (Knox and Gilman, 1997).

Cancer incidence and mortality in proximity to a petrochemical plant in South Wales, studied in response to concerns of alleged clusters in a population of 112,000, found that there were 5417 incident cancers and 2458 cancer deaths within 7.5 km of the plant. There was no apparent decline of solid cancers or leukemias with distance from the plant, at all ages, or in children (Sans et al., 1995).

This, to our knowledge, is the first time that dimethyl sulfate, a "one-hit" IARC class 2A carcinogen with well-defined genotoxic effects in airborne mixtures from seven industry types, has been statistically associated with female breast cancer. Given the ubiquity of airborne sulfur and airborne dioxin contamination from industry, a further study is urgently needed. This suggests that DMS has been overlooked or, worse, ignored, in earlier studies concerning the health effects of airborne sulfur.

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This study would not have been possible without the discovery of the transformation of SO_2 to DMS in the downwind plume, by Professor Delbert J. Eatough and his colleagues at Brigham Young University, which he described to me as "that old stuff!", and Professor Ian B. MacNeil, Professor Emeritus Department of Statistics and Actuarial Science University of Western Ontario, for conversations about everything, and many solutions. This analysis is possible because of the RASH methodology of Troyce Jones and colleagues at ORNL, Oak Ridge, TN; Dr. Yang Mao, Cancer Bureau, Health Canada Ottawa, provided the opportunity to develop the EQDB system. Rick Fry of the same office provided able and untiring technical support. Don Cameron of CameronSofware.com built the software for the EQDB.

References

Argo J. Retrospective Exposure Assessment with Emission Inventories: a new approach to an old problem in Retrospective Exposure Assessment and Enhanced Cancer Surveillance in Canada. Mao Y., and Argo J. (Eds.). *Environmetrics* 1998: 9(5): 505–518.

Argo J. Downwind distribution of all-cancer relative risk about a point source: single source with reactive and unreactive plumes. *Environ Sci Technol* 2000: 34: 4214–4220.

Argo J. Cancer and early exposure to air-borne mixtures: part 1 The EQDB. *Environ Sci Technol* 2007a: 41: 7178–7184.

Argo J. Cancer and early exposure to air-borne mixtures: part 2 Exposure Assessment. *Environ Sci Technol* 2007b: 41: 7185–7191.

Argo J. Response to comment on "Chronic disease and Early Exposure to Air-Borne Mixtures 2. Exposure Assessment". *Environ Sci Technol* 2008: 42: 2202–2203.

Auer J. Title unavailable. *Proc Soc Exp Biol* 1918: 15: 104.

Auer J. Title unavailable. *J Exp Med* 1922: 35: 97.

Birnbaum L.S., and Fenton S.E. Cancer and developmental exposure to endocrine agonists. *Environ Health Perspect* 2003: 111(4): 389–394.

Blasiak J., Arabski L., Krupa R., Wozniak K., Rykala J., Kolacinska A., Morawiec Z., Drzewoski J., and Zadrozny M. Basal, oxidative and alkylative DNA damage, DNA repair efficiency and mutagen sensitivity in breast cancer. *Mutat Res* 2004: 554(1–2): 139–148.

Bonner M.R., Han S.D., Nie J., Rogerson P., Vena J.E., and Muti P., et al. Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. *Cancer Epidemiol Biomarkers Prev* 2005: 14(1): 53–60.

Brown N.M., and Lamartinere C.A. Xenoestrogens alter mammary gland differentiation and cell proliferation in the rat. *Environ Health Perspect* 1995: 103(7–8): 708–713.

Canada Minister of National Health and Welfare. *Canadian Cancer Incidence Atlas Appendix B* 1995, p. 135.

Davies D., and Mes J. Comparison of the residue levels of some organo-chlorine compounds in breast milk of the general and indigenous Canadian populations. *Bull Environ Contam Toxicol* 1987: 39: 743–749.

Dewailly E., Nantel A., Weber J-P., and Meyer F. High levels of PCBs in breast milk of Inuit women from Arctic Quebec. *Bull Environ Contam Toxicol* 1989: 43: 641–646.

Doll R., and Peto R. *London in The Causes of Cancer Quantitative Estimates of Avoidable Risks of Cancer in the United States Today*. Oxford University Press: London, 1981.

Duarte-Davidson R., Harrad S.J., Allen S.C., and Jones K.C. The relative contribution of individual PCB's, PCDDs, and PCDFs to toxic equivalent values derived for bulked human breast milk samples from the UK. *Chemosphere* 1992: 25: 1653–1663.

Eatough D.J., Peterson M., Bartholomew D., Hansen L.D., Cheney J.L., and Eatough N.L. The identification and chemistry of Dimethyl sulfate in the atmosphere. *Proc 7th World Clean Air Congress* 1986a, 393–401.

Eatough D.J., White V.F., Hansen L.D., Eatough N.L., and Cheney J.L. Identification of gas-phase dimethyl sulfate and monomethyl hydrogen sulfate in the Los Angeles USA atmosphere. *Environ Sci Technol* 1986b: 20: 867–872.

Environment Canada. *Government of Canada, Canadian Climate Normals*, vol 5, Wind, Ottawa, 1981, pp. 1951–1980.

Fenton S.E., Hamm J.T., Birnbaum L.S., and Youngblood G.L. Persistent abnormalities in the rat mammary gland following gestational and lactational exposure to TCDD. *Toxicol Sci* 2002: 67(1): 63–74.

Fleischer O., Wichmann H., and Lorenz W. Release of polychlorinated dibenzo-p-dioxins and dibenzofurans by setting off fireworks. *Chemosphere* 1999: 39(6): 925–932.

Gammon M.D., Sagiv S.K., Eng S.M., Shantkumar S., Gaudet M.M., and Teitelbaum S.L., et al. Polycyclic aromatic hydrocarbon-DNA adducts and breast cancer: a pooled analysis. *Arch Environ Health* 2004: 59(12): 640–649.

GreenFacts Dioxins:6 Evaluations and Conclusions http://www.greenfacts.org/dioxin/1-2/dioxins-99.html.

Glass L.R., Easterly C.E., Jones T.D., and Walsh P.J. Ranking of carcinogenic potency using a relative potency approach. *Arch Environ Contam Toxicol* 1991a: 21: 169–176.

Glass L.R., Jones T.D., Easterly C.E., and Walsh P.J. Use of short-term test systems for the prediction of the hazard represented by potential chemical carcinogens. *Environmental Auditor* 1991b: 2: 103–169.

Greene J.F., Hays S., and Paustenbach D. Basis for a proposed reference dose (Rfd) for Dioxin of 1–10 pg/Kg–Day: a weight of evidence evaluation of human and animal studies. *J Toxicol Environ Health B Crit Rev* 2003: 6(2): 115–159.

Hackland S. Smoking Habits of Canadians 1965–1974 Canada, Health Canada, Health Protection Branch, Non-Medical Use of Drugs Directorate, Technical Report Series No. 1 1976.

Hansen L.D., and Eatough D.J. Organic oxysulphur compounds in the atmosphere. In: Hansen LD., and Eatough, D.J. (Eds.). *Organic Chemistry of the Atmosphere*. CRC Press, Boca, Raton, 1991, pp. 199–231.

Hilakivi-Clarke L., and de Assis S. Fetal origins of breast cancer. *Trends Endocrinol Metab* 2006: 17(9): 340–348.

Hirono I. Problems of environmental carcinogenesis. *Gan To Kagaku Ryoho* [article in Japanese Abstract only] 1983: 10(10): 2085–2092.

Hoffman G.R. Genetic effects of dimethyl sulfate, diethyl sulfate and related compounds. *Mutation Res* 1980: 75: 63–129.

IARC. *Dimethyl Sulphate, IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*. International Agency for Research on Cancer, Lyon, in Some Aromatic Amines, Hydrazine, and related substances, N-nitroso compounds and miscellaneous alkylating agents, 1974, pp 271–281.

IARC. *Dimethyl Sulphate, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Supplement 4, International Agency for Research on Cancer, Lyon, in Chemicals, Industrial Processes and Industries Associated with Cancer in Humans, 1982, pp. 200–201.

Johnson K.C., Mao Y., Argo J., and Dubois S. Enhanced Cancer Surveillance – Case–Control Component, Proposal for a Collaborative Project January Health Canada and Canadian cancer Registries Epidemiology Research Group, 1994.

Jones T.D., and Easterly C.E. A RASH analysis of National Toxicology Program Data: predictions for 30 compounds to be tested in rodent carcinogenesis experiments. *Environ Health Perspect* 1996: 104(Suppl 5): 1017–1030.

Jones T.D., Walsh P.J., Watson A.P., Owen B.D., Barnthouse L.W., and Saunders D.A. Chemical scoring by a rapid screening of hazard (RASH) method. *Risk Anal* 1988: 8: 99–118.

Jones T.D., Walsh P.J., and Zeighami E.A. Permissable concentrations of chemicals in air and water, derived from RTEC entries: a ''RASH'' chemical scoring system. *Toxicol Ind Health* 1985: 1: 213.

Jongbloet P.H., Roeleveld N., and Groenewoud H.M. Where the boys aren't. Dioxin and the sex ratio. *Environ Health Perspect* 2002: 110(1): 1–3.

Kaiserman M.J., and Rogers B. Forty year trends in Canadian Tobacco Sales. *Can J Pub Health* 1992: 83: 404.

Kanji G.K. *100 Statistical Tests*. Sage Publications, London, Table 5, 1999.

Knox E.G., and Gilman E.A. Hazard proximities of childhood cancers in Great Britain from 1953–1980. *J Epidemiol Community Health* 1997: 51(2): 151–159.

Knudsen L.E., Norppa H., Gamborg M.O., Nielsen P.S., Okkels H., and Soll-Johanning H., et al. Chromosomal aberrations in humans induced by urban air pollution: influence of DNA repair and polymorphism's by glutathione *S*-transferase M1 and N-acetyltransferase 2. *Cancer Epidemiol Biomarkers Prev* 1999: 8(4 part 1): 303–310.

Kogevinal M., Kaupinnen T., Winkelmann R., Becher H., Bertazzi P.A., Bueno-de Mesquita H.B., Coggan D., Green L., Johnson E., and Littorin M., et al. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy-herbicides, chlorophenols, and dioxins: two nested case–control studies. *Epidemiology* 1995: 694: 397–402.

Koopman-Esseboom C., Huisman M., Weisglas-Kuperus N., Boersma E.R., de Ridder M.A., and Van der Paauw C.G., et al. Dioxin and PCB levels in blood and human milk in relation to living areas in the Netherlands. *Chemosphere* 1994: 29: 2327–2338.

Koppe J.G., Pluim H.J., Olie K., and van Wijnen J. Breast milk, dioxins, and the possible effects on the health of newborn infants The Science of the Total. *Environment* 1991: 106: 33–41.

Lee M.L., Later D.W., Rollins D.K., Eatough D.J., and Hansen L.D. Dimethyl and monomethyl sulfate: presence in coal fly ash and airborne particulate matter. *Science* 1980: 207: 186.

Lewis-Michl E.L., Melius J.M., Kallenbach L.R., Ju C.L., Talbot T.O., Orr M.F., and Lauridsen P.E. Breast cancer risk and residence near industry or traffic in Nassau and Suffolk Counties, Long Island, New York. *Arch Environ Health* 1996: 51(4): 255–265.

Littler T.R., and McConnell R.B. Dimethyl sulfate poisoning. *Br J Ind Med* 1955: 12: 54–56.

Mandal P.K. Dioxin: a review of its environmental effects and its aryl hydrocarbon receptor biology. *J Comp Physiol [B]* 2005: 175(4): 221–230.

Masters G.M. *Atmospheric Dispersion Sec. 7.5 Introduction to Environmental Engineering and Science*. Prentice Hall, Toronto, 1991 pp. 313ff.

Mathison B.H., Frame S.R., and Bogdanffy M.S. DNA methylation, cell proliferation and histopathology in rats following repeated inhalation exposure to dimethyl sulfate. *Inhal Toxicol* 2004: 16(9): 581–592.

Mihaltz P., Pal F., Siska J., and Duchateau F. The evaluation of Dioxin emissions from pilot scale incineration of organochlorine compounds. *Cent Eur J Public Health* 2000: 8(Suppl): 12–13.

Molau F.D. Report of two cases of dimethyl sulfate poisoning. *J Ind Hyg Toxicol* 1920: 2: 238–239.

National Cancer Institute of Canada. *Canadian Cancer Statistics*, Appendix II: Table 1, New Cases of Cancer by Site and Sex Canada, 1993, 1998, p. 67.

National Cancer Institute of Canada. *Canadian Cancer Statistics*, Appendix II: Table 1, New Cases of Cancer by Site and Sex Canada, 1994, 1999, p. 67.

National Cancer Institute of Canada. *Canadian Cancer Statistics*, Appendix II: Table 1, New Cases of Cancer by Site and Sex Canada, 1995 2000, p. 71.

Owen B.A., and Jones T.D. Hazard evaluation for complex mixtures: relative comparisons to improve regulatory consistency. *Regul Toxicol Pharmacol* 1990: 11: 132–148.

Pandompatam B., Kumar Y., Guo I., and Liem A.J. Comparison of PCDD and PCDF emissions from hog fuel boilers and hospital waste incinerators. *Chemosphere* 1997: 34(5–7): 1065–1073.

Paustenbach D.J., Sarlos T.T., Lau V., Finley B.L., Jeffrey D.A., and Ungs M.J. The potential inhalation hazard by dioxin contaminated soil. *J Air Waste Manage Assoc* 1991: 41(10): 1334–1340.

Rippey J.C., and Stallwood M.I. Nine cases of accidental exposure to dimethyl sulfate — a potential chemical weapon. *Emerg Med* 2005: 22(12): 878–879.

Ryan J.J., Amirova Z., and Carrier C. Sex ratios of children of Russian pesticide producers exposed to dioxin. *Environ Health Perspect* 2002: 110(11): A699–A701.

Sans S., Elliott P., Kleinschmidt I., Shaddick G., Pattenden S., Walls P., Grundy C., and Dolk H. Cancer incidence and mortality near the Baglan Bay petrochemical works, South Wales, 1995: 52(4): 217–224.

Schettgen T., Broding H.C., Angerer J., and Drexler H. Dimethyl sulphate: a hidden problem in occupational medicine. *Occup Environ Med* 2004: 61(1): 73–75.

Smith A.H. Infant exposure assessment for breast milk dioxins and furans derived from waste incinerator emissions. *Risk Anal* 1987: 7: 347–353.

Solomon G.M., and Schettler T. Environment and health: 6 endocrine disruption and potential human health implication. *Can Med Assoc J* 2000: 163(11): 1471–1476.

Statistics Canada Census of Canada, 1991.

Strosher M. Investigations of Flare gas Emissions in Alberta Final report to: Environment Canada, Conservation and Protection, the Alberta Energy Utilities Board and the Canadian Association of Petroleum Producers 1996.

Thilly W.G. Looking ahead: algebraic thinking about genetics, cell kinetics and cancer. In: Bartsch H., Hemminki K., and O'Neil I.K. (Eds.). *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention*. No 89 IARC, Lyon, 1988 pp. 486–492.

Turner D.B. *Workbook of Atmospheric Dispersion Estimates US*. Department of Health Education and Welfare, Cincinnati, OH, 1961.

US-EPA. *United States Environmental Protection Association Factor Information and Retrieval FIRE* v 2.6 1998.

van Duuren B.L., Goldschmidt B.M., Katz C., Seidman I., and Paul J.S. Carcinogenic activity of alkylating agents. *J Natl Cancer Inst* 1974: 53: 695–700.

Whitely K.T. The physical characterization of sulfur aerosols. *Atmos Environ* 1978: 12: 135–159.

Yasuhara A., Katami T., Okuda T., Ohno N., and Shibamoto T. Formation of dioxins during the combustion of newspapers in the presence of sodium chloride and Poly(Vinyl Chloride). *Environ Sci Technol* 2001: 35(7): 1373–1378.