EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Childhood cancers and atmospheric carcinogens

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J Epidemiol Community Health 2005;**59**:101–105. doi: 10.1136/jech.2004.021675

Study objectives: To retest previous findings that childhood cancers are probably initiated by prenatal exposures to combustion process gases and to volatile organic compounds (VOCs); and to identify specific chemical hazards.
Design: Birth and death addresses of fatal child cancers in Great Britain between 1966 and 1980, were linked with high local atmospheric emissions of different chemical species. Among migrant children, distances from each address to the nearest emissions ''hotspot'' were compared. Excesses of outward over inward migrations show an increased prenatal or early infancy risk.
Setting and subjects: Maps of emissions of many different substances were published on the internet by the National Atmospheric Emissions Inventory and ''hotspots'' for 2001 were translated to map coordinates. Child cancer addresses were extracted from an earlier inquiry into the carcinogenic effects of obstetric radiographs; and their postcodes translated to map references.
Main results: Significant birth proximity relative risks were found within 1.0 km of hotspots for carbon monoxide, PM10 particles, VOCs, nitrogen oxides, benzene, dioxins, 1,3-butadiene, and benz(a)pyrene. Calculated attributable risks showed that most child cancers and leukaemias are probably initiated by such exposures.
Conclusions: Reported associations of cancer birth places with sites of industrial combustion, VOCs uses, and associated engine exhausts, are confirmed. Newly identified specific hazards include the known carcinogens 1,3-butadiene, dioxins, and benz(a)pyrene. The mother probably inhales these or related materials and passes them to the fetus across the placenta.

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Accepted for publication 28 May 2004

Previous studies have shown (1) that childhood cancers and leukaemias in Great Britain exhibit geographical clustering of birth places: (2) they occur at increased densities around industrial sites with large scale combustion processes or using volatile organic compounds (VOCs), or which incinerate waste: (3) among children who moved house between birth and death the first addresses were closer to these hazards than were the later ones and migrations were more often directed away from a nearby hazard than towards one.[1–7] The increased effectiveness of early exposure, combined with the known effects of obstetric radiation exposures,[8] suggests that these diseases are often initiated prenatally.

The use of hazard proximity birth-death comparisons was initially dictated by the absence of a suitable set of non-cancer controls in the study from which the case material was extracted. These data were designed to measure the effects of obstetric radiation by comparing cases with paired non-cancer controls[8]; but the controls had been geographically matched with the cases and could not then be used to make geographical comparisons. The migration based method gave coherent results but was open to the possible objection that the migration patterns in the cancer children may have reflected a general population movement, perhaps related to area demolitions and subsequent rehousing. The recent publication of independent and comprehensive national pollution data now affords an opportunity to retest the atmospheric birth hazard hypothesis, and to identify specific chemical hazards. This is the objective of this study.

The UK National Atmospheric Emissions Inventory (NAEI) has recently published through its web site, detailed geographical displays of emissions of many different chemical species for 2001. These maps[9] were downloaded and individual pixels—resolved at 412.8 metres per pixel—were translated to grid references (see appendix, available on line http://www.jech.com/supplemental). Emission levels are expressed '''per square km per year'' on a seven point colour coded scale, using units that vary from grams (dioxins), through kilograms (chromium, nickel), to tonnes (sulphur dioxide, PM10 particles). Some were measured directly and others by ascertaining activities with known emission characteristics. Lower scale values are indicated as broad map zones, but the highest levels are shown as small clusters of red pixels or by individual pixels, often appearing to represent individual sources. The maps are readily available for inspection.

Except for the red pixel hotspots, the main scale divisions were too broad for effective comparisons of birth and death addresses. NAEI also points out that because of atmospheric diffusion the emission estimates do not directly represent the air we breathe. However, as in earlier studies, it is possible to compare birth and death addresses by measuring hotspot distances. The ''case centred'' method, used again here, examines the surroundings of each address in turn to identify the nearest of the hotspots. The selection is entirely objective and the resulting comparative distance measurements are available in very large numbers.

METHODS

The case material was extracted from a file of all 22 458 deaths from leukaemia or other cancer occurring before the 16th birthday in Great Britain between 1953 and 1980. They were classified into 11 main groups (lymphatic, myeloid, monocytic and unclassified/other leukaemias: lymphomas, nephroblastoma, CNS tumours, neuroblastoma, bone cancers, other solid cancers, and fatal ''benign'' tumours). Home addresses at death were always recorded and where parents

Abbreviations: VOC, volatile organic compound; NMVOC, non-methane volatile organic compound; NAEI, National Atmospheric Emissions Inventory

Table 1 Combustion products of fossil fuels

	Carbon dioxide (as C)	Sulphur dioxide	PM10	Nitrogen oxides	Carbon monoxide
Hotspot criteria*	1264	10	4	25	160
Number of hotspots	64625	12817	39744	53875	13371
Number of children†	1246	2008	2908	2072	2943
Outward migration	838	1034	2074	1501	2324
Inward migration	408	974	834	571	619
Ratio out/in	2.054	1.062	2.487	2.629	3.754

*Lower limits for hotspots in tonnes/km^2/year; †children migrating >1.0 km and with one address within 1.0 km of nearest hotspot and the other address outside 1.0 km.

were subsequently interviewed, the birth address was also obtained and the postcode later identified. Map references were extracted from the Central Postcode Directory. Most were probably accurate to within 0.1 km of the actual address although larger PCs may have incurred errors up to about 1.0 km. This dataset has been described in detail elsewhere.[3 4] To ameliorate the effects of the interval between the survey dates and the 2001 date of the NAEI maps, this analysis is based upon those children who died in the second half of the study period, 1966–1980. Orkney and Shetland are excluded. Each leukaemia type and cancer type was analysed individually, together with the grouped reticuloendothelial cancers, the grouped ''solid'' cancers, and all cancers together.

The UK emissions maps were downloaded from the NAEI web site[9] into a bitmap file (*.bmp) and unwanted areas were edited out. Relations between pixel northings/eastings and grid coordinates were solved against small islands and promontaries (see appendix). The maps are orientated true (grid) north-south with identical northing and easting scales of 412.8 metres per pixel. Subsequently measured distances from addresses to hazardous emission locations are accurate to within about 500 metres. Mean nearest hotpoint distances (truncated to a maximum 50.0 km), and means of individual distance differences, were tested against standard errors: and outward/inward ratios through χ^2 tests. All results subsequently quoted were extremely significant and p values are not individually set out.

Estimates of the relative risks of being born close to, or distant from, an emission hazard were first calculated among children who had moved more than 1.0 km between birth and death, and who had one address within 1.0 km of the nearest and the other address more than 1.0 km away from the nearest hazard point. Viewed against a presumed overall short term cross boundary equilibrium of migrations in the general population (see later), outward/inward ratios substantially greater than 1.0 were taken to represent the selective cancer-initiating effects of the birth locations themselves. These relative risks were then used to calculate the proportions of sub-1.0 km cancer births attributable to each hazard; and then, through reference to the total number of sub-1 km births, to estimate the proportion of all cancers that might be so caused.

RESULTS

Large scale combustion emissions

Table 1 gives the migration patterns in relation to the major fossil fuel emissions, within the above subset. Carbon dioxide (expressed as tonnes of carbon) represents the entire sum of fossil fuel use including coal, oil, and gas. The outward/inward ratio of 2.05 indicates a movement of cancer migrants away from zones of high fuel consumption and, presumably, high population densities and industrial concentrations. Sulphur dioxide emissions, which arise mainly from coal burning, failed to mirror this net outward movement suggesting that the main correlates of the differential migration must be oil and/or gas combustion. PM10, nitrogen oxides, and carbon monoxide are all preferentially associated with oil burning, particularly in internal combustion engines, and their high outward/inward ratios indicate that transport emissions contribute a major part of the overall carbon related effect.

Viewed against a presumed overall migration equilibrium, these ratios show the relative cancer risks among inner zone compared with outer zone births. The findings were mirrored in significant excesses of mean death distances over birth distances. The mean within-pair differences also differed from zero.

Volatile organic compounds

Non-methane volatile organic compounds (NMVOC) are discharged in quantities comparable with materials listed in the last section. In roughly equal proportions they reflect (a) solvent use, (b) engine exhaust fuel residues and fuel evaporation, and (c) other industrial/refinery processes. They include benzene, benz(a)pyrene, and 1,3-butadiene, each of which is discharged in tonnage or subtonnage quantities; also dioxins, whose upper range is lower bounded by only 0.1 gram/km^2/year. Benzene is a suspected leukaemogen while benz(a)pyrene, 1,3-butadiene, and dioxins are known carcinogens. Benzene is a major component of motor fuel while atmospheric 1,3-butadiene is largely derived from petrol and diesel engine exhausts. Table 2 shows the results of migration analyses.

The very high outward/inward ratio (3.78) within 1.0 km of the 1,3-butadiene hotspots strongly suggests a specific

Table 2 Emissions of volatile organic compounds

	NMVOC	Benzene	Benz(a)-pyrene	1,3-Butadiene	Dioxins
Hotspot criteria	28*	3*	0.03*	0.25*	0.1 grams
Number of hotspots	53297	59811	150617	11949	1078
Number of children†	1409	1308	580	2775	670
Outward migration	951	889	381	2194	461
Inward migration	458	419	199	581	209
Ratio out/in	2.076	2.122	1.915	3.776	2.206

*Lower limits for hotspots in tonnes/km$_2$/year; †children migrating >1.0 km and with one address within 1.0 km of nearest hotspot and the other address outside 1.0 km.

Table 3 Emissions of metals (1)

	Copper	Zinc	Beryllium	Lead	Calcium	Cadmium	Mercury
Hotspot criteria*	0.1	1.0	1.0	3 0	50.0	0.01	0.1
Hotspots (1000s)	121	83	3	47	40	156	26
Number of children†	1307	2458	689	2585	2605	477	3107
Outward migration	679	1332	353	1664	1564	290	1835
Inward migration	628	1126	336	921	1041	187	1272
Ratios out/in	1.081	1.183	1.051	1.807	1.502	1.551	1.443

*Lower limits of hotspots in kg/km^2/year; †children migrating >1.0 km and with one address within 1.0 km of nearest hotspot and the other address outside 1.0 km.

association. Despite the fogging effects of the limited map resolutions, crossings of a 0.7 km boundary returned a ratio of 4.66 (1273/273); while 0.5 km and 0.3 km gave 7.65 (819/107) and 8.39 (411/49). The butadiene analyses were repeated with biases attached to all the hotpoint locations. When they were "moved" by 1.0 km south and west, the 7.65 ratio (above) was reduced to 2.50 and a similar north easterly bias reduced it to 2.34. These findings indicate a ground level source with distance dilution and a very local carcinogenic action. They also confirm the precision of the map location data for 1,3-butadiene.

Dioxins also showed increasing ratios at shorter distances; from 2.21 at 1.0 km to 3.15 at 0.7 km and 3.24 at 0.5 km. Carbon monoxide showed a qualitatively similar, but much weaker, effect.

Metals and non-metals

Table 3 summarises results for copper, zinc, beryllium, lead, calcium, cadmium, and mercury, and table 4 for nickel, manganese, tin, vanadium, arsenic, selenium, and chromium. None showed birth-death asymmetries comparable with those shown in tables 1 and 2. Lead and cadmium showed small birth proximity excesses but discharges of these metals are closely associated with the fuel hungry processes represented in tables 1 and 2 and the effect is almost certainly indirect. Despite the near eradication of leaded petrol, the linear distributions of lead on the NAEI maps show that it is still related to transport. Calcium discharges also showed a small emigration excess but are associated with lime and cement manufacture, processes using large amounts of fossil fuel. Mercury, another metal with a modestly asymmetric migration pattern, is associated with waste incineration and hence with dioxins. All of these relations are probably indirect, with the high points for each substance acting as proxy for other emissions.

Several substances showed small reverse effects; an excess of death place proximities. Arsenic, nickel, and vanadium recorded inward/outward ratios of 1.391, 1.597, and 1.718 respectively. Arsenic is associated with industrial coal burning, vanadium with industrial fuel oil uses, and nickel with both, and we might have expected to see parallels rather than the inverse. NAEI data again suggest an indirect origin. All three emissions have been greatly reduced in recent years and their recent topographical distributions all show major conurbations with "hollow emission centres", presumably arising from changed fuel uses in city centres. The probable explanation is through an inverse statistical relation with high traffic densities.

Risk assessments

Tables 1 to 4 optimised birth-death contrasts by excluding children who had not moved very far and those who had moved entirely within high exposure or entirely within low exposure zones. However, this prior selection barred assessment of an "attributable risk" (AR) in the total population, an assessment demanding inclusion of children who did not cross any critical boundaries or who did not move house at all. The most strongly interacting emission types were therefore reanalysed with such children included and the results are presented in table 5. The outward/inward ratios in table 5 are less dramatic than those in tables 1 and 2 because they incorporate many less discriminatory records, but they are still highly significant .

Table 5 uses relative risks (RR) from tables 1 and 2 to calculate attributable proportions (RR−1)/RR for the inner zones and applies them to all those born inside 1.0 km—that is, rows 2 to 4 of the table. Absolute attributable numbers are then derived and expressed as a proportion of all cancer children, giving an overall attributable risk (AR).

It is difficult to compare results for different emissions, whether in terms of RR or AR, because of the varying ways in which different hotspot cut off points were defined. Less extreme cut off values will generate a less extreme RR, but the concomitant increase in numbers of hazard points may then increase estimates of AR. In Table 5 the hotspots for dioxins and for 1,3-butadiene were comparatively infrequent and gave the highest RRs; while the abundant hotspots for NMVOC and nitrogen oxides gave lower RR values, yet "accounted for" larger proportions of child cancers. The several AR estimates can not be simply added together as each emission type acts to some extent as proxy for others but it is clear that these migration derived RR and AR estimates have important implications. They show that most childhood cancers are probably initiated by close perinatal encounters with one or more of these high emissions sources. The low atmospheric concentrations of these substances, and a timing analogy with the effects of fetal irradiation[8] suggest that the mother may act as an accumulating filter and pass carcinogens across the placenta. However, effective direct exposures

Table 4 Emissions of metals (2) and non-metals

	Nickel	Manganese	Tin	Vanadium	Arsenic	Selenium	Chromium
Hotspot criteria*	1.0	4.0	1.0	0.3	0.1	0.1	0.1
Hotspots (1000s)	71	48	55	188	174	91	120
Number of children†	2703	2500	2475	1582	1083	2232	1771
Outward migration	1041	1143	1108	582	453	1024	837
Inward migration	1662	1357	1367	1000	630	1208	934
Ratios out/in	0.626	0.842	0.811	0.582	0.719	0.848	0.896

*Lower limits of hotspots in kg/km^2/year; †children migrating >1.0 km of one address within 1.0 km of nearest hotspot and the other address outside 1.0 km.

Table 5 Birth addresses relative to a 1.0 km boundary selected hazards

	1,3-butadiene	Carbon monoxide	PM10	Dioxins	Benz-pyrene	Benzene	NMVOC	Nitrogen oxides	Merged groups
	1	2	3	4	5	6	7	8	1 to 4
Number of hotpoints	11949	13371	39749	1078	13813	59811	53279	53875	48697
Internal non-migrants	895	1308	1889	140	832	2924	2855	2381	2188
Internal migrants	1368	2226	3164	67	1120	5844	5636	4558	3969
Migration out	2227	2349	2118	467	1265	899	958	1528	1853
Migration in	604	653	877	214	698	434	468	597	760
External migrants	3425	2422	1493	6319	4570	476	591	968	1070
External non-migrants	2764	2351	1770	3519	2827	735	804	1278	1471
Total inside births	4490	5883	7171	674	3217	9667	9449	8467	8010
Total outside births	6793	5426	4140	10052	8095	1645	1863	2843	3301
All births*	11283	11309	11311	10726	11312	11312	11312	11310	11311
Relative risk	3.81	3.75	2.49	2.21	1.92	2.12	2.08	2.63	2.52
Attributable risk/100	29.3	38.1	37.9	3.4	13.6	45.1	43.4	46.4	42.7

*Numbers differ slightly between hazard types. Migrants with both addresses far distant (>50.0 km) from any hazard, or with a very short radial difference (<0.1 km) were excluded.

in early infancy, or through breast milk, or even preconceptually, cannot be excluded.

The migration phenomena described in tables 1 to 5 refer to the sum of all leukaemias and cancers but they were equally evident in each tumour class separately and in children dying at different ages. The mean age at death among migrants (97.4 months) was greater than among non-migrants (70.8 months) but this was simply because a later death allowed more time to become a migrant. Both 1,3-butadiene and dioxins are believed to disturb sex determination so the data were examined for sex ratio differences at shorter and longer distances from their emission hotspots. No evidence of any gradient was found.

DISCUSSION

The time interval between the cancer records and the emissions data must be considered. NAEI describes many recent changes in fuel uses and in manufacturing, power production, and waste disposal practices. However, most of them were improvements and while previous high emissions may have diminished, most of those still existing in 2001 would be at least as active when these children were born. These changes underline the special advantages of basing analyses upon hotspot distances rather than emission levels.

The basic method, and all the results, depend upon the premise of a migration equilibrium between hotspot related inner and outer zones in the general child population. The differential migrations among the cancer children, an approximate 0.1% subset of the total, can then be seen as a consequence of early risk variations in different places. In the early postwar years, however, much substandard and bomb damaged city centre housing was demolished and replaced, some of it by out of town building, and families with young children may have been motivated on amenity grounds to move away from emission sources such as oil storage facilities, gasworks, factories, chimneys, railways, and road traffic; at least where work and family economics and municipal housing waiting lists permitted. We have to ask whether such selective population movements could have accounted for the findings in the cancer subset.

A first consideration is the necessary scale of any explanatory demographic movements. For example, the 1,3-butadiene findings in table 5 would require a general emigration rate of 49.6% (2227 of 4490) among children born within 1.0 km over a period corresponding with the mean age of these cancer deaths (7.4 years). After allowing for incoming replacements the net outward flow is still 36.1% (2227–604)/4490; sufficient over the full survey period to have depopulated all near contact zones. Personal preferences in the face of competitive domestic economics are an integral part of migration dynamics but there are no grounds for supposing that children incubating cancer should be any different in these respects from other children.

A second consideration is the universality of the findings around the high risk sites, irrespective of the varying sizes of their inside populations and outside populations. A third is the absence of any evidence of major outward demographic movements around other industrially related emissions such as zinc, copper, tin, nickel, chromium, arsenic, and sulphur dioxide. A fourth is the specificity of the significant emission types; which compels a specific interpretation. All of them are associated with waste incineration or with oil combustion or evaporation and several are known carcinogens. Some showed an increasing relative risk at shortening ranges and a sharp decrease when their given locations were marginally displaced; and all of them correspond with previously identified types of hazardous industrial installation.

It is always difficult to say whether any particular result points to a specific carcinogenic effect, or whether it is acting as proxy for other geographically associated substances. For example, carbon monoxide is a powerful indicator of

Key points

Childhood cancer/leukaemia births are closely associated with high atmospheric emissions from combustion processes, mainly oil based, and from organic evaporation. Demonstrated associations with 1–3,butadiene, dioxins, and benz(a)pyrene, but possibly others as well, are probably causal. Such toxic emissions may account for a majority of all cases.

Policy implications

The main policy implications are a need to regulate carcinogenic atmospheric emissions, especially 1,3-butadiene; and for a redirection of research efforts relating to childhood cancer. This research should now try to determine the exact timings of chemically determined air mediated cancer initiations—whether in early infancy or prenatally, or even preconceptually; and to seek engineering and social solutions.

transport activity, itself a generator of many other substances, so we need not conclude that it must itself be an active substance. (Although it may be.) Benzene is also difficult to assess because the original leukaemogenic suspicion might itself spring from indirect associations. Nitrogen oxides, with their complex trains of secondary atmospheric reactions raise similar issues, as do many other substances, including 1,3-butadiene.[10 11] However, the present associations with 1,3-butadiene, dioxins, and benz(a)-pyrene are sufficiently specific to conclude that they are probably among the truly active agents.

A literature search returned no similar studies and no similar findings. Systematic attempts to link the birthplaces of cancer children to specific exposures have been largely limited to ionising and electromagnetic radiations. There are some cancer studies around incinerators in the general population, but not specifically related to children or to birthplaces. There are many reports of the carcinogenic effects of 1,3-butadiene and dioxins in rats and mice[12]; and of human occupational exposures to 1,3-butadiene in the synthetic rubber industry. Some of the human reports have decided that 1,3-butadiene and dioxins are significant human carcinogens,[13 14] while others give more cautious ''probable'' or ''possible'' verdicts[15–17] and yet others report doubtful or negative effects.[18–21] Two mass exposure episodes to carcinogens so far remain uninformative including the major escape of dioxins at Seveso and a possible relation between an alleged leukaemia epidemic in Basra and the Gulf war oil well fires in Kuwait and southern Iraq. These uncertainties have inhibited any consistent public health policy. For example, some countries are taking serious efforts to control emissions of 1,3-butadiene,[22] while others have decided to await more information.[23] The massive evidence on this substance, reported here, should allow no further delays.

The main additional policy implications are for a major redirection of the research effort relating to childhood cancer. This should now concentrate on determining the exact timings of these chemically determined initiations—whether in early infancy or prenatally, or even preconceptually; and a search for appropriate engineering and social solutions.

ACKNOWLEDGEMENT
The cancer data were supplied by the late Professor A M Stewart.

The appendix is available on line (http://www.jech.com/supplemental).

Funding: the postcoding of the cancer records was supported by the Medical Research Council and by the Three Mile Island Public Health Fund (USA).

Conflicts of interest: none declared.

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