Childhood cancers and atmospheric carcinogens

E G Knox

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.

Previous studies have shown (1) that childhood cancers and leukemias 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. The increased effectiveness of early exposure, combined with the known effects of obstetric radiation exposures, 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; 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 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 leukemias: 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
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. 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 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) northings and eastings and casting 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 from addresses to hazardous emission locations are accurate to within about 0.1 km of the actual address.

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/km2/year. Benzene is a suspected leukae- 
omogen 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 1: Combustion products of fossil fuels

<table>
<thead>
<tr>
<th></th>
<th>Carbon dioxide (as C)</th>
<th>Sulphur dioxide</th>
<th>PM10</th>
<th>Nitrogen oxides</th>
<th>Carbon monoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotspot criteria*</td>
<td>1264</td>
<td>10</td>
<td>4</td>
<td>25</td>
<td>160</td>
</tr>
<tr>
<td>Number of hotspots</td>
<td>64625</td>
<td>12817</td>
<td>39744</td>
<td>53875</td>
<td>13371</td>
</tr>
<tr>
<td>Number of children†</td>
<td>1246</td>
<td>2008</td>
<td>2908</td>
<td>2072</td>
<td>2943</td>
</tr>
<tr>
<td>Outward migration</td>
<td>838</td>
<td>1034</td>
<td>2074</td>
<td>1501</td>
<td>2224</td>
</tr>
<tr>
<td>Inward migration</td>
<td>408</td>
<td>974</td>
<td>834</td>
<td>571</td>
<td>619</td>
</tr>
<tr>
<td>Ratio out/in</td>
<td>2.054</td>
<td>1.062</td>
<td>2.487</td>
<td>2.629</td>
<td>3.754</td>
</tr>
</tbody>
</table>

* Lower limits for hotspots in tonnes/km²/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 2: Emissions of volatile organic compounds

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

* Lower limits for hotspots in tonnes/km²/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 hotspot 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. The low traffic densities. However, effective direct exposures 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 (PR = 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-butaadiene 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 irradiation4 suggest that the mother may act as an accumulating filter and pass carcinogens across the placenta. However, effective direct exposures

**Table 3** Emissions of metals (1)

<table>
<thead>
<tr>
<th>Metal</th>
<th>Copper</th>
<th>Zinc</th>
<th>Beryllium</th>
<th>Lead</th>
<th>Calcium</th>
<th>Cadmium</th>
<th>Mercury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hotspot criteria*</td>
<td>0.1</td>
<td>1.0</td>
<td>1.0</td>
<td>3.0</td>
<td>50.0</td>
<td>0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>Hotspots (1000s)</td>
<td>121</td>
<td>83</td>
<td>3.0</td>
<td>47</td>
<td>40</td>
<td>15.6</td>
<td>26</td>
</tr>
<tr>
<td>Number of children</td>
<td>1307</td>
<td>2458</td>
<td>689</td>
<td>2585</td>
<td>2605</td>
<td>477</td>
<td>3107</td>
</tr>
<tr>
<td>Outward migration</td>
<td>679</td>
<td>1332</td>
<td>353</td>
<td>1664</td>
<td>1564</td>
<td>290</td>
<td>1835</td>
</tr>
<tr>
<td>Inward migration</td>
<td>628</td>
<td>1126</td>
<td>336</td>
<td>921</td>
<td>1041</td>
<td>187</td>
<td>1272</td>
</tr>
<tr>
<td>Ratios out/in</td>
<td>1.081</td>
<td>1.183</td>
<td>1.051</td>
<td>1.807</td>
<td>1.502</td>
<td>1.551</td>
<td>1.443</td>
</tr>
</tbody>
</table>

*Lower limits of hotspots in kg/km²/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 4** Emissions of metals (2) and non-metals

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

*Lower limits of hotspots in kg/km²/year; †children migrating >1.0 km of one address within 1.0 km of nearest hotspot and the other address outside 1.0 km.
facilities, gasworks, factories, chimneys, railways, and road 

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!

...!
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. 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; 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, while others give more cautious “probable” or “possible” verdicts and yet others report doubtful or negative effects. Two mass exposure episodes to carcinogens so far remain uninformative including the major escape of dioxins at Seveso and a possible relation to carcinogens so far remain uninformative. The massive evidence of cancer children to specific exposures have been largely limited to ionising and electromagnetic radiations. These uncertainties have inhibited any consistent public health policy. For example, some countries are taking serious efforts to control emissions of 1,3-butadiene, while others have decided to await more information. 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.

The author is Emeritus Professor, University of Birmingham, UK

REFERENCES

23. Fielder BJ. Risk assessment of butadiene in ambient air; the approach used in the UK. Toxicology 1996;113:221-5.