# Correlation between car ownership and leukaemia: Is non-occupational exposure to benzene from petrol and motor vehicle exhaust a causative factor in leukaemia and lymphoma?

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*Received 24 May 1991; accepted 12 September 1991*

*Abstract.* Although there is widespread agreement that many cancers have environmental causes we are often unable to see associations between specific cancers and exposure to environmental chemicals. One might also speculate that the more widespread, common-place and 'normal' a chemical exposure is perceived to be then the less likely it will be that the exposure is recognised, let alone be considered to cause cancer. Widespread contamination of air by chemicals associated with internal combustion may be an example of one such 'invisible' carcinogenic exposure. Yet evidence is available which suggests that many leukaemia and lymphoma cases, as well as other cancers, may be caused by this mundane and ubiquitous environmental contamination. The hypothesis is developed that leukaemia 'clustering' as well as national leukaemia incidence may be related to non-occupational exposure to benzene formed by petrol combustion and resulting from petrol evaporation[1]. The possible association between exposure to fuel vapours, internal combustion products and cancer merits much closer examination than it receives at present.
*Key words.* Leukaemia; benzene; motor vehicle; air pollution; socioeconomic indicators.

*"Almost all cancers appear to be caused by exposure to factors in the environment. The most promising approach to the control of the disease is to identify those factors and eliminate them"*[2].

*"Epidemiological evidence suggests that present levels of chemical use do not lead to widespread harmful contamination of the human environment"*[3].

Locally increased rates of leukaemia in the vicinity of nuclear plants such as the Sellafield nuclear reprocessing plant in Cumbria, UK, have been noted and have aroused considerable interest[4]. The possibility that factors other than ionizing radiation could contribute to the elevated incidence of leukaemia/lymphoma in the vicinity of such installations has been raised by 1) the observation that elevated local rates of leukaemia occur at sites distant from nuclear power installations[5] and by 2) reports that area incidence of lymphoproliferative cancer increases with higher area socioeconomic status[6-11]. Areas close to nuclear installations appear to have a high proportion of higher occupational class households so that the risk may simply be associated with higher socioeconomic status, rather than radiation.

Since car ownership is not homogeneous throughout society (but is concentrated within the higher socioeconomic strata) it is conceivable that the leukaemogenic risk factor associated with a higher socioeconomic status is a potentially greater level of exposure to chemical leukaemogens associated with motor vehicle usage. Petrol, diesel fuel and internal combustion emissions contain many potentially carcinogenic hydrocarbons, such as benzene, which is a known human leukaemogen.

Benzene is present at a concentration of circa 5% v/v in European petrol, and is also produced by the thermolytic dealkylation of alkylbenzenes during internal combustion[12-14]. Levels of airborne benzene are closely related to traffic density[15] and, although generally in the range of 1–4 parts per billion (ppb) in urban areas, have been reported to reach 150 ppb in densely-trafficked areas[16]. Highest levels of benzene are, however, present within the cars themselves and may reach US occupational exposure limits (780 ppb compared with 1000 ppb) although the typical range is in the order of 10–20 ppb[17]. Exposures during vehicle refuelling are, briefly, in the range of a few parts per million[18].

The hypothesis, then, is that non-occupational exposure to benzene from petrol evaporation and car exhaust contributes to national leukaemia incidence. Specifically, the higher levels of benzene exposure encountered by travelling inside cars, or being in cars during refuelling would add substantially to the risk accumulated as a result of long-term exposure to ambient levels of airborne benzene and would thus contribute to increased incidence of leukaemia in regions where a greater use of cars is predicted to occur.

## *Methods*

The Leukaemia Research Fund has mapped the incidence of leukaemia and lymphoma in 22 counties in the UK for the years 1984–1988[19]. Data of relative risk by county from the Atlas can be related to information on car ownership by county for a slightly earlier period (1981) using the Great Britain Population Census[20] and published Transport Statistics[21].

## *Results and discussion*

The table shows Spearman rank correlation coefficients between incidence of leukaemia/lymphoma (age- and sex-standardized relative risks for 22 counties and 21 072 total cases in England and Wales from 1984–1988) and

Spearman rank correlation coefficients

| Diagnostic group | Number of cases | Cars per household | Cars per thousand |
|---|---|---|---|
| All myeloproliferative disease | 6222 | 0.17 | 0.12 |
| Acute myeloid leukaemia | 1991 | 0.38* | 0.32 |
| Chronic myeloid leukaemia | 678 | 0.08 | 0.20 |
| Myeloid dysplastic states | 1806 | 0.21 | 0.10 |
| Other myeloproliferative disease | 1747 | 0.07 | 0.07 |
| All lymphoproliferative disease | 14850 | 0.40* | 0.35 |
| Acute lymphoblastic leukaemia | 775 | 0.44** | 0.35 |
| Chronic lymphoid leukaemia | 3340 | 0.41* | 0.34 |
| Low-grade non-Hodgkin lymphoma | 2415 | 0.66*** | 0.68*** |
| High-grade non-Hodgkin lymphoma | 2550 | 0.21 | 0.08 |
| Hodgkin disease | 1799 | 0.21 | 0.10 |
| Multiple myeloma | 3223 | 0.27 | 0.18 |

*$p < 0.05$; **$p < 0.025$; ***$p < 0.001$.

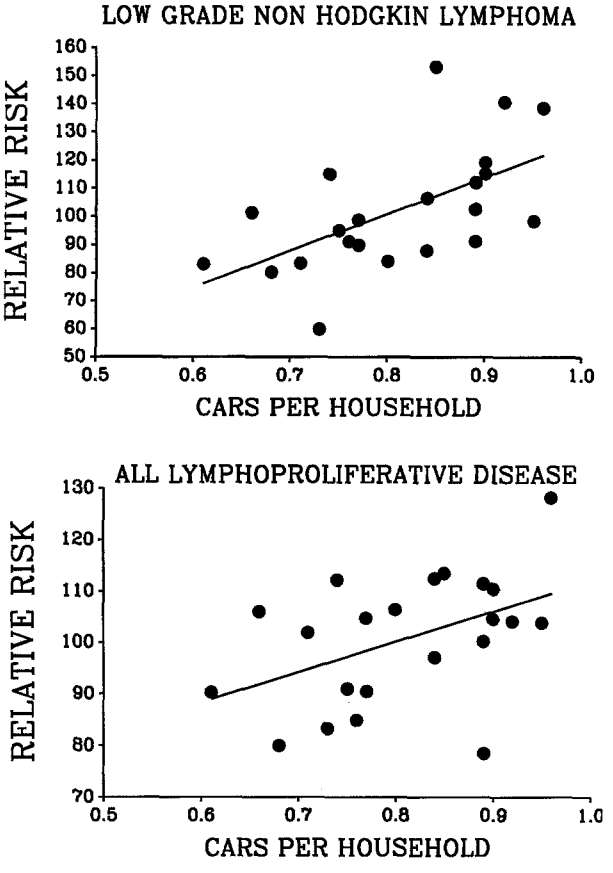


Figure 1. Data distribution for relationship between low-grade non-Hodgkin lymphoma, all lymphoproliferative disease and level of car ownership.

car ownership. There is a statistically significant association between car ownership and acute myeloid leukaemia (which comprises 9% of total cases in the Leukaemia and Lymphoma Atlas), the cancer specifically associated with benzene exposure, as well as between all lymphoproliferative diseases (70% of total Atlas leukaemia/lymphoma cases) and car ownership. Within the category of lymphoproliferative disease there is greatest association with car ownership for low grade non-Hodgkin's lymphoma (comprising 11% of total leukaemia/lymphoma cases reported in the Atlas) but a significant association also exists for acute lymphoblastic leukaemia (4% of total cases), the type common in children, as well as for chronic lymphoid leukaemia (16% of total cases). Associations appear generally stronger (achieving statistical significance in most cases) when calculated against cars per household rather than cars per thousand population. This could be taken to indicate association of personal risk of leukaemia with car ownership rather than association of risk simply with local car density.

Figure 1 shows data distribution for all lymphoproliferative disease as well as low-grade non-Hodgkin lymphoma and car ownership, confirming the geographical association. The higher the county level of car ownership, the greater the risk of lymphoproliferative disease. Greater levels of car ownership could, of course, merely reflect county differences in rural/urban status and thus the presence of some leukaemogenic factor present in rural areas to a greater extent. However, correlation coefficients remain essentially unchanged when corrected for population density (data not shown) so that differences in rural/urban status appear not to be an important factor in the correlations observed. Correlations of home ownership and overcrowding with leukaemia were, by contrast, close to zero[22].

These cross-sectional epidemiological data based on geographical differences in cancer incidence and car ownership must, of course, be regarded as preliminary and cannot show that car ownership is a causative factor in leukaemia/lymphoma. But if the associations are real then it is probable that benzene, a well-characterised leukaemogen, is responsible since it causes leukaemia and can reach high levels in cars[13,14]. The correlations between car ownership and leukaemia are also in agreement with those obtained by Robinson[23] who showed a strong relationship between Australian leukaemia mortality and vehicle usage, as monitored by the rate of vehicle fatalities.

A greater level of car ownership and usage at certain locations compared with the national or regional average, could thus (according to this hypothesis) be responsible for the emergence and detection of leukaemia 'hot spots' as small, but statistically significant fluctuations above leukaemia incidence baseline, if non-occupational levels of benzene can cause cancer. A corollary to the hypothesis that a greater local level of car ownership/usage is responsible for a locally-elevated incidence of leukaemia, would be that national and regional background leukaemia incidence is related to the same underlying causative factor. This would be an attractive explanation for the large increase in childhood and adult leukaemia from the early 1920's to the end of the 1960's[24,25]. The 'clusters' might thus be the visible tips of large icebergs of benzene-related leukaemia.

There is little doubt that exposure to the high levels of benzene associated with many industrial settings causes leukaemia[26,27]. On the basis of epidemiology performed on exposed worker populations it has been estimated that there will be 10 excess deaths per 1000 employees exposed for a working lifetime to 1 part per million, the current US occupational exposure standard[28]. This corresponds to a unit risk (estimated by the US Environmental Protection Agency[29]) of $7 \times 10^{-6}$ for death due to leukaemia as a result of lifetime exposure to 0.3 ppb (1 $\mu g/m^3$). The World Health Organisation sets the unit risk somewhat lower at $4 \times 10^{-6}$ [30]. Both these risk estimates assume no 'threshold' and a linear exposure-cancer dose-response curve. Acute myeloid leukaemia is the most common form of leukaemia in benzene-exposed adults (for which the above unit risk estimates have been calculated) but acute lymphoblastic leukaemia, chronic myeloid leukaemia, lymphoma and multiple myeloma may also occur[31-36].

There is evidence that car-derived carcinogen exposure might cause leukaemia since Savitz and Feingold observed that rates of leukaemia were higher in areas of higher traffic density in a study of childhood leukaemia incidence in Denver, Colorado[37]. The authors, although cautious about relating their observations to benzene, found that children living in areas with more than 10,000 vehicles a day had an odds ratio (OR) of 4.7 (confidence interval 1.6–13.5) for leukaemia. The OR was 2.7 for more than 5000 vehicles per day and was greater for 0–4 year olds (OR = 5.6) in the 'exposed' group; defined as those living in areas with more than 500 vehicles per day. Consistent with a hypothesis of motor vehicle emissions as risk factor for cancer it has been shown that rates of leukaemia and other cancers are higher in areas of higher traffic density and correlate with local deposition of vehicle-derived hydrocarbons[38-41].

The hypothesis that low levels of environmental benzene exposure associated with fuel vapours and internal combustion could be responsible for leukaemia may be greeted with scepticism since there remains a residue of debate about the carcinogenic potential of exposure to benzene even in the 1–10 ppm range[42]. Certainly, although very high (occupational) levels of benzene are linked with leukaemia[14] any risk of cancer at lower levels of benzene appears to disappear into the background of 'spontaneous' leukaemia incidence (fig. 2). The existence of the background rate, and the shape of the graph in figure 2, is used as an important justification for the concept of the 'threshold' dose which, translated into biological terms, argues for the presence of detoxification and DNA repair/maintenance mechanisms which operate efficiently at lower concentrations of carcinogen but which can be saturated at higher doses. However, such an interpretation depends very much on how one views this graph (fig. 3). The hypothesis that the background 'spontaneous' leukaemia incidence may also be related to non-occupational benzene exposure casts the threshold dose

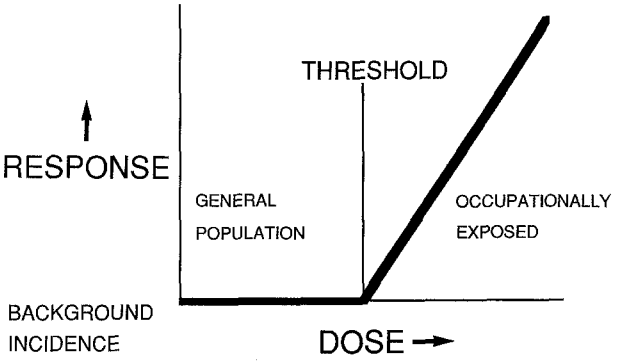


Figure 2. Dose-response curve for relationship between benzene exposure and leukaemia assuming that background incidence of leukaemia is 'spontaneous' and unrelated to non-occupational exposure.

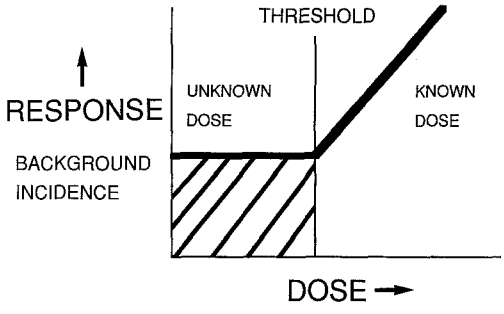


Figure 3. Revised dose-response curve for relationship between benzene exposure and leukaemia suggesting that background incidence is related to non-occupational benzene exposure and that threshold dose is arbitrary dividing line between known and unknown doses.

in a new light. In this instance, the threshold becomes the artificial dividing line between the high (and fairly well-defined) levels of occupational exposure, to which thousands of adults are exposed, and the less-defined and generally lower levels to which millions of people are exposed in the course of their day-to-day activities. This background level of exposure to benzene is suggested to contribute to the background level of leukaemia and lymphoma in the non-occupationally exposed population.

The Leukaemia and Lymphoma Atlas study population was 15,265,000 individuals (both sexes, all ages) of which 1991 were diagnosed as having acute myeloid leukaemia in the 5-year period: i.e. an annual risk of death from acute myeloid leukaemia of circa $3 \times 10^{-5}$. Assuming that diagnosed individuals had already received their 'lifetime' dose this would correspond to an exposure of 1–2 ppb (70–140 ppb-years), using the risk estimates given above, and thus well in the range of the non-occupational exposure anticipated to occur as a result of car usage.

Various large-scale surveys of risk factors for leukaemia and lymphoma are now being planned by Government agencies and charities concerned with leukaemia[43]. There is considerable interest in the analysis of factors such as radon exposure and unusual responses to infec-

tions. However, analysis of a dominant source of leukaemogen exposure, namely non-occupational exposure to benzene as a result of vehicle usage and traffic, is not being considered. Clearly, it is difficult to assess differences in levels of an exposure which is now virtually ubiquitous in developed countries and considered a healthy and desirable aspect of national development. Indeed, Lutz and colleagues have recently reviewed the evidence which suggests that regulation of benzene exposure is controlled more by psychology, sociology, economics and politics rather than medical or scientific considerations[44]. Detailed measurements of benzene and hydrocarbon exposure would, however, allow support for, or refutation of the hypothesis that internal combustion-powered vehicles cause cancer. There is a pressing need for biological and epidemiological investigation of non-occupational benzene exposure.

Acknowledgments. I am grateful to John Adams and George Stern for helpful discussions.

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