Committee on CARCINOGENICITY

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON THE REVIEW OF THE POSSIBLE ASSOCIATIONS BETWEEN CHILDHOOD LEUKAEMIA AND RESIDENCE NEAR SOURCES OF TRAFFIC EXHAUST AND PETROL FUMES

Background to review

Vehicle-related air pollution has increased considerably over the last 45 years, due to the increased numbers of vehicles on the roads (IEH, 1999). Traffic exhaust contains a complex mixture of many chemicals, of which several are known or suspected to be carcinogens. These include benzene, 1,3-butadiene and diesel-particulate matter. Diesel engine exhaust has been classified by IARC as Group 2A (i.e. probable human carcinogen) and gasoline[1] engine exhaust as Group 2B (i.e. possible human carcinogen) (IARC, 1989). The nature of traffic exhaust has, however, changed over the years following legislation about the composition of fuel.

Evaporative fuel emissions also contribute to vehicle-related air pollution. High airborne concentrations of fuel vapour are present in petrol stations and garages. Given that benzene is a component of both petrol/diesel exhaust and petrol vapour and is well documented as a cause of leukaemia in adults[2], there has been some concern as to whether residence near petrol stations/garages could be associated with an increased incidence of childhood leukaemia (petrol stations/garages are unlikely to generate sufficient traffic on their own to cause a substantial increase in pollutants from vehicle exhaust).

The Committee was asked by the Department of Health Air Pollution Unit to review three recent epidemiological studies which report an association between residence near to petrol stations and garages and/or road traffic exhaust fumes and the occurrence of childhood leukaemia. The Committee considered these studies (http://www.advisorybodies.doh.gov.uk/pdfs/cc0437.pdf) at the November 2004 meeting, but were unable to reach definitive conclusions on whether the studies indicated a causative link. The Committee therefore conducted a full review of the epidemiology literature on this issue, including studies reporting on benzene exposure and leukaemia in children.

Information reviewed

1. Childhood leukaemia: current perspectives on incidence trends and aetiology

The Committee first reviewed the incidence trends and potential chemical causes of childhood leukaemia in 2004, as part of a horizon scanning exercise to examine

[1] Gasoline is the US term for petrol
[2] Benzene has been reported to cause Acute Myelogenous Leukaemia in occupationally-exposed adults

evidence for a possible role for chemicals in childhood cancer (http://www.advisorybodies.doh.gov.uk/pdfs/cc0431.pdf).

Of the two main types of leukaemia that occur in children[3], Acute Lymphoblastic Leukaemia (ALL) is the most common. There is evidence suggesting that the incidence of childhood ALL in the UK is increasing but members questioned whether this increase was real or an artefact resulting from better ascertainment of cases. An expert opinion was sought from the UK Childhood Cancer Research Group (UKCCRG) and the Newcastle Childhood Cancer Group who advised that the increase in ALL was, at least in part, real.

Only two non-hereditary risk factors are clearly associated with the development of leukaemia in children: intrauterine exposure to diagnostic X-rays and postnatal exposure to therapeutic doses of ionising radiation. In recent years, the use of these medical procedures in pregnant women and children has been extremely rare, and so it is likely that these aetiological factors now account for only a small percentage of leukaemia cases. The Committee noted that there is strong evidence for the involvement of non-chemical factors in the aetiology of childhood leukaemia (IARC, 1999). However, this does not preclude the possibility that there may be chemical risk factors, as childhood leukaemia is a biologically and clinically diverse disease and is likely to arise via a number of aetiological pathways (Greaves & Alexander, 1993).

2. Exposure to vehicular emissions as a possible cause of childhood leukaemia

The Committee considered that, because benzene is a well established leukaemogen in adults, benzene in vehicle exhaust and/or fuel vapour could represent a potential risk factor in the development of childhood leukaemia. Both vehicle exhaust and fuel vapour also contain several other carcinogenic compounds[4], although there are differences in the profile of these carcinogenic constituents (and thus the carcinogenic potential). The Committee decided that there are differences in the hazards presented by these two types of emissions and, therefore, considered that information on exposure to fuel vapour should be discussed separately from information on exposure to vehicle exhaust.

(a) Exposure to fuel vapour

Exposure to fuel vapour arises largely from the evaporation of fuel from the tanks and engines of parked vehicles. Petrol evaporates more readily than diesel because diesel has a lower vapour pressure. Therefore, there are only a limited number of studies examining the risk of inhalation exposure to diesel vapour.

The Committee reviewed a draft report by the Oil Companies' European Organisation for Environment, Health and Safety (CONCAWE) on the risk assessment of

[3] Acute leukaemia tends to affect younger people with symptoms developing rapidly. The most common types are Acute Lymphoblastic Leukaemia (ALL) and Acute Myeloid Leukaemia (AML; also termed Acute Non-Lymphoblastic leukaemia (ANLL)). Chronic leukaemia tends to occur in older people and has a slow progression rate.

[4] Most tailpipe emissions consist of many hydrocarbons, including benzene, which itself is likely to derive from a mixture of unburnt benzene and benzene formed from the combustion of other aromatic petrol components.

inhalation exposure to 'gasoline[5]' (petrol) and benzene vapour by the general public (CONCAWE, 2004). Members commented on CONCAWE's main findings in relation to childhood exposure as described below.

1. CONCAWE assessment of exposure to petrol vapour

CONCAWE prepared separate risk assessments for three child-relevant scenarios:
(i) visiting service stations
(ii) travelling in cars
(iii) residing indoors at locations near petrol vapour sources

The report calculated typical and reasonable worst case (RWC) airborne concentrations (mg/m^3) and average daily doses (ADD) (mg/kg/day) for inhalation exposure to petrol for each of the above scenarios as shown in Table 1. (See http://www.advisorybodies.doh.gov.uk/pdfs/cc058.pdf for rationale)

Table 1. Summary of the exposure results for petrol vapour inhalation for several consumer scenarios (CONCAWE, 2004)

Scenario	Airborne Concentration (mg/m^3)		Estimated Inhalation Intake (mg/kg/day)	
	Typical	RWC	Typical	RWC
Visiting service stations				
Adults*	2.7	3.83	0.0005	0.0006
Children**	2.7	3.83	0.0011	0.0015
Travelling in cars				
Adults	3.15	3.94	0.04	0.06
Children	3.15	3.94	0.12	0.15
Staying indoors (residence)				
Adults	2.07	7.16	0.25	0.87
Children	2.07	7.16	1.66	5.71

**Body weight used for adults = 70 kg*
***Body weight used for children = 9 kg*

The Committee noted that children had considerably higher estimated inhalation intakes than adults. It was further noted that children staying in their homes received the highest estimated airborne exposures to petrol vapour (largely due to the amount of time spent indoors) with an ADD (RWC) value approximately ten-fold greater than that estimated for a service station attendant working a full shift (data not shown). However, it was further noted that much of the difference was due to variations in the duration of exposure represented by the three scenarios. The Committee accepted that these estimates were very conservative[6] and so were likely to have overestimated true exposures.

2. CONCAWE assessment of exposure to benzene vapour

The Committee also considered data from the CONCAWE report, as presented in Table 2, on airborne concentrations and estimated ADD for inhalation exposure to benzene vapour. Similar trends to those seen in the petrol vapour exposure

[5] CONCAWE referred to petrol as gasoline in their report.
[6] Many of the underlying assumptions used to derive these estimates were based on the regulatory requirements of the risk assessment process. For example, CONCAWE used guidance provided in the EU Existing Substances Risk Assessment Technical Guidance Document to convert air concentrations of chemicals into daily doses. CONCAWE states that these estimates represent industry obligations in the process rather than the organisation's view of the current situation.

assessment were apparent, i.e. indoor rather than outdoor exposures to benzene from petrol fumes appear to be of more significance. Again, the duration of exposure represented by the three scenarios accounted for much of the difference in intake between them.

Table 2. Summary of the exposure results for benzene vapour inhalation for several consumer scenarios, (CONCAWE, 2004) *(Figures have been converted into µg/m³ and µg/kg/day for ease of reference)*

Scenario	Airborne Concentration (µg/m³)		Estimated Inhalation Intake (µg/kg/day)	
	Typical	RWC	Typical	RWC
Visiting service stations				
Adults*	12	17	2.0E-03	2.9E-03
Children**	12	17	4.7E-03	6.7E-03
Travelling in cars				
Adults	14	18	0.2	0.3
Children	14	18	0.5	0.7
Staying indoors (residence)				
Adults	10.7	26	1	3
Children	10.7	26	9	20

**Body weight used for adults = 70 kg*
***Body weight used for children = 9 kg*
NB. The current levels of exposure to benzene from gasoline are likely to be lower than those estimated above. This is because the data was obtained from studies conducted prior to the 2000 European EU directive 98/70/EC, (in which levels of benzene in gasoline was reduced from 5% to 1%)

A substantial amount of information was available to the Committee from the published literature on levels of benzene inside and outside the home. This enabled the Committee to obtain a greater understanding of the issues relating to inhalation exposure to benzene vapour, and to generate a more considered view on the above exposure assessment.

(i) Work by the Building Research Establishment showed that the mean indoor benzene concentrations in 174 homes within the Avon area (UK) were higher than outdoor levels, especially in those households with an attached garage (Duarte-Davidson et al., 2001). Furthermore, benzene concentrations in rooms directly above an integral garage have been reported to be 2.5 times the ambient air standard (Mann et al., 2001). See (http://www.advisorybodies.doh.gov.uk/pdfs/cc058.pdf) for further details.

(ii) Studies providing data on mean air concentrations of benzene outdoors showed that UK levels were consistent with levels in the US and Canada. These levels varied depending on the proximity of parked or moving traffic - the highest levels of benzene were documented to be within the cars [up to 2527.2 µg/m³ (780 ppb)[7]] and may even reach the US Occupational Exposure Limit of 3240 µg/m³ (1000 ppb), although Wolff (1992) reports that the typical range is in the order 32.4 – 64.8 µg/m³ (10-20 ppb). Table 3 provides a summary of the range of benzene levels detected inside and outside the home.

(iii) Members noted that there were a number of national and international initiatives intended to reduce population exposure to benzene. In a

[7] 1 ppb = 1 part by volume, in one thousand million i.e. 1 in 10^9; 1 ppb of benzene ≡ 3.24 µg/m³ at 20ºC and 1013 millibars (http://www.defra.gov.uk/environment/airquality/aqs/benzene/4.htm)

personal communication to the Committee, CONCAWE identified four important technological developments designed to reduce current levels of benzene emissions from automobiles (see http://www.advisorybodies.doh.gov.uk/pdfs/cc058.pdf). Air Quality Objectives in the UK are for an annual running mean standard[8] for benzene of 5 µg/m^3 (1.54 ppb) in England and Wales, and 3.25[9] µg/m^3 (1 ppb) for Scotland and Northern Ireland by 31 December 2010 (http://www.ehsni.gov.uk/pubs/publications/AQS_addendum_web.pdf). In Europe, the ambient air limit value[10] for benzene is 5 µg/m^3 (to be met by 1 January 2010, as set by the European Community Directive 2000/69/EC) (http://europa.eu.int/comm/environment/air/pdf/ppbenzene.pdf).

Table 3. Ambient air concentrations of benzene (taken from Duarte-Davidson et al., 2001; Mann et al., 2001 and Wolff, 1992).

	[Benzene]/(µg/m^3)
Air Quality Objective	**5**
Outdoor*†	1 – 8
Indoor	4 – 40
Outdoor (20m busy road)*	10 - 45
Outdoor (kerbside)*	118
Cars (inside)*	32 – 2527
US Occupational Limit	**3240**

* *It would be difficult to determine the contribution of evaporative emissions or vehicle exhaust to the benzene levels detected.*
† *Levels of benzene in outdoor air during winter can be three times the level detected in summer.*

(iv) The Committee was also reminded of the findings of the Working Group on Benzene (1998), which conducted a similar assessment of the potential risks from benzene exposure to the general population as part of a process to deal with "Ambient Air Quality Assessment and Management". These also suggested that children received much higher intakes of benzene than adults.

On the basis of the available information on levels of evaporative emissions inside and outside the home, the Committee concluded that exposures of children to benzene and petrol vapour inside the home could be greater than outside the home and that the significance of indoor exposures to petrol vapour and benzene should be considered further.

(b) Exposure to vehicle exhaust

One of the major challenges in epidemiological studies investigating the effects of exposure to vehicle exhaust is quantifying the exposure. This is because vehicle

[8] the annual running mean standard refers to a value calculated from data collated for the 12 months prior to the quoted date
[9] 3.246 µg/m^3 rounded to nearest 2 decimal places
[10] the air limit value is a legislative standard, which takes cost and benefit into account and provides a date for when the legislation must be effected. The long term policy aim for England and Wales is to achieve an Air Quality Objective of 1 ppb annual mean concentration.

exhaust is a chemically complex mixture and its components derive from multiple sources (see Table 4 for a list of compounds present in vehicle exhaust). It was noted by the Committee that most epidemiological studies examining the effects of vehicular emissions have focussed on the combustion of fuel rather than on fuel evaporation. Therefore, the subject of exposure to vehicle exhaust is discussed further in the following section.

Table 4. Some compounds and classes of compounds in vehicle engine exhaust (IARC, 1989)

Gas phase	**Particulate phase*** **
Acrolein Ammonia *Benzene* *1,3-Butadiene** Formaldehyde Formic acid Heterocyclics and derivatives* * Hydrocarbons (C1-C18) and derivatives* * Hydrogen cyanide Hydrogen sulphide Methane Methanol Nitric acid Nitrous acid Oxides of nitrogen *Polycyclic aromatic hydrocarbons and derivatives** * Sulphur dioxide Toluene	Heterocyclics and derivatives Hydrocarbons (C14-C35) and derivatives Inorganic sulphates and nitrates Metals (e.g., lead and platinum) *Polycyclic aromatic hydrocarbons and derivatives*
(Source: IARC, 1989) *compounds in italics have been classified by IARC as either carcinogenic to humans, probably carcinogenic to humans or possibly carcinogenic to humans (Groups I, IIA or IIB, respectively) **derivatives include acids, alcohols, aldehydes, anhydrides, esters, ketones, nitriles, quinines, sulphonates and halogenated and nitrated compounds and multifunctional derivatives ***diesel exhaust particulates are reasonably anticipated to be human carcinogens according to the National Toxicology Program 10th Report on Carcinogens NB. Nitroarenes are also present in engine exhaust and are produced in large amounts from diesel engines. They are formed when nitric acid reacts with PAHs to form nitrated PAHs.	

3. Epidemiological studies of exposure to traffic-derived pollutants and childhood leukaemia

The Committee was provided with information from 17 studies (sixteen[11] published as peer-reviewed papers), which have investigated the possible association between proximity of residence to road traffic exhaust fumes, and/or petrol stations and garages, and either childhood cancer or childhood leukaemia. Table 5 provides a summary of the 17 studies reviewed by the Committee. Three of the studies were from the UK and only nine specifically investigated childhood leukaemia http://www.advisorybodies.doh.gov.uk/pdfs/cc058.pdf. Two studies examined exposures to vehicle evaporative emissions; vehicle exhaust was the predominant chemical exposure evaluated.

[11] The unpublished results of a study by Urayama et al. (2004) were presented as a poster at an international conference on ‘Children with Leukaemia’ in London (2004).

Ten of the 17 studies reported some positive significant associations, although three authors concluded that their positive findings were only suggestive of an association due to the qualitative limitations of the study.

Evaluation of epidemiological evidence

The Committee reviewed the methodology used in the studies to help formulate its conclusions and proposed that, based on the quality of the study designs, the actual number from which conclusions could be drawn was much lower than 17. Only two studies were considered to have adopted an adequate method for the assessment of exposure to petrol fumes and exhaust (i.e. Raaschou-Nielsen et al., 2001, and Reynolds et al., 2002). Both of these studies reported null results. However, Members considered it would be inappropriate to dismiss completely the 10 studies reporting positive findings.

Most of the studies were population-based, case-control studies where cases were identified from cancer registries. One study identified cases and controls from hospitals (Steffen et al., 2004) and five were geographical studies. Controls for population based studies were mostly selected from registers of the general population or via random digit dialling (RDD) – the latter method was considered to be a source of selection bias. In Steffen et al. (2004), controls were selected from children in the same hospital receiving treatment for acute pathologies such as trauma or orthopaedic diseases. The majority of studies matched controls for age, sex and area (for more information on control selection see http://www.advisorybodies.doh.gov.uk/pdfs/cc058.pdf).

In general, researchers based exposure assessments on objective measurements such as residence, traffic counts and/or measurements of concentrations of air pollutants, which are not affected by recall bias. However, Steffen et al. (2004) cited possible recall bias in that the mother of cases may have over-declared previous exposures to sources of hydrocarbons; Crosignani et al. (2004) suggested that the method used by his group to sample controls could be a source of selection bias.

Few of the 17 studies obtained comprehensive information on the child's or parent's past exposures to chemicals and other potential confounders.

Members considered a suggestion that a meta-analysis be carried out on the studies but concluded that the methodologies used in the studies were too divergent for this to be feasible.

Members made the following observations and suggestions:

(a) Sample size

With the exception of Reynolds et al. (2003), most of the papers reporting a positive association were based on much smaller sample sizes (the average number of leukaemia cases = 394) than those reporting a null association (average no.= 861). The two negative studies with adequate exposure asssessment referred to above (Raaschou-Nielsen et al. (2001) and Reynolds et al. (2002)) were noted to be among the largest.

(b) Exposure Assessment

Most of the studies used area-based measures as proxies for traffic-exhaust exposures (See http://www.advisorybodies.doh.gov.uk/pdfs/cc058.pdf for further details). The Committee suggested that, although the methods currently used to assess exposure to petrol fumes/exhaust have generally improved with time, there is still potential for further development/refinement. However, useful information can be obtained from existing studies provided it is clear what the exposure metric represents. It was suggested that the distance-weighted traffic density metric was a useful approach although it should be made more specific for each pollutant to give greater utility in the ensuing risk estimation (http://www.advisorybodies.doh.gov.uk/pdfs/cc058.pdf).

(c) Case-control distance comparison

The Committee also considered the distance between the source of traffic exhaust/petrol fumes and the index[12] child's house. The impact of main roads on air quality is not considered to be detectable above local background air pollution more than 100-200m away. Therefore, those studies in which concentrations of pollutants were measured or estimated in homes that were located more than 200m away from traffic roads or petrol stations and garages were considered to provide little useful relevant information..

(d) Age-related factors and residential history

The Committee noted that most studies of traffic and childhood leukaemia examined exposure potential based on a child's residence at either diagnosis or birth. Only two investigations obtained information on residence of the parent prior to birth, usually due to limitations in the recorded information available at the time, although the Committee noted that the study by Raaschou-Nielsen et al (2001) collated data spanning a child's complete residential history and encompassed an exposure window from 9 months before birth through to the child's date of diagnosis. The Committee suggested that, ideally, future studies should take into account a child's complete residential history and not just residence at diagnosis, although it was recognised that this would be difficult.

(e) Genetic susceptibility

Finally, the Committee considered the question of genetic susceptibility to possible traffic fumes/fuel vapour related childhood leukaemia, in the context of the study by Urayama, 2004. This investigated the combined effects of genetic polymorphisms and traffic exposure on risk of childhood leukaemia and found an association between leukaemia and traffic only in those with the CYP1A1 m2 allele. Interestingly, without accounting for individual genetic susceptibility, the authors found no association between risk of childhood leukaemia and traffic density. The Committee noted that the study was not in line with the COC criteria for the design of gene-environment studies because it lacked a prior hypothesis and hence the power of the study was lower than that assumed in the analysis.

[12] child diagnosed with cancer of interest

Conclusion

The Committee concluded that the available evidence provided insufficient evidence from which to conclude that there was an association between risk of childhood leukaemia and proximity to petrol stations, garages and road traffic.

The Committee considered that further studies to examine the possibility of an association between residence near traffic exhaust/petrol fumes and leukaemia would be valuable. The Committee concluded that there are differences in hazard between vehicle exhaust and evaporative emissions. Therefore, it considered that information on exposure to fuel vapour should always be discussed separately from exposure to vehicle exhaust. It requested that indoor exposures of children to petrol vapour and to benzene should be considered in a separate review.

It was recommended that future studies should also investigate leukaemia on a subtype basis (ALL, ANLL) rather than leukaemia as a whole, and any evaluation of genetic susceptibility should include the examination of a comprehensive range of Phase I and II enzymes involved in the metabolism of compounds deriving from traffic.

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Table 5. Summary of epidemiological studies examining the relationship between childhood cancer and/or leukaemia and traffic exhaust/petrol fumes

Study Period Country Aim of study/	**Cohorts description/*size***	**Age of subjects (years)**	**Exposure measure**	**Distance from traffic /petrol source**	**Account of confounding exposures?**	**Findings (note: all CIs are 95%)**	**Criticism of study**	**Comments**	**Refs**
POSITIVE ASSOCIATIONS: TOTAL NO. STUDIES=10									
1976-1983 Denver, USA To establish whether an association exists between high traffic density and childhood cancer	Population based Case Control Study Cancer cases (328) - Leukaemia (103) - ALL (76) Controls (262) – recruited by random digit dialling and matched for age, sex and telephone exchange area of cases	0 - 14	Traffic count in road in front of house at diagnosis used to generate traffic density (vehicles per day- VPD)	N/A	Subset of parents (71% of cases and 80% of controls) interviewed to obtain information on family demographics, cancer history, exposure to X-rays, medications during pregnancy, parents occupational history, maternal smoking during pregnancy, etc	Children living in areas ≥10K VPD: OR=4.7[1.6-13.5] > 5K VPD: OR= 2.7 [1.3-5.9] Children (0-4 yrs) living in areas > 500 VPD: OR=5.6[1.9-16.7] Adjustment of results for subset whose parents were interviewed provided evidence against substantial confounding by measured potential risk factors. Concluded that the data is suggestive of an association between high traffic density and childhood cancer.	Although subjects were interviewed to obtain data on potential confounders there was no discussion of recall bias. Use of a crude measure of exposure based on the subject's residence at diagnosis with no information on residential history Possible exposure misclassification as no account of exposures from surrounding streets Small number of cases and controls in each exposure category.	Overall response rate 75%. Adjusted data accounted for child's past exposures to agents and activities thought to be associated with cancer Selection bias was not thought to be apparent since referents were adjusted for a number of potential sources of selection bias. Other potential sources of bias included: non-response; differential mobility of cases and referents; unmeasured confounders; nondifferential exposure misclassification. NB. Authors considered that non-response was unlikely to have biased the odds ratios.	(Savitz & Feingold, 1989)
1976-1983 Denver, USA Used same data as Savitz & Feingold (1989) study with enhanced exposure assessment	Population based Case Control Study Cancer cases (320) - Leukaemia (97) - ALL (78) Controls recruited by random digit dialling and matched for age, sex and telephone exchange area of cases (259)	0 – 14	Distance-weighted traffic metric (VPD)	Highest trafficked street within a 1500ft (457 m) radius of residence of case at time of diagnosis	No	Children living in areas ≥ 20K VPD: for the 750 ft metric: OR=8.28 [2.09-32.80[Concluded that data are suggestive that distance weighted traffic density is a risk factor for childhood leukaemia	As above	Use of distance-weighted traffic metric which takes into account decay of air pollution concentration with distance from street This study does not use any of the confounders investigated in the previous study with these subjects (above) since the adjusted estimates were found to be very similar to the unadjusted estimates in previous study.	(Pearson et al., 2000)
1953-1980 England, Scotland & Wales To examine patterns of spatial clustering in children who have died of cancer	All children dying from leukaemia or cancer (22,458)	0 - 15	Mapped birth/death addresses to hazardous industrial businesses to generate standardised density ratios (SDR)	Up to 10km	Not specified	An excess of deaths from childhood leukaemia was found in proximity to motorways and industrial plants. Largest excesses of cancer associated with traffic were found 1 km or less from motorways. (SDRs were only presented graphically) Concluded that childhood cancers are geographically associated with	Used a crude measure of exposure No data relating to microenvironmental exposures	COC concluded in 1997 that results there were major limitations in the methodology used and no conclusions could be drawn from the study..	(Knox & Gilman, 1997)

						petroleum-derived volatiles and effluent from internal combustion engines			
1960-1985 Sweden To establish whether an association exists between motor vehicle exhaust and childhood cancer	Population-based case control study which used data from a previous study of childhood cancer All cases (n=142) - leukaemia (39) Controls (550) – matched for age and residence. Four controls per case were selected at random from the study base	≤ 15	Estimate made of NO_2 content of outdoor air in power-line corridor where subjects lived closest to date of diagnosis of the case.	N/A	Results adjusted for confounding from magnetic fields and socioeconomic status	At ≥ 50 ug/m^3 NO_2 RR=2.7[0.9-8.5] (all cancers), relative to referent level of ≤39 ug/m^3. At ≥ 80 ug/m^3 NO_2 RR=3.8[1.2-12.1], relative to referent level of ≤49 ug/m^3. Risk estimates for leukaemia elevated but imprecise due to small numbers. Concluded that the finding was suggestive of an association between childhood cancer and motor vehicle exhaust	Number of leukaemia cases small Possibility of exposure misclassification (due to use of NO_2) Limited adjustment for confounders	Selection bias was minimized due to the approach used to identify cases and referents Unmeasured confounding factors were thought to have possibly biased the results	(Feychting et al., 1998)
1975-1985 Sweden To investigate the possible association of exposure to gasoline (vapour/exhaust) and leukaemia in children and young adults	Geographical study. Registered cases of leukaemia in Sweden between 1975 and 1985 (n=277) (ALL/AML)	0-24	No of cars per area and amount of gasoline sold per area in 1975-1985.	N/A	No	> 20 cars/km^2: IR=5.5[4.4-6.8] cases AML per 1 million person-years < 5 cars/km^2: IR=3.4[1.9-5.7] (P=0.05) No association was found for the other leukaemia types studied Concluded that there is an apparent association between AML and car density.	No information on individual confounders. No age stratified analyses (since included young adults)	Showed that car density correlated with gasoline density (R=0.098) It was suggested that there may have been information bias due to differential diagnoses between hospitals Record-based design may minimise problems of selection bias.	(Nordlinder & Jarvholm, 1997)
1978-1997 Italy To assess the effect of road traffic exhaust on childhood leukaemia	Population-based case control study No of cases (n=120) Four controls per cases matched for age and gender	0-14	Gaussian diffusion model to estimate annual mean benzene concentration outside the subject's home	Main roads within 300m radius of child's residence at diagnosis	Deprivation index for municipality of residence	Heavily exposed children (over 10ug/m^3 estimated annual average of benzene, relative to referent level of <0.1ug/m^3): RR=3.91[1.36-11.27] for all leukaemias and RR=5.49 [1.72-17.51] for ALL No increased risk in children < 1 year Concluded it was possible that motor vehicle emissions are a aetiological factor	No information of index child's benzene exposure history Differential time period during which traffic data was abstracted (up to 11 years different)	Additional study to address lack of information on benzene exposure history in progress Avoided contact with families of subjects to minimise selection bias but the method used to sample controls (for cases diagnosed before 1987) was thought to be a potential source of selection bias	(Crosignani et al., 2004)
1995-1999 France To determine the role of hydrocarbon exposure from proximity of residence to sources of petrol fumes/exhaust and acute childhood leukaemia	Multicentre hospital-based case-control (n=280) - ALL(240) - ANLL(40) Controls matched for age, sex, race and location (291) obtained from the same hospitals as cases hospitalised for acute pathologies	0-14	Questionnaire used to obtain data on exposure to hydrocarbons in residences from conception to diagnosis or interview (controls), especially on proximity to either car repair garage, petrol station	Within 50m of children's homes	Questionnaire used to obtain data on residential history (from conception to diagnosis) and family medical history, occupational history pertinent to benzene exposure, maternal solvent exposure, etc	Positive association found for proximity to repair garage or petrol station during childhood (OR=4.0[1.5-10.3], n=17). Re-analysis according to leukaemia: ANLL OR= 7.7[1.7-34.3] ALL OR= 3.6[1.3-9.9] No associations found between leukaemia incidence and other close neighbouring businesses or with proximity to high traffic roads	Exposure assessment (wrt high traffic roads) based on self declaration by mothers interviewed – possibility of recall bias.	Response rates 99% for both eligible cases and controls Specifically looked at association with childhood leukaemia Acquired data on residential history and addressed potential confounders for exposure to benzene A new case-control is study in progress Sources of selection bias considered in design of study.	(Steffen et al., 2004)

			or heavy traffic						
1988-1994 California, US To investigate the possible association between childhood cancer and exposure to Hazardous Air Pollutants (HAP)	Geographical study All cases (n=7143 of which 6989 included in analysis) - Leukaemias (2443) - ALL (1938) - ANLL(368)	<15	For each census tract, calculated outdoor average [HAP] levels as modelled by US EPA, combined with carcinogenic potency factor for each HAP.	No case distance analysis	None	Increased risks of leukaemia in census tracts with:- highest HAP (overall): RR=1.21[1.03-1.42 highest HAP from point sources: RR=1.32[1.11-1.57] Greater association found in 0-4 age group Benzene and perchloroethylene were the main compounds found to contribute to calculated exposure scores	No account of other significant sources of HAP e.g. ETS or microenvironmental exposures Used census tract (group level) exposure data for which there exists significant variation in concentration of air pollution Used residence at time of diagnosis; no information on residential history No information on possible confounders.	Large diverse population of children included in the study 1st epidemiological study using modelled concentrations of multiple chemicals @ census tract level to evaluate cancer. Record-based design may minimise problems of selection bias. Additional study in progress	(Reynolds et al., 2003)
1989-1997 The Netherlands To examine the effect of residency along busy roads in Amsterdam and incidence of cancer, in particular blood-borne malignancies in children NB. Copy of paper obtained termed uncorrected proof.	Population-based study. All cases of cancer diagnosed in individuals residing in Amsterdam at date of diagnosis. N=3384 adults and children; 10 children Age group and sex-specific cancer incidence rates for 1989-1997 in the population not residing along 'main roads' was used as a reference (23,773)	Children defined as <15	Traffic Intensity Scores (TIS) calculated for individual addresses by multiplying the distance between road axis and front of house against type(size) vehicle. 'Main road' defined as TIS ≥ 10K	Less than 50 m from main road	SES	Five cases of ALL in children, all lived along busiest main roads. Standardised incidence ratio (SIR): 4.9[1.6-11.4] Cannot exclude an association with haematological malignancies in females and children	No. of cases small Possible differential misclassification due to change in residency of subjects SES differences	Record-based design may minimise problems of selection bias. Study found no clear evidence for an association between residence along main roads and the incidence of cancer in adults. A separate sample were interviewed about smoking, SES and duration of residence (54% response) and showed no difference in these variables for those living near main roads or not.	(Visser et al., 2004)
1995- California, US To investigate the combined effects of genetic polymorphisms and traffic exposure on risk of childhood leukaemia	Population-based case control study No of cases (N=183) Matched controls (for age, sex and race (202) Two controls were selected per case: one from among children identified from birth records and the other from a roster of friends	<15	Traffic density Vehicle Miles Travelled (VMT)/miles 2	500ft (152 m) radius of child's house	Accounted for maternal race and whether one parent is of Hispanic status	Children carrying the variant CYP1A1m2 allele and exposed to the highest level of traffic density had > 2-fold increased risk of leukaemia (OR=2.4[1.0-5.8]) compared to children with homozygous wild type genotype and exposed to the lowest level of traffic density Without accounting for individual genetic susceptibility, traffic density did not appear to be associated with childhood leukaemia (OR=0.9[0.5-1.6]). Authors concluded that children carrying the high risk CYP1A1m2 allele might be more susceptible to the carcinogenic effects of traffic-related exposures.	Crude measure of traffic exposure Although cases were interviewed to aid in selecting controls there was no mention of recall bias or response rates in the paper. There was no mention of selection bias in the paper	NOTE: Results of study have not been peer-reviewed i.e. is unpublished data Biomarker of susceptibility measured in study	(Urayama, 2004)

NULL ASSOCIATIONS: TOTAL NO. STUDIES=7									
1990-1994 West Midlands, UK To investigate whether there is an excess of leukaemias in 0-15 year old children among those living in close proximity (within 100 m) of a main road or petrol station.	Geographical study with case-control analysis Cases of children diagnosed with leukaemia (130) Analysis used children diagnosed with solid tumours (251) as controls AND comparison of observed no. of leukaemia cases with expected number, calculated from health authority population numbers using indirect age and sex standardisation	0-15	Proximity to main roads and petrol stations from postcode of address at time of diagnosis	100 m		Results failed to achieve significance i.e.: (With solid tumours used as control) Odd ratios for residence within 100m of: Main road OR=1.61[0.9-2.87] Petrol station OR= 1.99[0.73-5.43] (With population used as control) Incidence ratios for residence within 100m of: Main road IR=1.16[0.74-1.72] Petrol station OR= 1.48[0.65-2.93]	Use of children with solid tumours as controls would be inappropriate if disimilar aetiologies for leukaemia and some solid tumours No control for individual confounders No information on residential history No adjustment for age and sex in case-control comparison. IRs in second comparison were based on EDs rather than postcodes	Record-based design may minimise problems of selection bias.	(Harrison et al., 1999)
1978-1984 Los Angeles, US To investigate the relationship between traffic density and risk of childhood leukaemia	Population-based case control study No of cases (n=212) Age/sex matched controls (friends or random-digit dialled) (191 matched pairs)	0-10	An integrated distance-weighted traffic density measure	1500ft (457 m)	Yes (but unspecified except for magnetic field variables and wire code)	No evidence of an association i.e.: Traffic densities (distance weighted values only presented graphically). Wire code adjusted values. <2301 VPD OR=1 ref 2301-5997 VPD: OR=1.6 [0.8-3.6] 5997-13264 VPD: OR=1.1[0.5-2.4] 13264 -28497 VPD: OR=1.1[0.5-2.2] 28497+ VPD: OR=1.4[0.7-3.0]	Possibility of exposure misclassification error arising from differential time frames used for diagnoses and traffic counts. Used Randomised Digital Dialling (RDD) for controls which tend to be of higher SES and therefore less likely to live in high traffic areas Although cases were interviewed to obtain information on possible environmental and occupational exposure of parents there was no mention of recall bias or response rates in the paper.	Accounted for several potential confounders e.g. demographic factors, parental occupation Used distance-weighted traffic density values Selection bias was not thought to have influenced the results.	(Langholz et al., 2002)
1968-1991 Denmark To investigate the hypothesis that exposure to traffic-related air pollution increases the risk of developing cancer during childhood	Population-based case-control study. 1989 cases of leukaemia, CNS tumour or malignant lymphoma in children recorded in Danish Cancer Registry Leukaemia (986) - ALL (731) - ANLL (127) - Other (128) 5506 age/sex matched controls	<15	Residential histories traced from conception to diagnosis and average [NO_2]air (front door) and [benzene]air (front door) calculated, based on information on traffic and streets		Urban density, type of residence, mother's age, birth order, EMF near residence Length of residential period weighted for each child	No increased risk of leukaemia in children exposed to traffic-related air pollution during pregnancy or childhood i.e:- For leukaemias, during pregnancy at following traffic densities: <500: RR=1.0 ref 500 - <5000: RR=0.9[0.8-1.0] <5000 - <10000: RR=0.8[0.6-1.2] ≥ 10000: RR=0.8[0.5-1.3] During childhood: <500: RR=1.0 ref 500 - <5000: RR=0.9[0.8-1.1] <5000 - <10000: RR=0.8[0.5-1.2]	Proposed risk factors not adjusted for considered to include medication, maternal smoking, paternal occupation, pets and immunisations but this not considered to be a major problem. No consideration of microenvironmental exposure.	Separate validation study of NO_2 estimates in 204 children Large sample size Assessed both traffic density measures and modelled NO_2 concentrations for the full lifetime residential histories of the study children + several confounders Record-based design may minimise problems of selection bias. High quality study	(Raaschou-Nielsen et al., 2001)

						≥ 10000: RR=0.8[0.6-2.2]			
1988-1994 San Diego, California US To examine the relationship between traffic density and socio-economic indicators to early childhood leukaemia	Pilot study: population-based case control design No of cases =92 Controls were randomly selected (4 per case) matched for age and gender (total 349)	<5	Traffic density GIS to assess proximity of birth address to high traffic flow	550ft (168 m)	Median family income of block group	No evidence of association found i.e. Total average number of cars per day within 550ft No street segments within 550ft OR=2.00[0.97-4.10] <10000: OR=1.00 ref. 10000-19999: OR=1.38[0.61-3.15] ≥20000: OR=1.59[0.76-3.34]	Small number of cases Failed to acquire complete residential history from conception to diagnosis as used address at birth Limited assessment to early childhood leukaemia which provides a shorter window of observation and includes a population segment which may be more inclined to spend time at home.	Specifically examined leukaemia risk Accounted for decay of air pollution Record-based design may minimise problems of selection bias. Concluded study design may have influenced null result	(Reynolds et al., 2001)
1988-1994 San Diego, California US To examine risk of childhood cancer and residential proximity to high traffic areas	Geographical study All cancers (n=7143) - Leukaemia (2443)	<15	3 indices of traffic used: - high vehicle intensity - high road density - high traffic density CO and NO2 shown to correlate with above indices	Within a block group/ neighbour-hood	None	No elevated incidence of any childhood cancer in areas of high vehicle intensity, high road density or high traffic density found: RR for leukaemia = 1.15 [0.97-1.37] (>90th percentile vs <25th percentile for traffic density)	No information on residential history Lack of data on microenvironmental exposures.	Record-based design may minimise problems of selection bias. Used 3 measures of traffic patterns Although there was no direct quantification of air pollution, it compared surrogate measures with available ambient air monitoring data of five high vehicle emission compounds	(Reynolds et al., 2002)
1988-1994 San Diego, California US A follow-up study to examine the risk of childhood cancer in children under 5 years living in high traffic exposed areas	Population-based case control study Total number of cases (n=4369) - Leukaemias (1728) - ALL(1407) Area, age, sex matched controls (8730)	<5	Road density Traffic density	500ft (152 m)	None specified	No evidence of an association was found i.e: OR for leukaemia =0.8[0.64-1.01]	Used birth address only with no information on residential history Unmeasured confounders	Large sample size Record-based design may minimise problems of selection bias.	(Reynolds et al., 2004)
1984-1989 England and Wales To determine whether increased rates of childhood ALL in isolated areas could be attributed to higher proportions of households owning cars	Geographical analysis using data on ALL from specialist registry of haematopoeitic malignancies (n=438).	0-14	No. of cars owned from census data		SES	ALL at ages 1-7 inversely associated with car ownership (risk in wards with least cars relative to those with most cars = 2.28 [1.12-4.64]) Levels of car ownership cannot explain the increased rates of childhood ALL observed in isolated areas.	Used level of car ownership as surrogate measure for individual exposure to benzene from petrol No individual level data on confounders	Record-based design may minimise problems of selection bias. Quantified degree of isolation in terms of distance from built up areas and confirmed this was associated with increased incidence of ALL	(Alexander et al., 1996)