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CC/05/8

COMMITTEE ON CARCINOGENICITY OF CHEMCIALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT (COC)

REVIEW OF THE POSSIBLE ASSOCIATION BETWEEN CHILDHOOD LEUKAEMIA AND RESIDENCE NEAR SOURCES OF TRAFFIC EXHAUST AND PETROL FUMES

Introduction

1. Childhood leukaemia is the most common malignant disease in children. It is very rare with an incidence rate of 4 in 100,000 per year in developed countries, although incidence rates are increasing (IARC, 1999). Only a small number of risk factors have been identified and these were recently reviewed in a document (CC/04/31) presented at the November 2004 COC Meeting. The review examined the potential association between environmental chemical exposures and childhood cancer; exposure to air pollution was among the risk factors considered.

2. In many countries, the major source of ambient air pollution in urban areas is road traffic. 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 (See Glossary). Diesel engine exhaust has been classified by IARC as a Group 2A carcinogen and gasoline engine exhaust as Group 2B (IARC, 1989). Benzene is well documented as a cause of adult leukaemia (Rinsky et al., 1987) and, given that it is also a component of gasoline and diesel fuel/exhaust, there has been some interest in whether childhood leukaemia rates are increased in high traffic areas.

3. A preliminary discussion paper (CC/04/37) was presented at the November 2004 COC Meeting at the request of the DH Air Pollution Unit, which addressed the evidence from selected published epidemiology studies for an association between residence near to petrol stations and garages, and road traffic exhaust fumes and the occurrence of childhood leukaemia (all types of leukaemia in individuals aged 0 – 14 years). The Committee considered that no definite conclusions could be reached on the information provided in this paper. Members asked for a full review of the epidemiology literature on this issue. It was suggested that the review should include studies, which reported on benzene exposure and should consider information on all types of leukaemia. However, petrol stations and garages are notable for the evaporative emissions of hydrocarbons, including benzene, and are unlikely to generate sufficient traffic on their own to cause a substantial increase in pollutants from vehicle exhaust. Since these evaporative emissions also contain carcinogenic

compounds other than benzene, exposure to fuel vapour is discussed below separately from vehicle exhaust emission data. This paper also includes findings of a recent risk assessment of gasoline inhalation exposure as well as information on current legislation regarding ambient benzene air quality standards. Finally, this document provides a more in-depth review of the literature investigating proximity to high traffic areas and childhood leukaemia incidence and also considers studies examining any related associations of benzene exposure and childhood leukaemia.

Exposures to fuel vapour

4. Most engine-powered vehicles and equipment use either gasoline or diesel as a fuel. Both used for internal intermittent combustion engines, differing only in their ignition mechanism and constituents (IARC, 1989). Gasoline is mainly used as a light fuel in internal combustion engines for automotive (on-road) use in cars and motorbikes. It is also used in lesser quantities for off-road applications (CONCAWE, 2004) (See Glossary). Diesel fuel consists mostly of higher boiling range petroleum fractions and therefore because of its higher density yields more energy than gasoline (IARC, 1989) (See Glossary). For this reason, diesel is generally used to power passenger vehicles, and provide energy for industrial power heavy-duty applications and works.

5. Studies examining the risk of inhalation exposure to evaporative vehicle emissions from diesel are limited as it is thought to be relatively non-volatile (Knox & Gilman, 1997). CONCAWE (The Oil Companies European Organisation for Environment, Health and Safety) recently undertook a risk assessment of inhalation exposure to gasoline vapour and the main findings in relation to childhood exposure opportunities are described below (CONCAWE, 2004).

<u>CONCAWE risk assessment for exposure to gasoline vapour</u>

6. The following scenarios were considered by CONCAWE as potential routes of inhalation exposure to gasoline by the general public. Scenarios (ii), (iii) and (v) represented relevant exposure opportunities for childhood exposures and therefore CONCAWE prepared separate risk assessments for these exposure scenarios as detailed below:
   i. Filling fuel tanks
   ii. Time spent at service stations
   iii. Driving in cars
   iv. Refilling and use of gasoline-powered equipment
   v. Residing indoors at locations affected by gasoline sources

7. The first child-relevant scenario (ii) describes a visit to a gasoline service station for refuelling purposes, in which children often accompany adults. Assuming a typical refuelling operation lasts approx for 5 mins (one day per week, 52 weeks per year/based upon a 9 kg

child (average value for children less than 1 year old) CONCAWE calculated that children receive systemic doses of 0.0011 mg/kg/day[1] (Reasonable Worst Case (RWC)– 0.0015 mg/kg/day). These values were over twice that calculated for adults (0.0005 and RWC=0.0006mg/kg/day).

8. In scenario (iii), which suggests exposure to gasoline vapour also occurs while driving in motor vehicles, CONCAWE used previously measured benzene data to estimate gasoline vapour concentrations while driving in cars. Typical airborne concentration estimates of 3.15 mg/m^3 (RWC – 3.94 mg/kg/day) suggest children receive systemic doses of 0.12 mg/kg/day (RWC – 0.15 mg/kg/day). Again estimated inhalation intake for adults being considerably lower 0.04 and 0.06 mg/kg/day (RWC).

9. The final child-relevant scenario relates to gasoline vapour exposures at homes situated in roads with large numbers of parked vehicles or with cars parked in attached garages. Given that children spend a large amount of time indoors (on average 18 hrs per day) indoor gasoline exposures can be quite significant as reflected in CONCAWE's estimates. Using typical airborne concentrations of gasoline vapour of 2.07 mg/m^3 (with RWC: 7.16 mg/m^3) the systemic dose in children was calculated to be 1.66 mg/kg/day (RWC: 5.71 mg/kg/day), compared to adults: - 0.25 mg/kg/day and (RWC: 0.87 mg/kg/day).

10. Table 1. (below) shows that the RWC average daily dose (ADD) for children staying in their homes is approximately ten-fold greater than that estimated for a service station attendant working a full shift (5.71 mg/kg/day cf. 0.5 mg/kg/day respectively). However, this may overestimate true exposures because conservative estimates were used throughout the risk assessment. In conclusion, CONCAWE suggested that the risk measures currently deployed for gasoline exposure were adequate and no further information or testing was required. However, a risk assessment for inhalation exposure to benzene vapour was also performed, owing to the concern over its contribution to the overall carcinogenic burden of automobile emissions.

[1] Based on typical airborne concentrations of gasoline vapour estimated at 2.7 mg/m^3 (RWC – 3.83 mg/m^3)

Scenario	Exposure Factors				Airborne Concentration (mg/m^3)		Estimated Inhalation Intake (mg/kg/day)	
	Inhalation Rate (m^3/hr)	Exposure Duration (min/day)	Frequency day/wk	Frequency wk/yr	Typical	RWC	Typical	RWC
Filling fuel tanks	1.0	3	1	52	113 (1)	531 (1)	0.011	0.054
Staying at service stations								
Adults*	1.0	5	1	52	2.7 (2)	3.83 (2)	0.0005	0.0006
Children**	0.3	5	1	52	2.7	3.83	0.0011	0.0015
Driving in cars								
Adults	0.5	120	7	52	3.15 (3)	3.94 (3)	0.04	0.06
Children	0.4	51‡	7	52	3.15	3.94	0.12	0.15
Refilling gasoline-powered equipment	1.6	2	2	52	113‡‡	531‡‡	0.024	0.114
Use of gasoline-powered equipment (chainsaw)	1.6	240	2	52	22 (4)	69 (4)	0.57	1.8
Staying indoors (residence)								
Adults	0.5	17 hrs/day	7	52	2.07 (5)	7.16 (5)	0.25	0.87
Children	0.4	18 hrs/day	7	52	2.07	7.16	1.66	5.71

* *Body weight used for adults = 70 kg.*
** *Body weight used for children = 9 kg.*
‡ *Average value based upon 6 hours of exposure per week.*
‡‡ *Assumed same breathing zone concentration as "Filling fuel tanks."*
(1) *From Hakkola and Saarinen (2000).*
(2) *Inhalation exposure based upon calculated gasoline vapour concentrations using Raoult's Law. Ambient benzene concentration used in calculation from Vainiotalo et al. (1999).*
(3) *Inhalation exposure based upon calculated gasoline vapour concentrations using Raoult's Law. Ambient benzene concentration used in calculation from Rank et al. (2001).*
(4) *From Nilsson et al. (1987). Upper-end value for breathing zone concentrations of total hydrocarbons from operating a chain saw.*
(5) *Inhalation exposure based upon calculated gasoline vapour concentrations using Raoult's Law. Ambient BTEX compound concentrations used in calculation from Minoia et al. (1996).*

Table 1. showing summary of the exposure results for gasoline vapour inhalation for several consumer scenarios

<u>CONCAWE risk assessment for exposure to benzene vapour</u>

11. The results of CONCAWE's exposure assessment for benzene vapour inhalation are shown in Table 2. below. Similar trends to the gasoline vapour exposure assessment were apparent, in which indoor rather than outdoor exposures to petrol fumes appear to be of more significance. The following paragraphs briefly highlight key issues relating to indoor/outdoor benzene levels of relevance to CONCAWE risk assessment for exposure to benzene vapour.

Indoor levels of benzene

12. Despite the relatively low concentrations of benzene within the home (when compared with activities such as refuelling), because a large proportion of time is spent within the home, particularly at night, annual exposures tend to be high (Mann et al., 2001).

Scenario	Exposure Factors				Airborne Concentration (mg/m^3)		Estimated Inhalation Intake (mg/kg/day)	
	Inhalation Rate (m^3/hr)	Exposure Duration (min/day)	Frequency		Typical	RWC	Typical	RWC
			day/wk	wk/yr				
Filling fuel tanks	1.0	3	1	52	0.9 [1]	1.3 [1]	0.00009	0.00013
Staying at service stations								
Adults*	1.0	5	1	52	0.012 [2]	0.017 [2]	2.0E-06	2.9E-06
Children**	0.3	5	1	52	0.012	0.017	4.7E-06	6.7E-06
Driving in cars								
Adults	0.5	120	7	52	0.014 [3]	0.018 [3]	0.0002	0.0003
Children	0.4	51‡	7	52	0.014	0.018	0.0005	0.0007
Refilling gasoline-powered equipment	1.6	2	2	52	0.9‡‡	1.3‡‡	0.00019	0.00028
Use of gasoline-powered equipment (chainsaw)	1.6	240	2	52	0.7 [4]	2.3 [4]	0.02	0.06
Staying indoors (residence)								
Adults	0.5	17 hrs/day	7	52	0.0107 [5]	0.026 [5]	0.001	0.003
Children	0.4	18 hrs/day	7	52	0.0107	0.026	0.009	0.02

* *Body weight used for adults = 70 kg.*
** *Body weight used for children = 9 kg.*
‡ *Average value based upon 6 hours of exposure per week.*
‡‡ *Assumed same breathing zone concentration as "Filling fuel tanks."*
(1) *From Benzene RAR (draft – 2003).*
(2) *From Vainiotalo et al. (1999).*
(3) *From Rank et al. (2001).*
(4) *From Nilsson et al. (1987).*
(5) *From Minoia et al. (1996).*

Table 2. showing summary of the results for consumer exposure assessment for inhalation exposure to benzene

13. A wide range of potential sources of benzene occurs inside the home. These include building and furnishing materials, environmental tobacco smoke (ETS), photocopier and laser printed paper, particle board furniture, floor adhesives, paints, wood panelling, caulking[2] and paint remover (Duarte-Davidson et al., 2001; Edwards & Jantunen 2001, Atmos Environ 35:1411-20; Kim et al 2001, Environ Sci Technol, 35:997-1004). This, therefore, suggests that personal exposure to benzene can be much higher than otherwise indicated from studies monitoring potential exposures from outdoor air sources.

14. Several studies monitoring personal exposure have shown that indoor levels are considerably higher than those outdoors. The Building Research Establishment measured air levels of benzene inside the homes of 174 households as part of a longitudinal study in the Avon area, UK (Duarte-Davidson et al., 2001). Mean indoor concentration was 8 ug/m^3 compared with an outdoor mean of 5 ug/m^3. The higher concentrations of benzene in indoor air was associated with the presence of an attached garage; a car kept in the garage increased indoor air concentrations by 80% (Duarte-Davidson et al., 2001).

[2] a waterproof material used to seal cracks

15. In the UK, 22% of houses have an attached garage and many private motor vehicles are kept, when not in use, in a garage sharing a common wall with the vehicle owner's home, sometimes with an interconnecting door to the living area. In some of these homes, a room is located directly above the garage and therefore receives high exposures, as demonstrated in a detailed investigation by Mann et al. (2001) who measured benzene levels in five homes with either an attached or integral garage (Mann et al., 2001). Mean benzene concentrations in the room above the garage ranged from 3.7 ug/m^3 to 39.9 ug/m^3 (the latter being nearly 2.5 times the ambient air standard).

Outdoor levels of benzene

16. With regards to benzene levels outdoors, mean outdoor air concentrations in the UK are similar to those detected in US and Canada and usually fall within range 1-8ug/m^3 (Duarte-Davidson et al., 2001). Studies in the Netherlands have shown that concentration of benzene at the front of houses (and indoors) can be 1-52 times higher than those measured at the back of the houses. It is thought this is due to the evaporation of benzene from petrol tanks and engines of parked cars (Duarte-Davidson et al., 2001). Highest levels of benzene are, however present within the cars themselves i.e. 240 ug/m^3 (780 ppb) [3] and may reach US occupational exposure limits of 309 ug/m^3 (1000 ppb) although the typical range is in the order 3 – 6 ug/m^3 (10 – 20 ppb) (Wolff, 1992).

17. Benzene emissions to air have increased significantly in the period 1960-1990 as a consequence of the rapid increase in vehicle numbers. During 1995, an estimated 35 kilo tonnes of benzene were emitted to the United Kingdom environment. Benzene has been routinely monitored in ambient outdoor air in the UK since 1991 as part of the automatic hydrocarbon-monitoring network of the Department of the Environment, Transport, and the Regions (Duarte-Davidson et al., 2001). In the London area, benzene concentrations of 118 ug/m3 have been detected at roadside sites close to the kerbside (Duarte-Davidson et al., 2001). Mean benzene concentrations at sites within 20 m of busy roads seem to cover the range 10 - 45 ug/m^3. Seasonal variations in outdoor air concentrations of benzene have been observed with levels about 1.5-3 times higher in winter than during the summer period (Duarte-Davidson et al., 2001).

Air Quality standard for benzene

18. A number of national and international initiatives have been set up to reduce population exposure to benzene and the associated risk to health. In the UK, the United Kingdom Expert Panel on Air Quality

[3] 1 ppb = 1 part by volume, in one thousand million i.e. 1 in 10^9; 1 ppb of benzene ≡ 3.24 ug/m^3 at 20°C and 1013 millibars (http://www.defra.gov.uk/environment/airquality/aqs/benzene/4.htm)

Standards (EPAQS) recommends the running annual mean standard[4] for benzene of 16.25 ug/m^3 (5 ppb). The European Community Directive 2000/69/EC has an ambient air limit value[5] for benzene of 5 ug/m3 to be met by 1 January 2010 (http://europa.eu.int/comm/environment/air/pdf/ppbenzene.pdf).

19. CONCAWE has highlighted a number of important technological developments which they claim allay concerns over benzene exposures from automobile emissions in the general population (CONCAWE, personal communication 2004 [appended at Annex 3]):
    a. The vast majority of gasoline powered cars produced are now equipped with advanced exhaust after-treatment
    b. Vapour recovery mechanisms have been introduced both during the bulk supply of gasoline to petrol stations (mandated by European directive 94/63/EC) and on pumps of larger petrol stations
    c. The maximum level of benzene contained in gasoline has reduced from 5% to 1% (as mandated by European directive 98/70/EC, effective in EU countries on 1 January 2000)
    d. An Air Quality Limit Value for benzene has been established (mandated by European directive 2000/69/EC)

20. The potential risks from benzene exposure to the general population were also assessed as part of a process to deal with "Ambient Air Quality Assessment and Management (Working Group on Benzene, 1998). Assuming ambient exposure at the AQS of 5 ug/m^3, a 70 kg adult was calculated to have an inhaled intake of 0.86 ug/kg/day benzene. In children who have a lower body weight this value was almost 6-fold greater at 5.3 ug/kg/day. Given that these inhalation intakes were within the range judged acceptable, CONCAWE concluded that there was no need at present for further information and/or testing nor for risk reduction measures beyond those which are being applied already except in scenarios for use of gasoline powered equipment and residential exposures where the need for further information/testing is recommended.

Exposure to vehicle exhaust

21. Vehicle exhaust contributes significantly to urban air pollution. The type of exhaust produced generally depends on:
    - the type of engine,
    - whether the engine operates under diesel/gasoline,
    - whether the vehicle is a light-duty/heavy-duty one,
    - whether it possesses a catalytic converter
    - the engine operating conditions,

[4] the running annual mean standard refers to a value calculated from data collated 12 months prior to the quoted date
[5] 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

- fuel and lubricating oil composition and emission control system.

22. Tailpipe emissions consist of many hydrocarbons e.g. benzene, carbon monoxide, aldehydes and lead (Mann et al., 2001). A list of different compounds present in vehicle exhaust can be found in the glossary section. However, the benzene emitted from a car exhaust is likely to be a mixture of unburnt benzene and benzene derived from the combustion of other aromatic petrol components (i.e. the thermolytic dealkylation of alkybenzenes during internal combustion) (Mann et al., 2001).

22. Exposure to vehicle exhaust varies widely in intensity and duration. Exposures in the general public are highest where traffic is heaviest, such as along highways and in cities (IARC, 1989). However, it is difficult to quantify exposure, as exhaust is a chemically complex matrix and its components may also derive from many other sources. This has been a major challenge in epidemiological studies.

23. These factors all influence the composition and concentration of a chemical species in vehicle exhaust and therefore must be considered when interpreting results of experimental/ epidemiological studies (IARC, 1989). To date, the evidence for the carcinogenicity of traffic exhaust (gasoline/diesel) derives mainly from experiments in animals and studies of occupationally exposed persons. Studies in children are scarce. Epidemiological evidence suggesting a possible link to the development of childhood leukaemia are discussed in the next section.

Epidemiological studies

24. The earliest studies examining the relationship between traffic and childhood cancer were conducted in Denver, Colorado, USA to address concerns that traffic and associated socio-economic neighbourhood characteristics might be potential confounders in studies of electric and magnetic field (EMF) exposures. The hypothesis that exposure to traffic emission might explain the observed associations between EMF and childhood cancer was plausible because of the coincidental occurrence of power lines with roadways. Moreover, the observation in the earliest study of EMF that children living in close proximity to heavy traffic routes were more likely to have died from childhood cancer than control children, and the fact that children near the plant travelled more frequently by car than children in the reference group (Wertheimer & Leeper, 1979) and that, unlike for EMF, a biological mechanism could easily be invoked for many constituents of automotive exhaust, stimulated analyses in a subsequent case control study of childhood cancer incidence in the Denver area.

25. Sixteen epidemiological studies on air quality and childhood cancer that bear directly on the topic of residence near to petrol stations,

garages, and road traffic exhaust fumes have been published in the peer-reviewed literature. NB. Unpublished results of a study by Urayama et al. (2004) that were recently presented as a poster at the international conference on 'Children with leukaemia' in London (2004) have been included in this review (see Annex 4). These 17 studies in total are summarised in a table in Annex 1 and described in detail in Annex 2. Eight of these studies are from the US (Langholz et al., 2002; Pearson et al., 2000; Reynolds et al., 2001; Reynolds et al., 2004; Reynolds et al., 2002; Reynolds et al., 2003; Savitz & Feingold, 1989; Urayama, 2004); three are from UK (Alexander et al., 1996; Harrison et al., 1999; Knox & Gilman, 1997), two from Sweden (Feychting et al., 1998; Nordlinder & Jarvholm, 1997), and one each from Denmark (Raaschou-Nielsen et al., 2001), France (Steffen et al., 2004), The Netherlands (Visser et al., 2004) and Italy (Crosignani et al., 2004a). Nine specifically focussed on childhood leukaemia, and only two studies examined the potential association between proximity to petrol stations/garages and childhood leukaemia (Harrison et al., 1999; Steffen et al., 2004), the majority focusing on proximity to high traffic roads.

26. Positive significant associations between residential proximity to sources of traffic exhaust/petrol fumes and childhood leukaemia were reported in 10 of the seventeen studies reviewed here. However, with the exception of Reynolds et al. (2003), most of the papers reporting a positive association were based on much smaller sample sizes (average no. of leukaemia cases was 394) than the 7 investigations reporting a null association (average no. 861). Several authors reported that their positive findings were only suggestive of an association, given the qualitative limitations of the study. [NB. Point estimates that failed to reach statistical significance were categorised as having a null effect, irrespective of whether the authors quoted a positive finding as it provides no statistically strong evidence of an association].

27. The following paragraphs describe some of the factors that may have influenced the results obtained in these studies.

28. In view of the rarity of childhood cancer, the majority of studies were of case control design. Several investigations selected controls from registers of the general population or via random digit dialling (RDD)[6] (a method that does not depend on listing of the population). Langholz et al. 2002 applied this method in a study of childhood leukaemia risk and traffic density (Langholz et al., 2002) but, as pointed out by Reynolds et al. (2004), RDD is biased more against children whose births are closely spaced, which tends to arise in children of lower socio-economic status (SES) (Reynolds et al., 2004). Therefore,

[6] This process generates a set of telephone numbers without relying on a directory that would not have new or unpublished numbers

controls tend to be of higher SES and less likely to live in high traffic areas.

29. Most of the studies matched controls for geographical area, age and sex to help control against unmeasured confounders. Two studies also matched according to the ethnicity of the case subjects (Steffen et al., 2004; Urayama, 2004) because incidence rates of ALL vary with racial origin. Whether this difference in ALL incidence relates more so to social factors remains unclear. Data suggest that traffic density is higher in areas that are more urban, more industrial, more socio-economically disadvantaged and more likely to be populated by non-whites, thereby highlighting the importance of using suitably matched controls.

Exposure assessment

30. The studies to date have used various area-based measures as proxies for traffic-exhaust exposures. These surrogate measures of vehicle exhaust exposure have included measurement of traffic density (Langholz et al., 2002; Pearson et al., 2000; Raaschou-Nielsen et al., 2001; Reynolds et al., 2001; Reynolds et al., 2004; Reynolds et al., 2002; Savitz & Feingold, 1989; Urayama, 2004; Visser et al., 2004), car/vehicle density (Nordlinder & Jarvholm, 1997; Reynolds et al., 2002), car ownership (Alexander et al., 1996), road type/density (Feychting et al., 1998; Knox & Gilman, 1997; Reynolds et al., 2004; Reynolds et al., 2002; Reynolds et al., 2003), proximity to traffic/petrol fumes (Reynolds et al., 2001; Steffen et al., 2004; Visser et al., 2004) and estimated concentrations of air pollutant gases such as nitrogen dioxide or benzene (Crosignani et al., 2004a; Feychting et al., 1998; Raaschou-Nielsen et al., 2001; Reynolds et al., 2002).

31. While each of these may approximate different kinds of exposure to air pollutants, there is no clear evidence for consistency in risk associations for one measure compared to the others across studies. Furthermore, due to scarcity of ambient air quality data, it is often difficult to assess the degree to which proxy measures actually inform such exposures in residential areas. Few studies have obtained direct air measurements of benzene and nitrogen dioxide (NO_2) (which are the most commonly used markers of traffic-related air pollutants for external exposure assessments). However, in Denmark, an evaluation of traffic exposure estimates using measured levels of benzene found correlation coefficients of 0.68 for traffic density (Reynolds et al., 2004). A study by Reynolds et al. 2002 showed that levels of NO_2 correlated with three indices of traffic used; vehicle density, road density and traffic density. Similarly Wolff (1992) showed that levels of airborne benzene are closely related to traffic density.

32. Pearson et al (2000) used a distance-weighted traffic density approach as their metric of traffic exposure, on the basis that the concentration

profile of airborne exhaust pollution from motor vehicles travelling on a street approximates to a Gaussian (normal) distribution. In such a model, the gradient of traffic air pollution may be very steep and diminish rapidly with distance from street. Figure 1. shows an idealised profile of the distance-weighted traffic metric.

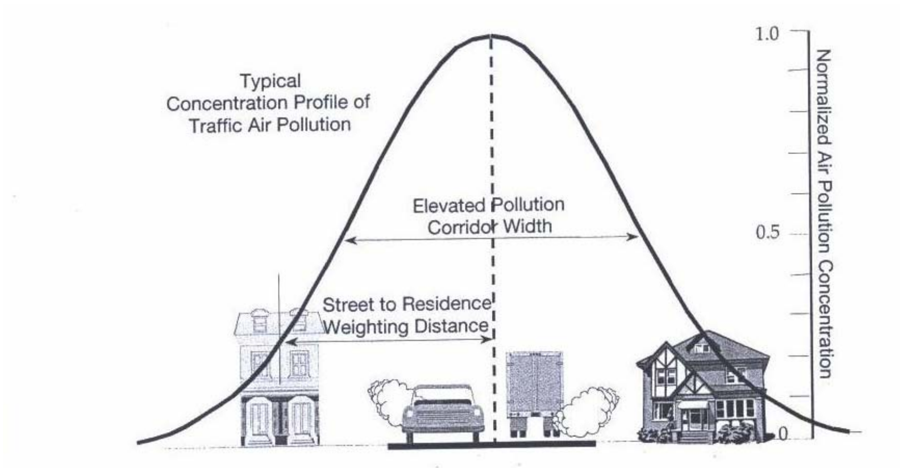

Figure 1. A generalised profile of concentration of airborne exhaust pollution from vehicular traffic in the absence of crosswind.

33. Many factors such as prevailing winds, turbulence generated by passing vehicles, and the dispersion blocking effect of nearby buildings and hillsides are thought to produce variability in profiles. Pearson et al (2000) calculated distance-weighted traffic density values by multiplying the traffic counts (in VPD - vehicles per day) for the highest trafficked street by the distance weighted value derived from the curve. For example, as illustrated in Figure 1. a street with a traffic count of 10K VPD located at the distance from the home shown on the left would have a distance weighted traffic density of 2500 VPD at the home. The distance-weighted approach was also used by Langholz et al. 2002 for assessing level of exposure to traffic.

34. Air pollution is greatly influenced by weather conditions i.e. wind speed, temperature, relative humidity and solar radiation. Concentrations of traffic-related pollutants close to roads are higher where the average wind speeds are low. Reynolds et al. (2001) accounted for the decay in concentrations of air pollutants from the effects of wind in their study investigating the relationship between traffic density and socio-economic indicators of childhood leukaemia. Similarly, Crosignani et al (2004) highlighted the effects of wind speed on higher ambient air levels of benzene in the Varese Province of northern Italy when compared to levels in Denmark (Crosignani et al., 2004). In the Varese Province, the annual average wind speed is known to be < 1 m/sec. In

Denmark the mean monthly wind speeds fall in the range 4.3-6.4 m/sec, thereby having a diluting effect on air pollution from traffic.

Case-control distance comparisons

35. A number of studies used either block areas, postcode units, census tracts or municipalities as the 'catchment area' for selecting their cases and controls. The sources of traffic exhaust/petrol fumes (contained within these areas) varied in their distance from the index child's[7] house and were either just infront (Savitz & Feingold, 1989), within 100 metres (Harrison et al., 1999) or up to 457 metres away (Pearson et al., 2000). However, given the impact of main roads on air quality is not thought to be measurable above the local background air pollution at distances beyond 100-200 m (Harrison et al., 1999), the credibility of results from studies where the homes are located > 200 m away from traffic roads or petrol stations/garages is questionable.

Age-related factors and residential history

36. Apart from two studies, one of which explored the possible risk of childhood leukaemia from exposure to traffic related sources in people aged between 0 and 24 years old (Nordlinder & Jarvholm, 1997) and one of which looked at the general population as a whole (Visser et al., 2004), all were conducted in children under 15 years of age. Age stratification is vital for any study of childhood cancer as the types and causes of cancer in children differ to those in adults. Furthermore, since so little is known about the causes of childhood cancer it is still unclear which time windows of exposure are most important.

37. Most studies of traffic and childhood leukaemia have examined exposure potential based on a child's residence either at diagnosis or birth. Few have also obtained information on residence of the parent prior to birth usually due to limitations in the existing recorded information available at the time. Raaschou-Nielsen et al (2001) collated data spanning a child's complete residential history encompassing an exposure window from 9 months before birth through to the child's date of diagnoses In two of the reviewed studies, children aged 0-4 years of age had higher point estimates for leukaemia than children 5-14 years old (Reynolds et al., 2003; Savitz & Feingold, 1989). It is possible that the address at diagnosis represents a more relevant measure of exposure for younger children due to the fact they generally spend more time at home and are less likely to have lived in other locations. Indeed studies that can better characterise patterns of residential mobility and measured air quality will be important in further elucidating these risk relationships.

Account of confounders

[7] child diagnosed with cancer of interest

38. Because most population-based studies collect exposure data solely from existing records (which are often limited in the type of information available for abstraction), investigations often require follow-up studies to complete the analysis as illustrated in several of the studies reviewed here (See Annex 1). Cigarette smoking / ETS exposure represents a significant confounder in cancer epidemiological studies (and also confounds for potential exposures to benzene). Only two studies specifically incorporated the effect of smoking (maternal smoking during pregnancy) in their analysis (Nordlinder & Jarvohlm, 1997; Visser et al., 2004); both reported positive results. However, none of the studies reviewed appeared to account directly for the effect of ETS exposure to the child, although several did collect information on parental occupational exposures to various chemical mixtures of which some have been linked to childhood cancer (See document CC/04/31) and Crosignani et al. (2004a) accounted for SES, which is well documented to be inversely correlated to parental smoking.

39. As mentioned previously, microenvironmental (individual) exposure data is vitally important as sources of petrol fumes/traffic exhaust components can vary immensely, even within a similar residential area. None of the reviewed studies used personal ambient air monitors, although questionnaires on index child's past exposure history have been used (Steffen et al., 2004). The lack of data on environmental benzene exposure in children may be in part due to the difficulty of equipping young children with personal samplers. Many investigators use estimates of personal exposure on the basis of time-weighted average concentrations. Kouniali et al (2003) compared personal exposure and inhalation uptake in children aged between 2 to 3 years to those of their parents (Kouniali et al., 2003). Although the estimated exposure for children (11.1 ± 6.2ug/m3) was significantly lower than the measured exposures in their parents (14.7 ± 7.7ug/m3), indoor concentrations of benzene were higher than those experienced outdoors.

40. Finally, as with most disease risks, genetic susceptibility can play a substantial role in disease outcome. Only one study investigated the combined effects of genetic polymorphisms and traffic exposure on risk of childhood leukaemia and found that children carrying the high risk CYP1A1 m2 allele were more susceptible to the carcinogenic effects of traffic-related exposures (Urayama, 2004; unpublished results)(see Annex 4 for copy of abstract). Interestingly without accounting for individual genetic susceptibility, the authors found no association between risk of childhood leukaemia and traffic density.

Conclusions

41. In conclusion, the available evidence is not convincing of an association between risk of childhood leukaemia and proximity to petrol

stations, garages and road traffic. Most of the studies were ecological in nature and few controlled adequately for potential exposures to indoor sources of petrol (or benzene) vapour, which appear to be more significant in relation to the systemic doses experienced in children. Future approaches that can more precisely assess microenvironmental exposure potential, and account more thoroughly for disease heterogeneity and host vulnerability, may further elucidate this biologically plausible risk association.

42. Wolff (1992) has postulated that a generalised background incidence of leukaemia exists nationwide with the risk increasing depending on the extent of car ownership and usage on local level. According to this hypothesis, the higher levels of benzene exposures encountered by travelling in 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 the increased incidence of leukaemia in regions where a greater use of cars is predicted to occur. In this way these ‘clusters’ represent the tips of a generalised increased risk of benzene-related leukaemias However, in view of the fact that higher exposures to gasoline/benzene vapours tend to arise indoors, especially in households with attached garages, it is possible that there is little scientific rationale in investigating a link between childhood leukaemia and proximity to petrol stations/high traffic roads and that efforts should focus more on assessing potential indoor concentrations and sources.

Questions for the Committee

43. Do members agree that the available evidence does not support an association between childhood leukaemia and residence near sources of traffic exhaust/petrol fumes?

44. Do members agree that the significance of indoor exposures to gasoline vapour/benzene from attached garages warrants further consideration?

45. Should studies measuring distances between residence and source of traffic exhaust/petrol fumes in excess of 200 metres should be discounted due to the air pollution decay issues raised by Harrison et al (1999)? Does the distance-weighted traffic approach provide a more accurate exposure metric?

46. Should future studies ideally take into account a child’s complete residential history from conception to birth, not just residence at diagnosis?

47. Do members consider that there should be separate analyses of the data on exposure to vehicle exhaust and exposure to vehicle evaporative emissions?

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Secretariat
April 2005

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Annex 1 to CC/05/8

Table of epidemiological studies examining the relationship between proximity of residence to 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=11									
1976-1983 Denver, USA To establish whether an association exists between high traffic density and childhood cancer	Case Control Study Cancer cases (328) - Leukaemia (103) - ALL (76) Control (262)	0 - 14	Traffic count in road in front of house used to generate traffic density (VPD)	N/a	Parents 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] > 500 VPD (0-4 yrs): OR=5.6[1.9-16.7] Concluded that the data is suggestive of an association between high traffic density and childhood cancer.	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 Unmeasured confounders associated with microenvironmental exposure to traffic fumes/exhaust Small number of cases.	Accounted for child's past exposures to agents and activities thought to be associated with cancer	(Savitz & Feingold, 1989)
1976-1983 Denver, USA Extension of Savitz & Feingold (1989) study to reduce exposure misclassification	Case Control Study Cancer cases (320) - Leukaemia (97) - ALL (78) Matched controls for age, sex and area (259)	0 – 14	Distance-weighted traffic metric (vehicles per day (VPD))	Highest trafficked street within a 1500ft (457 m) radius of case add	As above	≥ 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	Small no. of cases and controls in high exposure category No data on residential history	Use of distance-weighted traffic metric which takes into account decay of air pollution concentration with distance from street	(Pearson et al., 2000)
1953-1980 England, Scotland & Wales To examine patterns of spatial clustering in children who have died of cancer	Case-Control Study All cancer mortality cases (22,458) Total leukaemia (?) Matched controls available only for 2/3 cases	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 Lacks data on residence at conception No data relating to microenvironmental exposures Sample of postcodes for control children (Refer to paragraph X)	COC concluded in 1997 that results there were major limitations in the methodology used.	(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	Case Control Study All cases (n=142) - leukaemia (39) Controls (550)	≤ 15	Estimated NO_2 levels from historical data (ug/m3) Road type	N/A	No	At highest exposure category (≥ 80 ug/m3 NO) RR=3.8[1.2-12.1] (all cancers) Concluded that the finding was suggestive of an association between childhood cancer and motor vehicle exhaust	The number of cases for specific cancer analysis i.e. for leukaemia was too small at this exposure level Possibility of exposure misclassification (due to use of NO_2) Unmeasured confounders		(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	Ecological 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	Maternal smoking	> 20 cars/km2: IR=5.5[4.4-6.8] cases AML per 1 million person-years > 5 cars/km2: 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.	Unmeasured confounders: radiation from natural sources, building materials or during medical diagnoses during treatment, parental occupational exposure, plus those associated with microenvironmental exposures to traffic fumes /constituents e.g. ETS No age stratified analyses (since included young adults)	Showed that car density correlated with gasoline density (R=0.098)	(Nordlinder & Jarvholm, 1997)
1978-1997 Italy To assess the effect of road traffic exhaust on childhood leukaemia	Population based case control study (n=120) Matched controls used	0-14	Gaussian diffusion model to estimate [benzene]	Main roads within 300m radius	SES	Heavily exposed children (over 10ug/m3 estimated annual average of benzene): RR=3.91[1.36-11.27] No evidence 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 upon which traffic data was abstracted (up to 11 years different)	Follow up study to address lack of information on benzene exposure history in progress	(Crosignani et al., 2004a)
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)	0-14	Questionnaire used to obtain data on: Proximity to either car repair garage, petrol station or heavy traffic a	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 the childhood (OR=4.0[1.5-10.3], n=17). Re-analysis according to leukaemia ANLL = 7.7[1.7-34.3] ALL = 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.	Specifically looked at association with childhood leukaemia Acquired data on residential history and addressed potential confounders for exposure to benzene Follow-up study in progress	(Steffen et al., 2004)
1988-1994 California, US To investigate the possible association between childhood cancer and exposure to Hazardous Air	Population based study All cases (n=7143) - Leukaemias (2443) - ALL (1938) - ANLL(368)	<15	Outdoor average [HAP] levels as modelled by US EPA Categorised according to	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:	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	Large diverse population of children included in the study 1st epidemiological study using modelled concentrations of multiple chemicals @ census tract level to evaluate cancer	(Reynolds et al., 2003)

Pollutants (HAP)			whether they derive from mobile, area or point sources for each census tract			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 information on residential history No control for possible confounders	Follow-up study in progress	
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 patients residing in Amsterdam at date of diagnosis. N=3384 No of children (10) - those with ALL (5)	Varied Age group stratification Included children <15	Traffic Intensity Scores (TIS) involves multiplying the distance between road axis and front of house against type(size) vehicle	Less than 50 m from main road	Effect of smoking	Five cases of ALL in children, all lived along busiest main roads (standardised incidence ratio (SIR): 4.9[1.6-11.4]	Used residence at time of diagnosis No of cases small Possible differential misclassification due to change in residency of subjects SES differences		(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 (N=183) Matched controls (for age, sex and race (202)	<15	Traffic density Vehicle Miles Travelled (VMT)/miles2	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]), however with the inclusion of genetic factors an association was evident. 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 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.	Cases of children diagnosed with leukaemia (130) Case-control analysis using children diagnosed with solid tumours (251) as controls AND comparison of observed no. of leukaemia cases	0-15	Proximity to main roads and petrol stations from postcode address	100 m	None specified	Results failed to achieve significance	Use of children with solid tumours as controls would be inappropriate if similar aetiologies for leukaemia and some solid tumours?? No control for confounders		(Harrison et al., 1999)

	with expected number, calculated from health authority population numbers using indirect age and sex standardisation								
1978-1984 Los Angeles, US To investigate the relationship between traffic density and risk of childhood leukaemia	Case control study (n=212) Age/sex matched controls (202)	0-10	An integrated distance-weighted traffic density measure	1500ft (457 m)	Yes	No evidence of an association	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	Accounted for several potential confounders e.g. Demographic factors, parental occupation Used distance-weighted traffic density values	(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 study of cases 1989 cases of leukaemia, CNS tumour or malignant lymphoma recorded in Danish Cancer Registry Leukaemia (986) - ALL (731) - ANLL (127) - Other (128) Age/sex matched controls	<15	Traffic density [NO2]air (front door) [benzene]air (front door)		Residential histories traced from conception to diagnosis – 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.	Could have included other confounders such as medical history , maternal smoking, paternal occupation, microenvironmental exposure	Large sample size Assessed both traffic density measures and modelled NO2 concentrations for the full lifetime residential histories of the study children + several confounders	(Raaschou-Nielsen et al., 2001)
1988-1994 San Diego, California US To examine the relationship between traffic density and socio-economic indicators to early childhood leukaemia	Case control study (N=92) Controls (349)	<5	Traffic density GIS to assess proximity of birth address to high traffic flow	550ft (168 m)	Socio-economic status Wind	No evidence of association found Concluded study design may have influenced null result	Small number of cases Failed to acquire complete residential history from conception to diagnosis as used address at birth	Specifically examined leukaemia risk Accounted for decay of air pollution	(Reynolds et al., 2001)
1988-1994 San Diego, California US To examine risk of childhood cancer and residential proximity to high traffic areas	Population based 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/ neighbourhood	None	No elevated incidence of any childhood cancer in areas of high vehicle intensity, high road density or high traffic density found	No information on residential history Lack of data on microenvironmental exposures.	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	Case control study (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	Used birth address only with no information on residential history Unmeasured confounders (although this was because it relied on existing records)	Large sample size Didn't use RDD for control selection	(Reynolds et al., 2004)

1984-1989 UK To determine increased rates of childhood ALL in isolated areas could be attributed to higher proportions of households owning cars	Re-analysis of ecological data (n=438)	0-14	No of cars owned??? Measured distance from built up area	<5km 5-20km >20km	None specified	No evidence to support the theory	Used level of car ownership as surrogate measure for individual exposure benzene from petrol Unmeasured confounders	Quantified degree of isolation in terms of distance from built up areas and found this was associated with increased incidence of ALL	(Alexander et al., 1996)

Detailed account of epidemiological studies reviewed

A number of studies have reported that childhood cancer is associated with exposure to high levels of traffic (see Annex 1). However, the largest case-control studies have tended to find no association between traffic metrices and childhood leukaemia . A detailed account of the methodology and conclusions from all studies reviewed in this document is provided below. Note: in all cases the confidence intervals cited are 95%.

Studies reporting a positive association between childhood leukaemia and residential proximity to traffic exhaust/fumes

1. Savitz & Feingold (1989) conducted a case control study (using data from a previous ecological study) in children aged between 0-14 years diagnosed with childhood cancer between 1976 to 1983 (n=328 of which 103 were leukaemia ; ALL=76 leukaemia cases), and living in Denver, US. Parents of case and control children (n=262) were interviewed to obtain data about their child's past exposure to agents and activities potentially associated with cancer, including confounders such as parents' cigarette smoking and the use of pesticides in and around the home. Other confounders accounted for include child's age, gender, year of diagnosis and residential stability. Traffic density (VPD) was defined as the traffic count on the street address of the home, usually located in the front of the home. The authors found that children living in areas with more than 10K VPD had an odds ratio of 4.7 [1.6-13.5] for leukaemia. The OR was 2.7 [1.3-5.9] for traffic counts more than 5K VPD and was greater for 0-4 year olds (OR=5.6 [1.9-16.7]) living in areas with more than 500 VPD. It was concluded that the data is suggestive of an association between high traffic density and childhood cancer. However, the authors noted that the results should be interpreted with caution given the limitations of the study relating to use of a crude measure of exposure based on the subject's residence at diagnosis, exposure misclassification, unmeasured confounders and the small number of cases.

2. Pearson et al. (2000) introduced several improvements in their re-analysis of the above data to reduce exposure misclassification for traffic air pollution (Pearson et al., 2000). By using a GIS methodology that counted all surrounding streets, the authors developed an exposure metric based on the highest trafficked street surrounding the house (within 1500 ft in any direction from each home), as opposed to the street of the address located in front of the house. The study also took into account the decay of air pollution concentration with distance from the street and obtained traffic density data for 1979 and 1990 (the two years closest in time to the period of exposure of the cases studied in Savitz & Feingold study). Controls were matched for age, sex and area of residence. The results suggested that distance weighted traffic

density is a risk factor for childhood leukaemia. Elevated risks were found for traffic densities ≥ 20K VPD in areas 750 ft from index child's home (OR=8.28 [2.09-32.80]) – a substantially higher value than that reported by Savitz & Fiengold. It was suggested that the Savitz and Feingold study was limited by use of traffic density on the street address in front of a home that would not account for high exposure coming from a busy street either behind or beside a home. However, the study is limited by several factors including the small number of cases (5) and controls (2) in the high exposure category (≥ 20K VPD); and lack of data on the residential history during the relevant (and unknown) aetiological period of each child, (a consequence of deficiencies in data acquisition provided by previous study).

3. Knox and Gilman examined spatial clustering patterns among 22,458 children aged 0-15 years who died from leukaemia or other cancers in England, Scotland or Wales from 1953 to 1980 (Knox & Gilman, 1997). This study was previously reviewed in the 1997 COC Annual Report. (http://www.advisorybodies.doh.gov.uk/coc/1997ar.pdf). Birth and death addresses were mapped to potentially hazardous industrial/business addresses and the number of births and deaths at successive radial distances from these hazards sources (up to 10 km) counted to generate relative case density ratios or standardised density ratios (SDR). Matched controls were only available for 2 out every 3 cases. An excess of childhood leukaemia was found in proximity to motorways and industrial plants, which are likely to be sources of airborne toxic substances such as VOCs. The largest excesses of cancer associated with traffic were found 1 km or less from motorways. Knox and Gilman concluded that childhood cancers are geographically associated with petroleum-derived volatiles and effluent from internal combustion engines. However, the COC considered that the above results were inconclusive due to several major limitations in the methodology used.

4. In a small Swedish case-control study (142 cases; 550 controls) Feychting et al., 1998 used estimates of NO_2 levels from traffic data and road type as a measure of exposure to traffic air pollution in children aged 15 years or under, who had lived for at least 1 year on property located within 300m of high voltage power lines, during the period 1960-1985 (Feychting et al., 1998). Cases of cancer were obtained from the Swedish cancer registry; 39 cases were diagnosed with leukaemia. The results, calculated as risk per microgram of nitrogen dioxide per cubic metre, showed that, for the highest exposure category (≥ 80 ug/m3), the relative risk for cancer development was estimated to be 3.8 [1.2-12.1]. However, the number of cases for specific cancer analysis was too small at this exposure level. The authors concluded that the finding was suggestive of an association between childhood cancer and motor vehicle exhaust but noted the size of the study, possibility of exposure misclassification (due to use of NO2) and other unmeasured confounders limiting the study.

5. Crosignani and colleagues performed a population based case-control study in northern Italy, using 120 cases of childhood leukaemia registered between 1978-1997 and living near traffic (Crosignani et al., 2004). This study was discussed at the last COC Meeting in November 2004 (CC/04/37) and so will be briefly discussed here . Concentration levels of benzene were estimated from models of traffic density and information on vehicle emissions and weather conditions[8]. Address at diagnosis was obtained from the Lombardy Cancer Registry (LCR) and risk figures evaluated by considering, as a measure of exposure, distances from highly trafficked roads and also traffic intensities in the surrounding areas. Only main roads within a radius of 300 m were considered, in light of evidence suggesting that levels of gaseous pollutants emitted from sources at distances >300m are negligible. An approximate 4-fold elevated relative risk (RR=3.91 [1.36-11.27]) of childhood leukaemia was found for heavily exposed children (over 10ug/m3 estimated annual average of benzene) and it was suggested that motor vehicle emissions could be involved in the aetiology of childhood leukaemia. However, there was no evidence for an association between acute leukaemia and exposure to benzene in children below 1 year of age.

6. Crosignani and colleagues recently initiated a further analysis of the above study to obtain information on the index child's benzene exposure history, particularly during the natal and perinatal period (Crosignani et al., 2004b). Parents of each child were interviewed by telephone to obtain information on lifestyle, residential history (with particular reference to proximity to benzene sources), means of transport as well as other potential variables. The initial finding appears to support the earlier positive association, although further generation and analysis of data are required.

7. Nordlinder & Jarvholm (1997) conducted an ecological study to investigate the possible association of exposure to gasoline (vapour/exhaust) and leukaemia in children and young adults (Nordlinder & Jarvholm, 1997). The National Swedish Cancer Registry provided information on the incidence of leukaemia in young people aged between 0 to 24 years (at diagnosis) during 1975 – 1985. These rates were stratified according to age (5-year intervals). The authors used a surrogate measure of exposure to gasoline, based on data obtained from Statistics Sweden, on the number of cars per area and the amount of gasoline sold per area during 1975 - 1985. There was a high correlation between 'car density' (cars/$km^{2)}$ and 'gasoline density' (m^3/km^3) (R=0.998), with the largest cities having the highest car densities (Stockholm - 1026 cars/km^2). The results showed an apparent association between AML and car density. In municipalities

[8] A Gaussian diffusion model was used to estimate the mean concentration of benzene outside every child's home. This considers the distance from main roads, as well as traffic density (vehicles per day) and weather conditions.

with more than 20 cars/ km^2 the incidence of AML was 5.5 [4.4-6.8] cases per 1 million person-years compared with 3.4 [1.9-5.7] in areas with less than 5 cars/km2 (P=0.05). No association was found for the other leukaemia types studied (ALL, CML) nor for non-Hodgkin's lymphoma. Using data from Statistics Sweden, the authors showed that smoking habits of pregnant women from 1975-1985 were almost the same in all car-density groups. However, they could not rule out the possibility that exposure to radiation from natural sources, building materials or during medical diagnoses during treatment could confound the positive finding and suggested the data be interpreted with caution. Furthermore, given the subjects comprised of both children and adults, the findings of the study are limited owing to the absence of any age-stratified analyses presented in the documented results .

8. Steffen et al., 2004 conducted a multicentre hospital based case control study (INSERM) to determine the role of hydrocarbon exposure (in terms of proximity of residence to repair garages, petrol stations and high traffic roads) and acute childhood leukaemia (Steffen et al., 2004). This study was also discussed at the last meeting (CC/04/37). 280 leukaemia cases (with matched controls) were identified from four hospital centres in France in children aged between 0-14 years at the time of diagnosis during 1995 to 1999. Forty children were diagnosed with ANLL and 240 diagnosed with ALL. A questionnaire was used to obtain data on residential history. Since the study also aimed to evaluate the risk following *in-utero* exposure, the questionnaire also covered location of residence from the time of conception, pregnancy, birth and diagnosis. Questions were also asked to determine the existence of automobile repair garages or petrol stations and possible exposure to heavy traffic roads within 50 metres of the children's homes. The authors observed a statistically significant association between leukaemia and exposure to a close neighbouring repair garage or petrol station during the childhood (OR=4.0 [1.5-10.3], n=17). A positive association was also apparent during the *in-utero* period although this did not reach significance (OR=2.2 [0.9-5.7]). When the data was analysed according to leukaemia type, both ANLL and ALL showed strong significant associations with exposure to a close neighbouring repair garage or petrol station (7.7 [1.7-34.3] and 3.6 [1.3-9.9] respectively). No associations were found between leukaemia incidence and other close neighbouring businesses e.g. aluminium, plastic, wood, metalwork, horticultural, printing plants, etc. Furthermore, no associations were found between the existence of high traffic roads within a 50 metre distance of the children's home and acute leukaemia. The authors concluded that the study was limited by the use of measures of exposure to high traffic roads being self declared by mothers interviewed.

9. The authors are presently conducting a follow-up study to identify various uncertainties associated with possible confounders (e.g. family medical history, pesticide use, etc) and methodological design

(CONCAWE, personal communication 2004). All French hospitals will be included and potential exposures to benzene also assessed. The study will further characterise genetic polymorphisms associated with CYP 2E1 to evaluate the extent of individual susceptibility. CONCAWE believe that the new study, data collection for which is due to be completed by June/July 2005, will shed more light on the complex relationship between childhood leukaemia and the possible risk factors.

10. Reynolds et al (2003) conducted a population-based evaluation of childhood cancer incidence rates in California using census-tract hazardous air pollutant (HAP) levels, as modelled by the US EPA (Reynolds et al., 2003). Twenty-five of the 189 HAPs identified by the US EPA in 1990 as potential human carcinogens (which included benzene) were selected, based on documented evidence of their potential to cause cancer via inhalation. HAPs were categorised according to whether they derived from:
    a. mobile sources – (motor vehicles, planes, trains and ships)
    b. area sources – (dry cleaners, gas stations, residences, farm pesticide use, and forest fires)
    c. point sources – large industrial manufacturing facilities

    Of 7143 cases of cancer in children aged <15 years old, 2443 were diagnosed with leukaemia (1938 – ALL; 368 – ANLL). The study found no significant childhood cancer excess in census tracts with the highest exposure levels but the rate ratios for leukaemia appeared to be elevated in these areas. The risks for both types of leukaemia were elevated by 21% in census tracts with the greatest overall HAP exposure (RR=1.21[1.03-1.42]). A 32% increase in risk was found within census tracts with the highest HAP exposure from industrial facilities (RR=1.32 [1.11-1.57), where benzene and perchloroethylene were the main compounds found to contribute to calculated exposure scores. The association was greater in children aged 0-4 years, which the investigators speculated may be due to the fact that younger children tend to spend more time at home than older ones. However, the fact that potentially important indoor HAP sources such as ETS were not controlled for limits the findings of this analysis. It was suggested that traffic-related pollutants, in combination with pollutants from other sources, should be incorporated into future studies of childhood cancer risk and environmental exposure.

11. Visser and colleagues (2004) conducted a population-based study to examine the effect of residency along busy roads in Amsterdam and the incidence of cancer, in particular haematological malignancies in children (Visser et al., 2004). (**NB. This article has been classified as 'uncorrected proof'**). All cases of cancer diagnosed between 1989 and 1997 in patients residing in Amsterdam at the date of diagnosis were selected from the Amsterdam Cancer Registry. Data on the daily traffic intensity of the main roads (between 1986, 1991 and 1993) were collected from the Environmental Research Institute City of Amsterdam and the effect of smoking as a confounder was included in the analysis

from a separate survey. Age-group and sex-specific cancer incidences in the population not residing along the main roads were used as reference. There were five cases of ALL in children (aged < 15) and all had residence along the busiest main roads (standardised incidence ratio (SIR): 4.9 [1.6-11.4]. The authors commented that, although the number of cases of childhood leukaemia was small, the increased risk of ALL was significant although this was derived from a further subgroup analysis. Furthermore, the public health implications were estimated to have a relatively minimal effect whereby 1 excess case of ALL would occur every 3 years among children who lived among main roads in Amsterdam.

12. Urayama et al. (2004) conducted the first study to examine the combined effects of genetic polymorphisms (i.e. CYP1A1m1 and CYP1A1m2) and traffic exposure on risk of childhood leukaemia (Urayama, 2004 unpublished results). 183 cases of children diagnosed with leukaemia since 1995 were obtained from an ongoing population-based case control study (the Northern California Childhood Leukaemia Study or NCCLS) which was designed to investigate the aetiology of childhood leukaemias in US. Controls were matched for age and race and buccal samples were obtained for DNA genotyping. Traffic density provided a crude measure of exposure to traffic and was estimated from a combination of road lengths and vehicle traffic counts to yield the vehicle miles travelled per square mile within a 500-foot radius of each subject's residence at birth. The results showed that 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]). This suggests that children carrying the high risk CYP1A1m2 allele may be more susceptible to the carcinogenic effects of traffic-related exposures. Assuming that this study was conducted in a largely Caucasian population, the numbers with m2 allele are presumably small, with a population prevalence of <7%. NOTE. This study has not yet been published in the peer-reviewed literature.

<u>Studies reporting a null association between childhood leukaemia and residential proximity to traffic exhaust</u>

13. Harrison et al (1999) looked at cancer risk in children aged between 0-15 years old living within 100m of main roads and gas stations in the West Midlands. Cases of children diagnosed with leukaemia during the period 1990 to 1994 (n=130) were identified from West Midlands Cancer Intelligence Unit. Postcode addresses were used to locate the point of residence, which was compared to proximity to main roads and petrol stations operational during the study period. Two different approaches were used to investigate whether there was an excess

incidence of leukaemia around these sites. Firstly, odds ratios were calculated in a case-control method, which used as controls children diagnosed with solid tumours during the same period (n=251). The second method used indirect age and sex standardisation to examine the observed number of cases of leukaemia compared with what would be expected for the population of the health authority as a whole. Both methods showed an increased risk of childhood leukaemia within either 100m of a petrol station, or within 100m of a main road, but in neither case was the result statistically significant.

14. Langholz et al (2002) conducted a case control study to investigate the relationship between traffic density and the risk of childhood leukaemia (Langholz et al., 2002). Using data collated from a previous case-control study conducted in the Los Angeles area during 1978 to 1984 (London et al, 1999 Am J Epidemiol, 128;21-38), an integrated distance-weighted traffic density measure was calculated for each of the 212 child leukaemia subjects aged 0-10 years old. No evidence of an association of traffic density with childhood leukaemia was found and it was suggested that this may be partly due to the choice of traffic density measure and exposure misclassification error arising from differential time frames for when diagnoses and traffic counts were made.

15. The most comprehensive assessment of traffic-associated risks comes from a large population based study spanning 24 years in Denmark. Raaschou-Nielsen et al (2001) avoided the shortcomings of other studies by increasing sample size and designing a more refined method of exposure assessment to test the hypothesis that air pollution in traffic causes cancer in childhood. 1,989 children under 15 years old recorded in the Danish Cancer Registry as diagnosed with either leukaemia, CNS tumour or malignant lymphoma during 1968-1991 were enrolled in the study (Raaschou-Nielsen et al., 2001). 5,506 control children were selected randomly from the files of the Danish Population Registry. The residential histories were traced from 9 months before birth until time of diagnosis and information on traffic and street configuration were collected. Average concentrations of benzene and NO_2 were calculated for the relevant period and exposures during pregnancy and during childhood were collected separately. An attempt was made to adjust for urban density, type of residence, EMF in the vicinity of the residence, mother's age and birth order. Results showed no increased risk of leukaemia in children exposed to traffic-related air pollution during pregnancy or childhood, However, the risk of Hodgkin's disease diagnosed before the age of 12 years increased with increasing concentrations of ambient air pollution at the residence at the time the child was *in utero*. At the highest categories of exposure, the RRs were 4.3 [1.5-12.4] for benzene and ; 6.7 [1.7-26.0] for NO_2 . This is the only study that has assessed both traffic density measures and modelled NO_2concentrations for the full

lifetime residential histories of the study children.

16. Prompted from early studies investigating possible confounders to EMF exposure and childhood leukaemia as mentioned earlier, Reynolds et al (2001) examined the relationship between traffic density and socio-economic indicators to early childhood leukaemia in an urban area of California. Ninety cases of childhood leukaemia diagnosed between 1988 and 1994 among children under the age of five born in San Diego County were matched by gender and birth date. The pilot study also utilised modern GIS technology to assess geographic proximity of birth address to high flow traffic areas and thus provide an empirical analysis of any potential association to childhood leukaemia. Traffic density was measured using a variety of methods, including information on average daily traffic counts and road characteristics. The authors concluded that neither SES or traffic density near the birth address were strong enough risk factors for leukaemia to actually be considered as confounders, although several limitations with study design were noted and postulated to possibly account for this null result.

17. An extension study by Reynolds et al., (2002) evaluated the risks of childhood leukaemia and other cancers in Californian children under 15 years of age diagnosed between 1988 and 1994 living in neighbourhoods or block groups with high volume motor vehicle traffics (Reynolds et al., 2002). Three estimates of traffic patterns were used as a measure of traffic exhaust exposure. Over a third of cases were leukaemias (2443), with ALL accounting for 79% of cases. The results failed to show a substantially elevated incidence of any childhood cancer in areas of high vehicle intensity, high road density or high traffic density. This may partly result from the fact several confounding factors were not accounted for. There was no information on residential history, which poses a significant concern, as the address at the time of diagnosis may not represent the most relevant time window or location for exposures of interest. Furthermore there was a lack of data on other sources of air pollution (indoor and outdoor), traffic levels around schools, day-care centres and other places where children may spend substantial amounts of time; thus highlighting the importance of measuring microenvironmental exposures as opposed to group level exposures, which do not accurately reflect an individual's exposure profile. It was suggested that future studies be designed with more refined methods for measuring exposure to traffic exhaust and the time at which these exposures occurred.

18. In a follow-up study, Reynolds et al (2004) examined the risk of several cancers (including leukaemia) in 5177 children diagnosed between 1988 and 1997 all under 5 years of age and living in California. Controls were matched for age and sex. Information on mothers residential address at the time of child's birth was also collected and two traffic measures (road and traffic density) were used as surrogates for exposure to traffic emissions. The results provided little or no evidence for increased risk of cancer among children born in high traffic areas. For the leukaemias, the ORs were at or below unity for all exposure categories e.g., under the highest exposure categories ORs= 0.92[0.73-1.15] and 0.79[0.63-1.00] for traffic and road density values respectively. This study however had several advantages compared to previous work i.e. the large sample size (which provided heterogeneity in exposure potential), the acquisition of residential address at birth rather than at the time of diagnoses, and the non-self reporting of exposures (which removed potential recall bias).

19. Alexander et al. (1996) re-analysed ecological data to determine whether the reported increased rates of childhood ALL in isolated areas could be attributed to higher proportions of households owning cars. Using 1981 census data for England and Wales (to derive socio-economic background, level of car ownership and the degree of isolation up to 20 km) and information on children aged between 0-14 years old diagnosed with ALL (n=438) between 1984-1989 (taken from a specialist leukaemia registry for England & Wales) the study found no evidence that the incidence of ALL in children is increased in areas where more households possess cars. ALL at ages 1-7 years old was found to be inversely associated with car ownership. The authors further concluded that the finding fails to support the hypothesis that exposure of children to petrol and exhaust fumes in cars may increase their risk of ALL.

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Glossary

Some definitions

Vehicle density	Provides an estimate of potential exposure to evaporative emissions by measuring where vehicles are parked at night. An area with more cars per unit area may have higher ambient concentrations of volatile organic compounds, such as benzene, as a result of these evaporative emissions.
Road density	Reflects the miles of road within a block group per square mile of land area.
Traffic counts	Represent the number of vehicles per weekday travelling one way on a road segment. Used to generate traffic density. Often expressed as vehicles per day (VPD)
Traffic density/intensity	Provides proxy measures of exposures to chemical mixtures from mobile sources

Automobile emissions

Diesel fuel

Diesel fuel consists mostly of higher boiling range petroleum fractions and therefore because of its higher density yields approximately 13% more energy than a litre of gasoline. For this reason, diesel engines are the predominant source of industrial power and are most often used to power heavy-duty applications and works. They also produce 2-10 times more particulate emissions than gasoline engines (without catalytic converter) of comparable power output and two to 40 times more particulate emissions than gasoline engines equipped with a catalytic converter (IARC, 1989). A much larger percentage of passenger vehicles in Europe are powered by diesel engines than in the US (Frumkin & Thun, 2001). With regards to evaporative emissions diesel is relatively non-volatile (Knox & Gilman, 1997).

Gasoline

Gasoline is a derivative of petroleum and is used mainly as a light fuel in internal combustion engines in cars and motorbikes. However, motor gasoline is also used in lesser quantities (approximately 0.7% in 2000) for off-road applications such as professional and consumer equipment (chain saws, lawn mowers, garden tractors) and recreational vehicles (e.g. snow mobiles, water craft). A small quantity is also used for aviation purposes (CONCAWE, 2004).

Vehicle exhaust

The main sources of engine exhausts are vehicles: automobiles, buses, trucks, trains ships, boats, heavy construction equipment, fork-lift trucks, tractors and jet aircrafts, although diesel and gasoline fuelled engines are also used as stationary power sources. Stationary sources that also contribute toward the carcinogenic burden of urban air, include industrial emissions that elevate concentrations of volatile organic compounds, aromatics, industrial metal fumes and oxides of nitrogen and sulphur, which can also combine in the atmosphere and form secondary pollutants (Kelly et al 1994, Environmental Sci Technol, Vol 28; 378-87).

Table 3. lists some compounds and classes of compounds in vehicle engine exhaust (those considered as carcinogenic are italicised).

Gas 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
Particulate phase**	
	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
*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.

Evaporative emissions

Automobile fuel vapour emissions have been categorised according to the heating mechanism responsible for its evaporation (Mann et al., 2001). These vapour emissions can also occur during distribution and storage as well as incidental losses during spillage episodes from consumer refuelling.

Evaporative emissions can be further classified as the following:

Hot soak emissions	Diurnal emissions	Running losses	Resting losses
Result from the heating of the fuel system after engine shutdown (believed to be more applicable to carburetted	Result from cyclic heating and cooling of the fuel tank during the day and night	Result from the heating of petrol in the fuel tank to the extent that it boils and overwhelms the evaporative emission	Result from diffusion of fuel through plastic and rubber fuel system components and the escape of hydrocarbon vapours

engines, than in fuel injected engines)		control system	from the storage canister.

Benzene toxicity (carcinogenicity)

Benzene is formed during the incomplete combustion of fossil fuels (petroleum products, coal, and to a lesser extent, wood). The COM last reviewed benzene in 1998 (CC/04/37). Benzene is considered by IARC to be a definite human carcinogen inducing a variety of different types of leukaemia in occupationally exposed workers (CC/04/37). The International Agency for Research on Cancer has designated benzene as a Group 1 carcinogen. Most of the evidence in humans derives from industrial studies of workers exposed to benzene often as a constituent of a complex mixture. These include shoemaking, printing, petrochemical, chemical, coke production and rubber manufacturing industries.

There is in-vivo evidence to demonstrate both clastogenicity and gene mutations with benzene (CC/04/37). In addition more recent data are consistent with this view. Of particular note in this regard is the recent publication of a transgenic assay in mice using the bacterial lac1 gene as a marker, which shows benzene induces gene mutations in lung and spleen (CC/04/37).

The mechanism by which benzene is thought to induce tumours is thought to arise following its metabolism in the liver by the cytochrome P-450 system. Two metabolic pathways appear to be involved but its toxicity is thought to result from the interaction between benzene metabolites rather than the effects of a single metabolite acting independently (Courage, 1999).

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