DRAFT **CC/04/37**

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

CHILDHOOD LEUKAEMIA AND ENVIRONMENTAL EXPOSURES

Introduction

1. The COC has initiated a review of childhood cancer (CC/04/31). This additional preliminary discussion paper has been drafted at the request of the DH Air pollution unit to specifically address the evidence from selected published epidemiology studies for an association between residence near to petrol stations, garages, and road traffic exhaust fumes and the occurrence of childhood leukaemia (all types of leukaemia in individuals aged 0-14 y). In one of the studies, exposure to benzene was modelled and analyses undertaken on the estimated exposure to benzene as a surrogate chemical for exposure to road traffic exhaust fumes.

2. Benzene is considered by IARC to be a definite human carcinogen inducing a variety of different types of leukaemias in occupationally exposed workers. [1] The COM last reviewed benzene in 1998.[2] A comprehensive review of the health effects of benzene is provided in the IPCS Environmental Health Criteria document (No 150) published in 1993.[3] There is *in-vivo* evidence to demonstrate both clastogenicity and gene mutations with benzene.[4,5] 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.[4]

3. Benzene is present in road traffic exhaust, and is released at petrol stations and garages, and thus it is reasonable to assume that exposure to benzene occurs in these situations, although other carcinogenic agents may also be emitted from such sources such as PAHs.

Overview of selected studies.

Brief comments are given below. Relevant papers are appended.

Steffen C et al. Occupational and Environmental Medicine, vol 61, 773-778, 2004.

4. A hospital-based case control study was undertaken with 280 leukaemia cases (aged 0-14 with an acute leukaemia diagnosis between 1 Jan 1995- 31 December 1999 from 4 centres in France) and 285 controls (children admitted to the same hospitals with predominantly diagnoses of trauma and non-trauma orthopaedic disease). Children with congenital malformations were excluded. Children from the same administrative regions were included in the study, thus omitting cases from distant regions. There

were 240 cases of acute lymphocytic leukaemia and 40 cases with acute non-lymphocytic leukaemia. Data were collected by face-to face interview of the mothers during the first remission period after diagnosis (ca 2 months). Cases and controls were interviewed at the same period using a structured questionnaire. Exposure to hydrocarbons and existence of neighbouring businesses (adjoining the child's residence, in particular automobile repair garage or petrol station) were included in the questionnaire. Questions were also included about the possible exposure to heavy road traffic fumes (<50m from residence). Parental occupation and a categorisation of potential exposure to benzene were included.

5. The authors documented a statistically significant increased OR for residence adjoining a repair garage or petrol station (OR = 4.0 (95% CI 1.5-10.3)). An increased OR was documented for in-utero residence adjoining a repair garage or petrol station (OR = 2.2 (95% CI 0.9-5.7)). Residence during childhood adjoining a repair garage or petrol station was statistically significantly associated with either ANLL (OR= 7.7 (95% CI 1.7-34.3) and ALL (3.6 (95% CI 1.3-9.9)), although the analysis for ANLL was based on small numbers.

6. The authors undertook a duration of residence evaluation using a cut off period of 36 months. They reported a statistically significant duration trend (using ANLL and ALL combined). (OR per month 1.03 (95% CI 1.01-1.05) p = <0.05).

7. The authors undertook a sensitivity analysis to account for the potential impact of missing data and found that the association with residence near to petrol stations and repair garages remained statistically significant. There was no association between childhood leukaemia and a range of other businesses in close proximity to place of residence. No association was reported between high traffic roads within 50 m of residence and childhood leukaemia. Maternal occupation did not affect the results reported. Overall the authors conclude that the results could be due to chance but the strength of the association and evidence of a duration trend suggested that the findings were not a random association. It was suggested further studies which specifically looked at benzene exposure should be undertaken.

Crosignani P et al. Int J of Cancer, vol 108, 596-599, 2004.

8. A population based case-control study was undertaken using all incident cases of leukaemia (aged 0-14 y, all ICD codes -version IX- 204.0-208.9) diagnosed in the Province of Varese, northern Italy from 1978-97. Four controls were matched for each case (gender, date of birth (+/- 5 days). Exposure to benzene was estimated by application of Gaussian diffusion model to information on place of residence and exposure distances from highly trafficked roads and also traffic intensities in the surrounding area. Subjects were assigned to three exposure categories (<0.1µg/m^3, 0.1-10 µg/m^3 and >10 µg/m^3). The authors reported an increased relative risk of leukaemia with distance from major road and road traffic intensities, but for

these analyses none of the 95% lower confidence estimates were above 1. A concentration related increase in the rate ratio (RR) for leukaemia was documented (0.1-10 μg/m^3 (RR 1.51 (95% 0.91-2.51)) and >10 μg/m^3 (RR= 3.91 (95% CI 1.36-11.27)). The p-value for the trend test was significant (p= <0.005). The authors reported a statistically significant association when the analyses were based on ALL alone (which accounted for 79% of the 120 cases studies). The authors also analysed the data using cases identification from 1978-1986 and 1987-1997 (mainly to explore bias due to possible lack of representivity of the archive used to sample controls). The only significant increase (where the lower 95% CI was above 1) was for the highest exposed group in the 1987-1997 analysis (rate ratio 5.84 (955 CI 1.30-26.30), but this analysis was based on a small number of cases and controls (4/3 respectively). The authors noted that there was no evidence for an association between acute leukaemia and exposure to benzene in children aged below 1y. Parental occupation was not considered n this study. The authors reported that socio economic status had a minimal effect on the results.

9. The authors concluded that the results of the study supported the hypothesis that traffic exhausts are a factor in the etiology of childhood leukaemia,

Harrison RM et al Occupational and Environmental Medicine, vol 56, 774-780, 1999.

10. An analysis of incidence of childhood cancer in the West Midlands in proximity to main roads and petrol stations was undertaken using post code addresses for children and petrol stations. A cancer diagnosis (lymphoid, myeloid, monocytic, and unspecified leukaemia and solid cancers and benign neoplasms) between 1990 1994 was included in the study. Children with solid tumours were used as controls. An increased OR for residence near to a major road or petrol station (<100 m) was documented based on 3 leukaemias and one solid cancer control. (OR 5.61 (95% COI 0.61-57.3). Overall the results were not particularly persuasive of an association. The authors suggested a larger study was warranted to further investigate the potential association.

Discussion and questions for COC.

11. This is not intended to be a full evaluation of the literature. The evidence is suggestive that an association between exposure to pollutants and possibly also to benzene with the occurrence of acute leukaemia in children may exist. The potential for in-utero exposure has not been considered in this short review paper. It is noted that some investigators consider benzene to be associated with predominantly with acute myeloid leukaemia in occupational exposure. The evidence for an association with several forms of leukaemia in children represents a potentially new finding.

12. Members are asked to consider the following questions for advice.

a) Is the evidence presented suggestive of an association between exposure to pollutants from petrol stations, garages and road traffic and the occurrence of acute leukaemia in children (aged 0-14 y). Should a further more detailed review be undertaken?

b) Can any preliminary conclusions be reached with regard to exposure to benzene? Should a further more detailed review of benzene and the potential association with acute leukaemia be undertaken?

c) Is the evidence regarding environmental exposures (including benzene) suggestive of an association with one or more types of acute leukaemia? Should a furthermore detailed review of this aspect be undertaken?

Secretariat October 2004

REFERENCES

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4. Mullin AH, Rando R, Esmundo F, and Mullin DA. Inhalation of benzene leads to an increase in the mutant frequencies of a *lacI* transgene in lung and spleen tissues of mice. Mutation Research, **327**, 121-129, 1995.

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