Supplemental Material

Additional benzene information:

Exposure to benzene during refueling and driving, as well as the contribution of active and passive tobacco smoke, has been considered as part of the characterization of risk of the general population (Duarte-Davidson 2001). Childhood leukemia has been found to be associated with exposure to road traffic emissions and close proximity to gas stations. As an index of exposure to traffic exhaust, Crosignani et al. estimated the annual mean concentration of benzene outside the home using a Gaussian diffusion model. This model uses traffic density (vehicles/day) on nearby main roads, distance between roads and residence, and information on vehicle emissions and weather conditions to estimate benzene concentration. Compared to children whose homes were not exposed to road traffic emissions (<0.1 microg/m^3 of benzene as estimated by the model), the risk of childhood leukemia was significantly higher (RR = 3.91; 1.36-11.27) for heavily exposed children (over 10 microg/m^3 estimated annual average) (Crosignani 2004). In a case-control study by Steffen et al., positive associations were observed between acute leukemia and in-utero and childhood exposure to a close neighboring repair garage or petrol station. The association was statistically significant for the latter period (OR 4.0, 1.5 to 10.3). The odds ratios for the subgroups of AML and ALL were 7.7 (95% CI 1.7 to 34.3) and 3.6 (95% CI 1.3 to 9.9) respectively for exposure during childhood. A positive, statistically significant trend (OR 1.03, 95% CI 1.01 to 1.05, per month of exposure) was found between duration of childhood exposure to a neighboring repair garage or petrol station and acute leukemia. However, no association was found between the existence of high traffic roads within a 50 meter distance of the children's homes and acute leukemia (Steffen 2004).

Crosignani P, Tittarelli A, Borgini A, Codazzi T, Rovelli A, Porro E, et al. 2004. Childhood leukemia and road traffic: A population-based case-control study. Int J Cancer 108:596-9.

Duarte-Davidson R, Courage C, Rushton L, Levy L. 2001. Benzene in the environment: an assessment of the potential risks to the health of the population. Occup Environ Med 58:2-13.

Steffen C, Auclerc MF, Auvrignon A, Baruchel A, Kebaili K, Lambilliotte A. et al. 2004. Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. Occup Environ Med 2004 61:773-8.

Medications/therapeutic agents:

Little data exists about the relationship between parental medication use and childhood leukemia. Maternal use of vitamins and iron supplements during pregnancy has been associated with a decreased risk of ALL (Wen 2002). However, vitamin use may be a behavioral marker for other factors that are associated with decreased risk for disease, such as higher socioeconomic status and low alcohol consumption.

Wen et al. found that parental use of amphetamines or diet pills before and during pregnancy increases risk, though not significantly, for ALL, especially if both parents report using these drugs (OR 2.8, 0.5–15.6) (Wen 2002).

Maternal use of medications to treat morning sickness during pregnancy has been reported to increase the risk of AML in offspring (Robison 1989). Although the overall estimated relative risk was nonsignificant (RR 1.75, 0.98–3.2), a significant elevation (RR 2.8, $p < 0.05$) was associated with increased duration of usage (defined as greater than 10

weeks) compared to no use or use for less than 1 week.

Exposure of a child or adult to alkylating agents during chemotherapy is associated with an increased risk of secondary leukemia, particularly AML. Secondary leukemias typically develop 4 to 6 years after exposure to alkylating agents. Incidence of AML as a secondary leukemia appears to increase as intensity and duration of exposure increase (Tucker 1987). Prolonged exposure in children and adults to DNA topoisomerase II (DNAt2) inhibitors (i.e. epipodophyllotoxins, anthracyclines) during treatment used for refractory and advanced-stage malignancies has also been identified as a risk factor for developing AML (Le Deley 2003; Pui 1991; Ross et al. 1994b).

Le Deley MC, Leblanc T, Shamsladin A, Raquin MA, Lacour B, Sommelet D, et al. 2003. Risk of secondary leukemia after a solid tumor in childhood according to the dose of epipodophyllotoxins and anthracyclines: a case-control study by the Société Française d'Oncologie Pédiatrique. J Clin Oncology 21:1074-1081.

Pui CH, Ribeiro RC, Hancock ML, Rivera GK, Evans WE, Raimondi SC, et al.1991. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. NEJM 325(24):1682-7.

Ross JA, Potter JD, Robison LL. 1994. Infant leukemia, topoisomerase II inhibitors, and the MLL gene. J Natl Cancer Inst 86:1678-1680.

Tucker M, Meadows A, Boice JD Jr, Stovall M, Oberlin M, Stone BJ, et al. 1987. Leukemia after therapy with alkylating agents for childhood cancer. J Natl Cancer Inst 78:459-464.

Wen WQ, Shu XO, Potter JD, Severson RK, Buckley JD, Reaman GH, et al. 2002. Parental medication use and risk of childhood acute lymphoblastic leukemia. Cancer

95(8):1786-1794.

Military history:

Some researchers have suggested that military service may be a proxy for exposures with potential health risks, including leukemia in their offspring. For example, alcohol consumption and cigarette and marijuana use have been reported to be more prevalent among military personnel than among the general population (Bray 1989).

Wen et al. investigated the relationship between preconception paternal military service and the incidence of childhood leukemia (Wen et al. 2000). The authors reviewed three case-control studies conducted by the Children's Cancer Group that included approximately 3000 children with leukemia. They determined that overall paternal military service was not associated with leukemia risk. A nonstatistically significant increase in risk for AML was seen among offspring of veterans who had served in Vietnam or Cambodia (OR 1.7, CI 1.0–2.9). The risk was primarily present in children diagnosed before the age of 2 years (OR 4.6, CI 1.3–16.1) (Wen et al. 2000). However, the Centers for Disease Control and Prevention (CDC) Vietnam Experience Study did not find a statistically significant elevated risk for childhood leukemia among their offspring (The Centers for Disease Control Vietnam Experience Study 1988). A study to determine whether U.S. counties that had a military air base similar to Naval Air Station Fallon (Nevada), which is in a county with increased rates of childhood leukemia, found no evidence of such a relationship among any age group (Steinmaus 2004).

Bray RM, Guess LL, Marsden ME, Herbold JR. 1989. Prevalence, trends, and correlates of alcohol use, and tobacco use among US military personnel. Mil Med 154:1-11.

The Centers for Disease Control Vietnam Experience Study. 1988. Health status of Vietnam veterans, III, Reproductive outcomes and child health. JAMA 259:2715-2719.

Steinmaus C, Lu M, Todd R, Smith AH. 2004. Probability estimates for the unique childhood leukemia cluster in Fallon, Nevada, and risks near other US military aviationfacilities. Environ Health Perspect 112:766–771.

Wen WQ, Shu XO, Steinbuch M, Severson RK, Reaman GH, Buckley JD, et al. 2000. Paternal military service and risk for childhood leukemia in offspring. Amer J Epidemiol 151:231-240.

Nutrition:

Studies have evaluated diet as a potential risk factor for childhood leukemia including maternal dietary intake, breastfeeding, and food consumption by children. In a recent case-control study in which maternal dietary intake in the 12 months prior to pregnancy was obtained consumption of vegetables (OR = 0.53; 0.33-0.85), protein sources (OR = 0.40; 0.18-0.90), fruits (OR = 0.71; 0.49-1.04), provitamin A carotenoids (OR = 0.65, 0.42-1.01), and the antioxidant glutathione (OR = 0.42; 0.16-1.10) were inversely associated with ALL, although not statistically significant (Jensen 2004). In two recent meta-analysis studies, Guise et al. concluded that "there are few high-quality studies available that examine the potential for a protective effect of breastfeeding for childhood leukemia" (Guise 2005) and Martin et al. suggested lower risks associated with having been breast-fed of 9% (95% CI =

2-16%) for acute lymphoblastic leukemia and concluded that ever having been breast-fed is inversely associated with acute lymphoblastic leukemia (Martin 2005).

With regard to food consumption by children and the risk of acute leukemia, the relation between the intake of certain food items thought to be precursors or inhibitors of N-nitroso compounds (NOC) (e.g., luncheon meats, hot dogs) and risk of leukemia was investigated in a case-control study among children from birth to age 10 years in Los Angeles, California. The only persistent significant association was for children's intake of hot dogs (OR = 9.5, 1.6-57.6 for 12 or more hot dogs per month, trend P = 0.01) (Peters 1994). In a more recent study focused on the first two years of life, no association between eating hot lugs and lunch meats and risk of leukemia was found. Regular consumption of oranges and/or bananas (OR = 0.49, 0.26 – 0.94) and orange juice (OR 0.54, 0.31 – 0.94) was associated with a reduction in the risk of childhood leukemia diagnosed between the ages of 2 and 14 years (Kwan 2004).

Guise JM, Austin D, Morris CD. 2005. Review of case-control studies related to breastfeeding and reduced risk of childhood leukemia. Pediatrics 116:e724-31.

Jensen CD, Block G, Buffler P, Ma X, Selvin S, Month S. 2004. Maternal dietary risk factors in childhood acute lymphoblastic leukemia (United States). Cancer Causes Control 15:559-70.

Kwan ML, Buffler PA, Wiemels JL, Metayer C, Selvin S, Ducore JM, Block G. Breastfeeding patterns and risk of childhood acute lymphoblastic leukaemia. Br J Cancer 2005 93:379-84.

Martin RM, Gunnell D, Owen CG, Smith GD. 2005. Breast-feeding and childhood cancer: A systematic review with metaanalysis. Int J Cancer. 2005 117:1020-31.

Peters JM, Preston-Martin S, London SJ, Bowman JD, Buckley JD, Thomas DC. 1994. Processed meats and risk of childhood leukemia (California, USA). Cancer Causes Control 5:195-202.

Additional information on Nonionizing radiation:

The effect on childhood cancer of prolonged exposure to magnetic fields from electric appliances has also been studied. Prenatal electric blanket exposure had a nonstatistically significant association with childhood leukemia (OR 1.7, 0.8–3.6) as well as for postnatal exposure (OR 1.9, 0.6–6.5) (Savitz 1990). Results were limited due to rarity of appliance use. Children's use of other electrical appliances (e.g., hair dryers, video games) was associated with increased risk, but the patterns of risk for duration in years of use and frequency of use were inconsistent (Savitz 1990).

Savitz DA, John EM, Kleckner RC, Magnetic field exposure from electric appliances and childhood cancer, Am J Epidemiol 1990; 131:763-73.

Additional information on Population mixing:

Ecological studies have suggested that high levels of population mixing in Greece and Italy may have contributed to the high mortality rates from childhood leukemia during the 1950s and 1960s (Kinlen and Petridou 1995). Ecologic studies from other locations support their hypothesis (Gilman 1998; Langford 1991; Stiller and Boyle 1996). A strong, although indirect, association between incidence of ALL and areas with population mixing was shown

in Hong Kong during the 1970s and 1980s (Alexander et al. 1997). Significant clustering of childhood leukemia cases in the United Kingdom was found in two studies that used residential proximity as a proxy for shared social contacts (Alexander 1993; Smith 1976).

Alexander FE, Viruses, clusters and clustering of childhood leukaemia: a new perspective? Br J Cancer 1993; 29A(10): 1424-1443.

Alexander FE, Chan LC, Lam TH, Yuen P, Leung NK, Ha SY, et al. 1997. Clustering of childhood leukaemia in Hong Kong: association with the childhood peak and common acute lymphoblastic leukaemia and with population mixing. Br J Cancer 75:457-463.

Gilman EA, Knox EG. 1998. Geographical distribution of birth places of children with cancer in the UK. Br J Cancer 77:842-849.

Kinlen LJ and Petridou E, Childhood leukemia and rural population movements: Greece, Italy and other countries, Cancer Causes Control 1995; 6(5): 445-50.

Langford I, Childhood leukaemia mortality and population change in England and Wales 1969-73, Soc Sci Med 1991; 33:435-440.

Smith PG, Pike MC, Till MM, Hardistry RM, Epidemiology of childhood leukemia in Greater London: a search for evidence of transmission assuming a possibly long latent period, Br J Cancer 1976;33: 1-8.

Stiller CA and Boyle PJ, Effect of population mixing and socioeconomic status in England and Wales, 1979-85, on lymphoblastic leukaemia in children, BMJ 1996;313:1297-300.